

First Principles of Gastroenterology and Hepatology in Adults and Children

Volume II **Hepatology and Paediatrics**

A. B. R. Thomson, E. A. Shaffer, T. Gonska, Editors





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The Editors



Editor Biographies

Dr. Alan Thomson has been President of the Canadian Association of Gastroenterology, a member of the Bockus Society, two-term Governor for Western Canada for the American College of Gastroenterology, winner of the prestigious University Cup in 2001, a recipient of the Gold Medal in Medicine of the Royal College of Physicians and Surgeons (Canada), Chief Royal College examiner in Gastroenterology, Director of the Division of Gastroenterology, three-time Teacher of the Year at the University of Alberta, Award for Excellence in Mentoring Graduate Students and Postdoctoral Fellows, and awarded Distinguished University Professor. He helped found the Gastroenterology Training Fellows annual course, The Canadian Digestive Disease Foundation, The Canadian Helicobacter Study Group, The Canadian Journal of Gastroenterology, and First Principles of Gastroenterology. He joined the Faculty of Medicine at the University of Alberta in 1975, where he began his career as a clinician, teacher, and investigator. He cherishes the privilege of having helped train more than 60 GI training fellows and graduate students. Dr. Thomson's basic research interest is in the mechanisms of intestinal adaptation, the absorption of nutrients, and the modification of this adaptive response in health and in disease models. His clinical research interests involve the study of human gastric secretion and the coordination and conduct of clinical trials for patients with peptic disorders, as well as inflammatory and irritable bowel diseases. Dr. Thomson has authored over 700 scientific papers and review articles, and has written or edited ten books. Dr. Thomson is a Distinguished Emeritus University Professor, University of Alberta, and is currently an Adjunct Professor at Western University.

Eldon Shaffer is a Gastroenterologist who has held leadership positions in academic Medicine. At a university level, Dr. Shaffer was founding Division Head (Gastroenterology); founding chair, Gastrointestinal Research Group; Associate Dean (Clinical Affairs); Department Head (Internal Medicine), and Regional Clinical Department Head (Internal Medicine), all in the Faculty of Medicine, University of Calgary. At a national level, he was the first and founding President of Canadian Association for Study of the Liver; President, Canadian Association of Gastroenterology; President, Canadian Society for Clinical Investigation; Chair of the Medical Advisory Board, Crohn's and Colitis Foundation; President, Canadian Professors of Medicine; and Chair, Finance Committee of the Alberta Society of Gastroenterology. At an international level, he served on committees for the American College of Gastroenterology, the American Association for the Study of the Liver Disease and the American Gastroenterological Association, chairing the Liver Biliary section for the American Gastroenterological Association and sitting on the AGA Council and the Organizing Committee (Chair, Public Relations Committee) for the World Congress of Gastroenterology (Montreal 2005). His personal research activity has yielded over 500 papers, abstracts and edited texts. A recognized educator, Dr. Shaffer has received awards nationally from the Canadian Association of



Gastroenterology and regionally in Alberta and from his Faculty of Medicine. He currently is a Professor of Medicine in the Division of Gastroenterology and Hepatology, University of Calgary, where he enjoys an active consulting practice in Gastroenterology and continues to maintain his education and research interests that span from hepatobiliary diseases through functional gut disease and eosinophilic gastrointestinal disease.

Tanja Gonska is an Assistant Professor at the Division of Paediatric Gastroenterology, Hepatology and Nutrition, University of Toronto, with a subspecialty focus on paediatric pancreas diseases and Cystic Fibrosis. She holds an appointment at the Research Institute of the Hospital for Sick Children and the Institute of Medical Science, Toronto. Following Medical school in Muenster, Paediatric Residency training at the Children's Hospital in Freiburg, Germany, and Fellowship training at the Hospital for Sick Children, Dr. Gonska has decided to continue her academic career in Paediatric Pancreatology and Cystic Fibrosis as staff physician at the Hospital for Sick Children. She has enjoyed mentorship by Profs. Peter Durie, Christine Bear and Paul Quinton. Next to her involvement in an international consortium to advance the knowledge in paediatric pancreatitis, her research interest is focused on forwarding our understanding in transepithelial ion and fluid transport in airway and intestine. Further, her innovative approach to develop new measures of functional outcome supports current strategies to cure Cystic Fibrosis disease.



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First Principles and the CANMED Objectives

Medical expert

The discussion of complex cases provides the participants with an opportunity to comment on additional focused history and physical examination. They would provide a complete and organized assessment. Participants are encouraged to identify key features, and they develop an approach to problem-solving.

The case discussions, as well as the discussion of cases around a diagnostic imaging, pathological or endoscopic base provides the means for the candidate to establish an appropriate management plan based on the best available evidence to clinical practice. Throughout, an attempt is made to develop strategies for diagnosis and development of clinical reasoning skills.

Communicator

The participants demonstrate their ability to communicate their knowledge, clinical findings, and management plan in a respectful, concise and interactive manner. When the participants play the role of examiners, they demonstrate their ability to listen actively and effectively, to ask questions in an open-ended manner, and to provide constructive, helpful feedback in a professional and non-intimidating manner.

Collaborator

The participants use the “you have a green consult card” technique of answering questions as fast as they are able, and then to interact with another health professional participant to move forward the discussion and problem solving. This helps the participants to build upon what they have already learned about the importance of collegial interaction.

Manager

Some of the material they must access demands that they use information technology effectively to access information that will help to facilitate the delineation of adequately broad differential diagnoses, as well as rational and cost effective management plans.

Health advocate

In the answering of the questions and case discussions, the participants are required to consider the risks, benefits, and costs and impacts of investigations and therapeutic alliances upon the patient and their loved ones.

Scholar

By committing to the pre- and post-study requirements, plus the intense three day active learning Practice Review with colleagues is a demonstration of commitment to personal education. Through the interactive nature of the discussions and the use of the “green consult card”, they reinforce their previous learning of the importance of collaborating and helping one another to learn.



Professional

The participants are coached how to interact verbally in a professional setting, being straightforward, clear and helpful. They learn to be honest when they cannot answer questions, make a diagnosis, or advance a management plan. They learn how to deal with aggressive or demotivated colleagues, how to deal with knowledge deficits, how to speculate on a missing knowledge byte by using first principals and deductive reasoning. In a safe and supportive setting they learn to seek and accept advice, to acknowledge awareness of personal limitations, and to give and take 360° feedback.

Knowledge

The basic science aspects of gastroenterology are considered in adequate detail to understand the mechanisms of disease, and the basis of investigations and treatment. In this way, the participants respect the importance of an adequate foundation in basic sciences, the basics of the design of clinical research studies to provide an evidence-based approach, the designing of clinical research studies to provide an evidence-based approach, the relevance of their management plans being patient-focused, and the need to add “compassionate” to the Three C’s of Medical Practice: competent, caring and compassionate.

“They may forget what you said, but they will never forget how you made them feel.”

Carl W. Buechner, on teaching.

“With competence, care for the patient. With compassion, care about the person.”

Alan B. R. Thomson, on being a physician.



Prologue

HREs, better known as, High Risk Examinations. After what is often two decades of study, sacrifice, long hours, dedication, ambition and drive, we who have chosen Internal Medicine, and possibly through this a subspecialty, have a HRE, the [Boards] Royal College Examinations. We have been evaluated almost daily by the sadly subjective preceptor based assessments, and now we face the fierce, competitive, winner-take-all objective testing through multiple choice questions (MCQs), and for some the equally challenging OSCE, the objective standardized clinical examination. Well we know that in the real life of providing competent, caring and compassionate care as physicians, as internists, that a patient is neither a MCQ nor an OSCE. These examinations are to be passed, a process with which we may not necessarily agree. Yet this is the game in which we have thus far invested over half of our youthful lives. So let us know the rules, follow the rules, work with the rules, and succeed. So that we may move on to do what we have been trained to do, do what we may long to do, care for our patients.

The process by which we study for clinical examinations is so is different than for the MCQs: not trivia, but an approach to the big picture, with thoughtful and reasoned deduction towards a diagnosis. Not looking for the answer before us, but understanding the subtle aspects of the directed history and focused physical examination, yielding an informed series of hypotheses, a differential diagnosis to direct investigations of the highly sophisticated laboratory and imaging procedures now available to those who can wait, or pay.

This book provides clinically relevant questions of the process of taking a history and performing a physical examination, with sections on Useful background, and where available, evidence-based performance characteristics of the rendering of our clinical skills. Just for fun are included "So you want to be a such-and-such specialist!" to remind us that one of the greatest strengths we can possess to survive in these times, is to smile and even to laugh at ourselves.

Sincerely,



Emeritus Distinguished University Professor, U of A
Adjunct Professor, Western University



Acknowledgements

Patience and patients go hand in hand. So also does the interlocking of young and old, love and justice, equality and fairness. No author can have thoughts transformed into words, no teacher can make ideas become behaviour and wisdom and art, without those special people who turn our minds to the practical - of getting the job done!

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When Rebecca, Maxwell, Megan Grace, Henry, Felix, Toby and Grady ask about their Grandad, I will depend on James and Anne, Matthew and Allison, Jessica and Matt, and Benjamin to be understanding and kind. For what I was trying to say and to do was to make my professional life focused on the three C's - competence, caring, and compassion - and to make my very private personal life dedicated to family - to you all.



Dedication

Without the caring support from our families for our academic work, the meaning of our accomplishments would disappear.

To my loving wife, children and grandchildren, who give so much happiness and meaning to life.

May good health, happiness and Peace be yours for all the days of your lives.

Je me souviens.

A.B.R. Thomson

*

And to Noah and Zoe (Shaffer Gordon) and Jasper and Macy (Shaffer Nash) who represent the future in this 21st century.

E. A. Shaffer

*

I dedicate the Paediatric Chapter of this Textbook to Professor Anne Griffiths, Chief of the GI Division, the Hospital for Sick Children. Toronto, who managed so skillfully to create a supportive and inspiring atmosphere within our Division that makes it fun to go to work every day.

T. Gonska



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First Principles of Gastroenterology and Hepatology in Adults and Children

Volume II





HEPATOLOGY

Chapter 1: The Liver – Introduction

S.Jayakumar and E.A.Shaffer



1. Liver Anatomy

Located in the right upper quadrant of the abdomen, the liver is the largest and most metabolically complex organ in the human body. Surface anatomy markers for the normal liver are its superior border along the fifth intercostal space, lateral border at the right midaxillary line, and inferior edge along the costal margin. It is 8-12 cm long when measured in the right mid-clavicular line. The liver normally weighs approximately 2kg in healthy men, and 1.5 kg in healthy women. It is divided into two main lobes – the left and the right (see Figure 1).

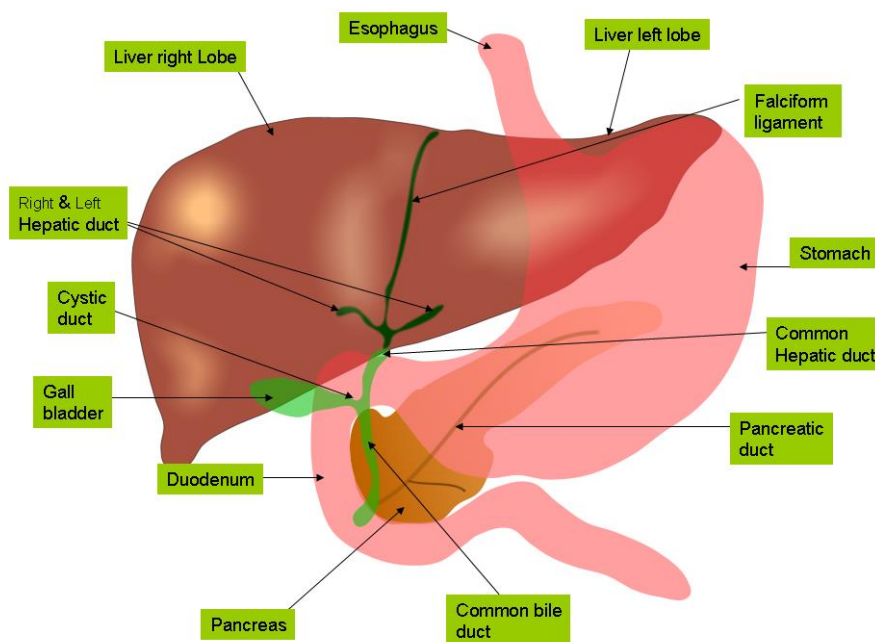


Figure 1. Anatomy of the liver in relation to other abdominal organs

Source: fr.wikipedia.org

The liver is smooth along the superior, anterior and right lateral surfaces, as they fit along the diaphragm. The posterior surface, which abuts the duodenum, colon, right kidney, and the stomach, has indentations to accommodate these organs. A fibrous capsule surrounds the liver. The posterior aspect of this capsule reflects back onto the diaphragm and the posterior abdominal wall, resulting in an area where the posterior liver is continuous with the retroperitoneum.

Multiple ligaments, formed by peritoneal reflections, support the liver. These are the coronary ligaments, the right and left triangular ligaments, the falciform ligament, and the round ligament. The latter is contained within the lower edge of the falciform ligament, and is formed from the obliterated umbilical vein. The falciform ligament separates the two lobes of the liver anteriorly, while the lesser omentum and the umbilical fissure separate the two main lobes posteriorly. The hepatoduodenal ligament



connects the liver to the superior part of the duodenum, and contains within it the hepatic artery, portal vein, bile duct, nerves and lymphatic vessels.

The liver is divided into eight segments (called Couinaud's segments) based on the distribution of blood vessels and bile ducts. Each segment contains a pedicle of portal vessels and bile ducts, and is drained by hepatic veins situated in the planes between the segments (see Figure 2). The caudate lobe (known as segment 1) is different from the other segments in that it receives blood from both the left and right branches of the portal vein and drains directly into the inferior vena cava rather than the hepatic vein. Although there are no surface markers between the segments, surgical dissection along these planes is relatively bloodless. The left lobe of the liver therefore is comprised of segments 1 through 4 (or the classic left lobe, and the caudate and quadrate lobes), and the right lobe of segments 5 through 8. There are many variations in the location and size of the segments, the most common of which is the Riedel's lobe, an elongation of the right lobe, which is often confused with hepatomegaly.

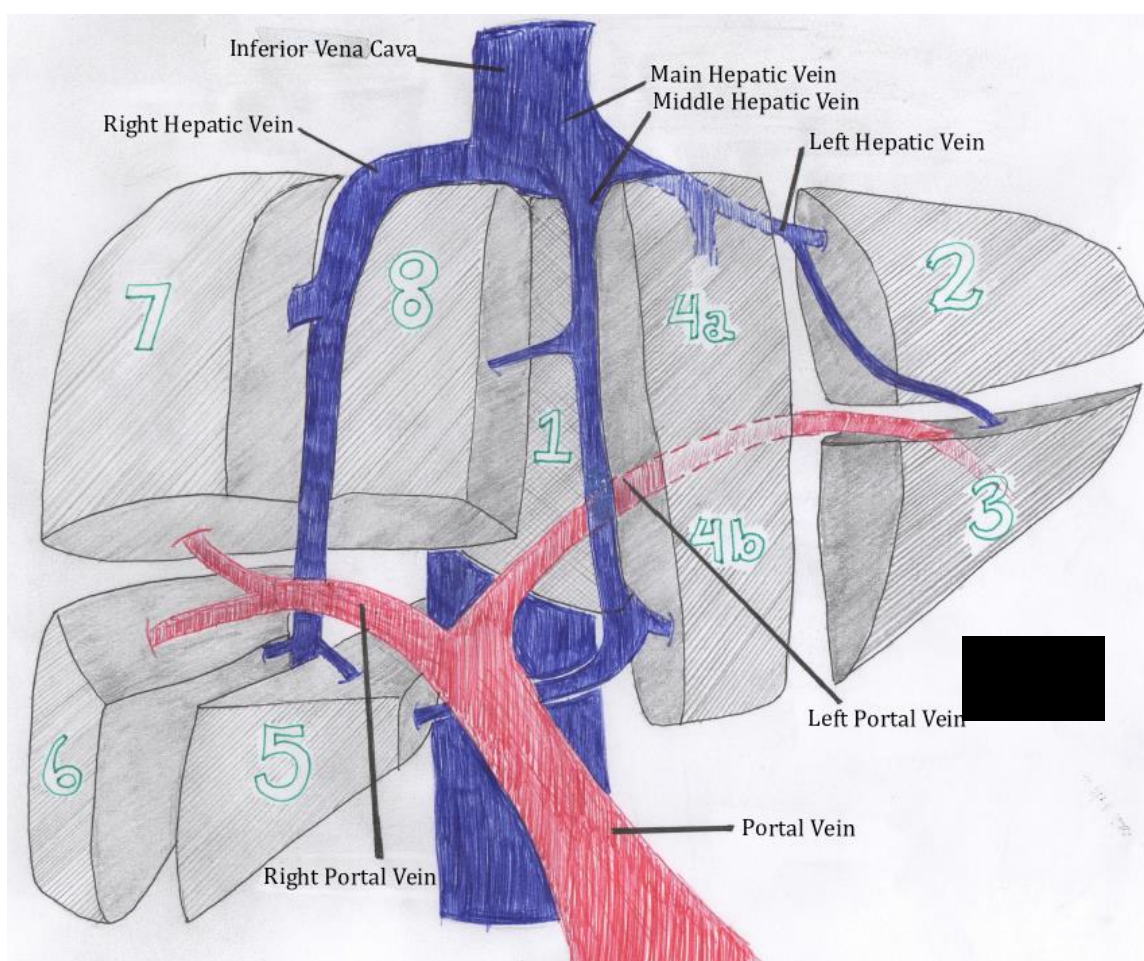


Figure 2. Couinaud's classification of segments of the liver



2. Vessels and Nerve Supply

The liver receives a dual blood supply from the hepatic artery and the portal vein (see Figure 2). The portal vein supplies 70% of the blood flow to the hepatic parenchyma and has quite high oxygen content, while the hepatic artery provides the remainder of flow necessary to sustain the liver. Further, the portal vein carries absorbed nutrients from the intestine to the liver, but also conveys ingested toxins and medications. All this makes the liver an important metabolic factory and clearing house.

In the setting of cirrhosis, the increasing fibrosis within the liver results in increased resistance to flow from the portal vein. The back pressure creates an extensive collateral circulation system (varices) is formed in the gastrointestinal tract and particularly the esophagus where there is an attempt to bypass the obstruction via draining into the azygous vein. The scarring also markedly impairs portal venous perfusion making the cirrhotic liver more dependent upon the hepatic artery.

The terminal hepatic venules, or central veins, coalesce to form sublobular veins, and then further coalesce to form hepatic veins. There are three main hepatic veins: left, right and middle. In most (~80%) people, the middle and left hepatic veins join together before entering the inferior vena cava.

The common hepatic artery arises from the celiac artery, ascends in front of the portal vein, and is located to the left of and behind the common bile duct. The common hepatic artery branches into the left and right hepatic arteries, with the cystic artery (which supplies the gallbladder) arising from the right hepatic artery.

The liver is innervated by both the sympathetic and parasympathetic nervous systems. Fibre arise from the thoracic ganglia, celiac plexus, vagal nerve, and the right phrenic nerve. The sympathetic system innervates the arteries, whereas both the sympathetic and parasympathetic nerves contribute to the innervation of the bile ducts.

3. Biliary System and Function

Bile is an aqueous solution comprised of bilirubin, phospholipids, cholesterol, bile acids, pigments, and inorganic electrolytes, and is iso-osmotic to plasma. The liver secretes approximately 500-600 mL of bile a day. Bile serves two major functions – digestive and excretory. Bile is necessary for the digestion and absorption of dietary fats and fat-soluble vitamins (vitamins A, D, E and K), cholesterol homeostasis, and for the hepatic excretion of toxins, drugs, and lipid waste products. Thus, abnormalities in either the synthesis or excretion of bile, as well as intestinal absorption can drastically alter hepatic and gastrointestinal function.

Bile secretion begins in canaliculus, the cleft between two liver cells (hepatocytes). (Figure 3) Bile then flows into a progressively large diameter collecting system: cholangioles, ductules, interlobular bile ducts, larger bile ducts, and eventually into the common hepatic duct. The common hepatic duct arises from the union of the right and left hepatic ducts, at the porta hepatis, outside of the liver. Once outside the porta hepatis, the common hepatic duct joins with the cystic duct (from the gallbladder) to form the common bile duct (CBD). Bile flows through the CBD, through the ampulla of



Vater, and into the second part of the duodenum. The sphincter of Oddi protects against the reflux of intestinal contents into the biliary tree and pancreatic duct. The function of the gallbladder is to store bile until it is needed for intestinal lipid absorption, such as at mealtimes, at which point the gallbladder contracts and excretes bile into the CBD and the duodenum.

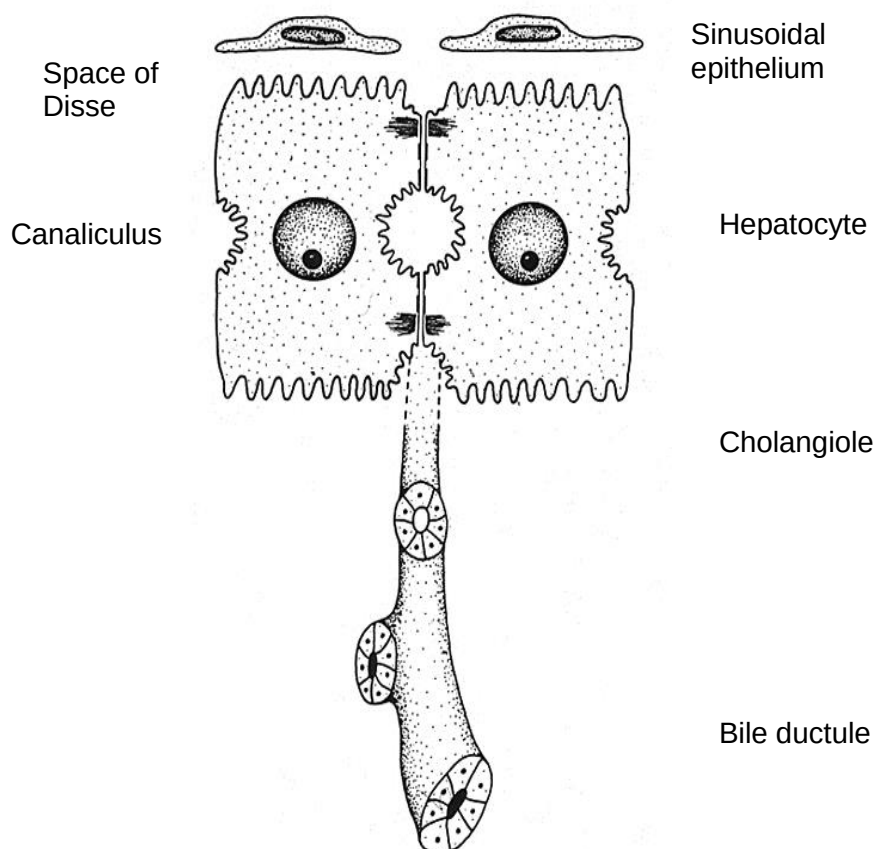


Figure 3. The hepatobiliary secretory apparatus. Bile acids are the driving force for bile secretion, reach the liver from the portal vein and then being taken up from the space of Disse. Translocated across the hepatocyte, bile acids are actively secreted into bile canaliculi, the clefts between adjacent hepatocytes. Bile then flows into a successively larger ductal system.

The major organic solutes in bile are bile salts, which, when actively secreted into the canalicular lumen by the hepatocyte, form an osmotic gradient, resulting in fluid formation in the canaliculus. There are a number of active pumps responsible for bile formation and secretion. Prominent are those responsible for uptake and secretion of organic anions like bile acids and unconjugated bilirubin. If unconjugated, these compounds are made more water soluble, being conjugated with simple saccharides or amino acids while in transit across the hepatocytes. Bile acids not only drive bile



formation but also solubilize cholesterol in micelles aiding its elimination. Indeed, because bile acids are synthesized exclusively from cholesterol, their metabolism is closely interwoven.

The liver transforms cholesterol into bile acids. The rate-limiting enzyme is cholesterol 7 α -hydroxylase (CYP7A1). The primary bile acids synthesized in humans are cholic acid and chenodeoxycholic acid, through either the “classic” pathway (which produces the former), or the “alternate” pathway (which favors formation of the latter acid). Conjugation with taurine or glycine then renders these two primary bile acids more water soluble, more resistant to precipitation in the presence of calcium and less likely to experience passive diffusion across cell membranes either in the biliary tree or the small intestine. Within the biliary system, bile is stored in the gallbladder, where it is concentrated 5-10 fold. Eating causes gallbladder emptying releasing these biological detergents into the duodenum to aid in the digestion of food. Only limited passive non-ionic absorption occurs in transit through the small intestine. Bile acids are actively absorbed in the terminal ileum and return to the liver via the portal vein. Some relatively minor bacterial deconjugation and dehydroxylation occurs, creating secondary bile acids like deoxycholic acid. Passively absorbed throughout the intestine, these too return via the portal vein to the liver where they are reconstituted and secreted into bile.

This recirculation of bile acids from the liver to the intestines and back again is termed the enterohepatic circulation (see Figures 4). On an anatomic level, the components of this circulation are the liver, biliary tract, small intestine, portal venous system, colon, and also to a lesser extent the systemic circulation and kidney. Through this system, ~ 95% of intestinal bile acids are reabsorbed, while the remainder is excreted in the feces. Such efficient recycling, occurring 10-15 times a day, permits a relatively small bile acid pool to be efficiently used for hepatic excretion and intestinal fat digestion. The enterohepatic circulation is therefore governed by 2 active transport sites (the liver and terminal ileum), and 2 mechanical pumps (gallbladder and small intestinal transit).

In the fasting state, bile is stored in the gallbladder and becomes concentrated nearly ten-fold. During feeding, the presence of fatty acids and amino acids in the duodenum causes the release of cholecystokinin (CCK) from the mucosa. CCK acts to relax the sphincter of Oddi and contract the gallbladder. Bile is then evacuated into the small intestine. Its content of mixed micelles, containing bile acids and the phospholipid, lecithin, function as a biological detergent to solubilize dietary fat and facilitate the hydrolytic action of pancreatic lipase, permitting fat digestion and absorption. Thus, during digestion, the enterohepatic circulation of bile acids increases during meals, and slows down during the interdigestive periods, particularly at night. With this process, the human liver secretes approximately 500mL of bile daily.



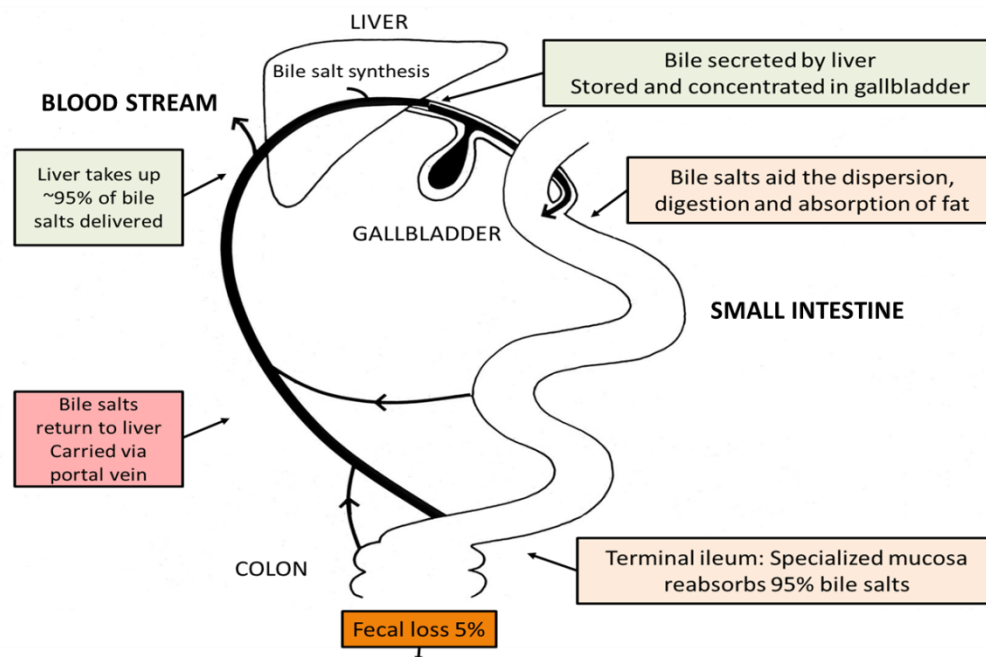


Figure 4. The enterohepatic circulation of bile salts. Conjugated bile acids are secreted from the liver, stored in the gallbladder, evacuated with meals into the duodenum, and actively absorbed from the terminal ileum into the portal vein. Only ~5% of the bile salts are lost to the colon.

This return of bile salts across the terminal ileum and through the portal vein regulates hepatic bile acid synthesis from cholesterol. In the liver, bile acids act as ligands to activate the nuclear receptor, farnesoid X receptor (FXR). FXR downregulates the gene encoding cholesterol 7 α -hydroxylase (CYP7A1), and thus represses bile acid synthesis. While traversing the ileal enterocyte, bile acids similarly activate FXR. This promotes the synthesis of fibroblast growth factor 19 (FGF19) in the ileum. FGF19, an endocrine factor, then enters the portal circulation and journeys back to the liver where it activates fibroblast growth factor receptor 4 (FGFR4) in hepatocytes. This depresses bile acid synthesis. Thus bile acids modulate their own synthesis through two negative feedback systems, locally in the liver and remotely through an ileal sensing mechanism.

Those bile acids that escape reabsorption and enter the colon are modified by intestinal bacteria to form the secondary bile acids, deoxycholic acid (DCA), and lithocholic acid (LCA). The colon then absorbs nearly half of the DCA but only a quite small amount of the LCA (most precipitating – hence the “litho”) into the bloodstream. Returned to the liver, these secondary bile acids are re-conjugated with either glycine or taurine. They are secreted mixed with the recycled and any newly synthesized bile acids.



4. Histopathology and Microanatomy

Much as the basic unit of the kidney is the nephron, the basic unit of the liver is the hepatic lobule. The lobule consists of a hexagonal hepatocyte bounded by four to six portal triads (containing a venule from the portal vein, and an arteriole from the hepatic artery, and a biliary ductule), and a terminal hepatic venule (the central vein, which drains into the hepatic vein). An alternate method of classifying the microanatomy is the acinus. In this classification, the centre of the unit is the portal triad, while the central vein is the periphery. This allows for the division of the hepatic unit into three zones based on proximity to feeding vessels: Zone 1 being closest to the portal triad (and therefore the blood supply) and Zone 3 being furthest from the blood supply, but closest to the central vein (See Figure 5).

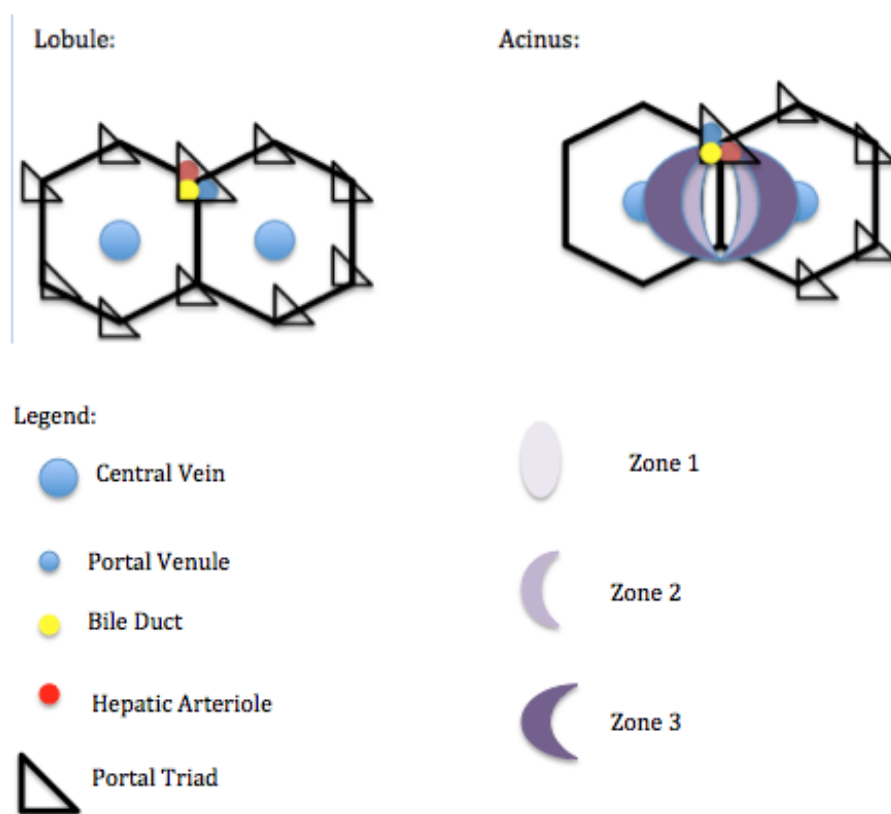


Figure 5. Hepatic lobule vs. acinus models of the hepatocyte

Blood enters acinus through the portal venule and hepatic arteriole in zone 1 (the portal triad), and then travels in the sinusoids (between the plates of the hepatocytes) to the terminal hepatic venule (central vein) in zone 3. The central vein receives blood from multiple acini.

Hepatocytes are arranged in plates that are one to two cells thick; these plates are called muralium, and are separated by sinusoids. There are four types of cells lining the sinusoids: endothelial, Kupffer, stellate, and pit cells. The flow of blood into, and out of, the sinusoids is controlled by the muscular contractions of nearby endothelial cells.



Sinusoidal endothelial cells lack a basement membrane, and are fenestrated, thus allowing for the migration of nutrients from the blood into the space of Disse, and then into the hepatocyte. The space of Disse contains plasma and various types of collagen. Also found in the perisinusoidal spaces are hepatic stellate cells or Ito cells, which are responsible for fat metabolism and the storage of vitamin A. In response to injury, stellate cells are activated and transform into myofibroblasts, which are responsible for the formation of fibrous tissue. Another cell found in the liver is the Kupffer cell, which is a type of spindle-shaped macrophage responsible for the phagocytosis of large particles, such as senescent red cells and toxins, and therefore is found predominantly in the periportal region. Kupffer cells are responsible for the production of inflammatory cytokines and hepatoprotective prostaglandins, thereby modulating the immune system. The fourth type of cell in the sinusoidal space is the pit cell, which is a sinusoidal lymphocyte that contains cytoplasmic granules. Pit cells have a role in killing tumour cells and virus-infected cells.

The extracellular matrix of the liver includes its reticulin framework and molecular forms of collagen, laminin, fibronectin and other extracellular glycoproteins.

5. Liver Function

The liver has a central role in the metabolism of carbohydrates, proteins and fats. The liver is the main organ to maintain glucose stores by synthesizing and storing glycogen (glycogenesis) and generating glucose by breaking down this glycogen (glycogenolysis). Glucose is formed through gluconeogenesis, using pyruvate, lactate, and amino acid precursors. In addition, many amino acid interconversions occur within the liver, where they are also catabolized to urea through nitrogen metabolism. During this process, ammonia is produced, consumed, and detoxified by the liver. The liver enjoys a large functional reserve. Approximately 80% of hepatic function needs to be lost before losing the ability to maintain glucose homeostasis.

In addition to glucose homeostasis, the liver is also responsible for fat and cholesterol metabolism. Fatty acids are transported to the liver from the small intestine via the portal venous system. Once in the liver, they are esterified to produce triglycerides, which are then packaged with cholesterol and phospholipids into lipoproteins to be then utilized or stored in adipocytes. Fatty acids serve as a major source of energy for the liver. Excess glucose can often be stored as fatty acids for future use.

The liver is also responsible for the synthesis of the majority of the circulating plasma proteins, such as albumin and various coagulation factors (fibrinogen, prothrombin, and factors V, VII, IX, and X). Albumin provides the majority of plasma oncotic pressure of plasma, and acts as a carrier for drugs and endogenous hydrophobic compounds.

The body considers all drugs as xenobiotics or foreign substances. As the major entry point to the systemic circulation, the liver is responsible for the modification of these substances, so that they can be modified for retention or eliminated through



excretion. These xenobiotics arrive at the liver via the splanchnic circulation, where they then undergo detoxification, thereby preventing said substances from entering the systemic circulation. This process is hazardous placing the liver at increased susceptibility to toxic injury, being the first organ that is exposed to these potentially noxious drugs/chemicals.

The liver is also responsible for converting lipophilic compounds into water-soluble agents, allowing for their urinary or biliary excretion. There are two major pathways for drug metabolism: 1) reactions involving oxidation, reduction, hydrolysis or hydration (phase 1 reactions), and 2) conjugation (phase 2) reactions. Phase 1 reactions are those mainly involved in the production of substances that can be readily conjugated or excreted without further modification. The major enzyme system responsible for the metabolism of drugs via phase 1 reactions is the cytochrome P450 pathways, and most phase 1 reactions are responsible for increasing the hydrophilic nature of a compound. It is during these reactions that the generation of toxic metabolites often occurs. Cytochrome P450 (abbreviated as CYP) is the collective term for a group of enzymes, thought to be the terminal oxidase component of the electron transport chain located in the endoplasmic reticulum. This diverse group of enzymes catalyze the oxidation of organic substances, hence their key involvement in drug metabolism and bioactivation. Phase 2 reactions are reactions in which another molecule (such as a sugar, sulphate, or amino acid group) is added to the drug, and, as such, often occur in the cytosol of the hepatocyte. Often, a phase 1 reaction prepares a substance for a phase 2 reaction, although certain compounds and drugs are directly metabolized by a phase 2 reaction, and others are excreted immediately after undergoing metabolism by a phase 1 reaction.



Chapter 2: Acute Viral Hepatitis

M. Ma



1. Introduction

The term acute hepatitis refers to recent, sudden injury to the liver. Acute hepatitis is usually a self-limited disease. Some patients however rapidly progress to fulminant liver failure, or the disease gradually evolves into chronic hepatitis with inflammation persisting beyond six months. Viral infection is amongst the commonest causes of acute hepatitis (Table 1).

Table 1. Causes of acute hepatitis

➤ Viruses	➤ Drugs and Toxins
○ Hepatitis A	➤ Alcohol
○ Hepatitis B	➤ Ischemia
○ Hepatitis C	➤ Wilson's disease
○ Hepatitis D	➤ Others
○ Hepatitis E	
○ Herpes simplex	
○ Cytomegalovirus	
○ Epstein-Barr	
○ Adenoviruses	

In North America, hepatitis A, B and C are the commonest causes of viral hepatitis (Table 2). Most acute viral hepatitis infections generally produce quite mild and non-specific symptoms. When the hepatitis is more profound, symptoms include malaise, fatigue, nausea, vomiting and low grade fever. Right upper quadrant abdomen discomfort is common and is due to hepatic swelling causing distension of the hepatic capsule. Marked abdomen pain is not a feature; when present, this warrants consideration of an “acute” abdominal process that should include surgical evaluation of the intra-abdominal contents, including the hepatobiliary system and the entire gastrointestinal tract. Patients with severe viral hepatitis might have clinical jaundice. Laboratory testing will show acute elevation of aminotransferases (AST and ALT); more severe cases may exhibit impaired hepatic synthetic function abnormalities including elevated bilirubin and INR. The mainstay of treatment is supportive care. The convalescent stage is usually 7 to 10 days, with the total illness lasting two to 6 weeks. An occasional case will progress to acute liver failure, requiring liver transplantation. It is important to provide post-exposure prophylaxis to close contacts and family members to avoid spreading the viral infection.

The key features of the different types of viral hepatitis are summarized in Tables 2 and 3.



Table 2. Overview of viral hepatitis

	Virus type	Transmission	Incubation (days)	Serologic diagnosis	Fulminant hepatitis	Chronicity
Fecal/oral						
HAV	RNA	Fecal/oral	20-35	HAV-IgM	0.1-2.0%	No
HEV	RNA	Fecal/oral	10-50	Anti-HEV	1-2%	No
					15-20% (pregnant)	
	Virus type	Transmission	Incubation (days)	Serologic diagnosis	Fulminant hepatitis	Chronicity
Percutaneous						
HBV	DNA	Percutaneous Venereal Perinatal (Asia)	60-110	HB _s Ag	0.1-0.5%	• Adults <5% • Preschoolers 25% • Neonates >90%
HCV	RNA	Percutaneous	35-70	Anti-HCV	<1%	> 80%
HDV	RNA	Percutaneous Venereal	60-110	Anti-HDV	1% especially addicts	• usual in superinfection • rare in co-infection

Table 3. Prevention and Treatment of Acute Viral Hepatitis

	Hepatitis A	Hepatitis B	Hepatitis C
➤ General	○ Need for good sanitation and hygiene. ○ Hepatitis A infection confers life-long immunity. ○ Effective vaccine	○ Vaccine synthesized from recombinant DNA ○ Minimal side effects ○ Confers protection from HDV	



	Hepatitis A	Hepatitis B	Hepatitis C
➤ Indications for vaccination	○ Occupational exposure (day care workers, military personnel, healthcare professionals, sewage workers) ○ Men who have sex with men(*) ○ Institutionalized ○ Residents and health care staff at chronic care facilities ○ Travellers to endemic areas ○ IVDU ○ Children ≥ 2 years of age in communities with high rates of Hep A ○ Chronic liver disease	Universal vaccination in Canada	No vaccine
➤ Prophylaxis on exposure	All household and sexual contacts ○ Immune serum globulin 0.02 mL/kg IM if within 2 weeks of exposure ○ No treatment for casual school or work contacts unless epidemic of HAV identified	Needle stick, sexual and household contacts - If seronegative, administer HBIG and start Hep B vaccine series within 12 hours of exposure Perinatal ○ Routine pre-natal screening with HBsAg ○ Within 24-48 hours of delivery, administer HBIG and start Hep B vaccine series ○ Consider oral antiviral therapy in expecting mothers who have very	Needle stick ○ Test for HCV-RNA, AST, bilirubin at baseline, 4 and 12 weeks – if positive, treat with PEG-IFN and Ribavirin Perinatal ○ Rare transmission- more likely if mother is immunosuppressed ○ Test infant with HCV RNA Sexual transmission ○ Rare ○ Condoms advised for multiple sex partners



	Hepatitis A	high HBV DNA Hepatitis B	Hepatitis C
➤ Treatment	○ Supportive care. Most cases resolve spontaneously. Hospitalization rarely needed. ○ Prophylaxis and prevention of secondary spread is perhaps the most important aspect of treatment. ○ <i>Activity</i> – Symptom-guided return to work; no activity limitations. ○ <i>Diet</i> – fatty foods poorly tolerated, exclude ethanol--no other restrictions. ○ <i>Drugs</i> – no role for corticosteroids (may increase the risk of a chronic carrier state); avoid sedatives, tranquilizers		○ Supportive care ○ If patient hasn't spontaneously cleared virus at 12 weeks. Start antiviral therapy. (Studies with IFN monotherapy only).

2. Hepatitis A Virus (HAV)

2.1. Epidemiology and Risk Factors

Previously termed “infectious hepatitis”, hepatitis A virus (HAV) is an RNA virus that belongs to the enterovirus family. This enteric viral infection is a common disease worldwide and tends to cause mild self-limited illness. Severe hepatitis and liver failure are rare. Transmission is via the fecal-oral route: poor public hygiene in many developing countries and in other settings, sexual and household contacts. The anti-HAV IgG can be detected in 90% of the population in developing countries and in 30-40% of the population in developed countries.

Food and water contamination may lead to epidemic outbreaks. Given the globalization of food distribution and tourism, HAV is no longer just a disease of developing countries, and outbreaks have occurred in developed countries. Recent North American outbreaks have been associated with the ingestion of contaminated strawberries imported from developed countries and of raw clams and oysters from polluted water. Person-to-person spread results in sporadic cases. The hepatitis A virus is present in the stool of patients during the prodrome or pre-icteric phase until about two weeks after the onset of jaundice. Parenteral transmission is also possible, especially in intravenous drug users, but is much less common. Travelers to endemic areas, children in daycare, health care professionals and homosexual males are at increased risk of contracting Hepatitis A.

2.2. Clinical Course and Treatment

HAV is transmitted by the fecal-oral route. In developing countries, the infection occurs in childhood so that most children have experienced exposure to the virus. HAV infection during childhood has very mild symptoms and results in lifelong immunity. In developed countries with good sanitation, “population immunity” to hepatitis A infection is low in children and young adults. Few therefore are exposed to the virus during childhood. As increased symptom severity correlates with older age, when hepatitis A infection does occur, these adults tend to be symptomatic.



The infection usually causes mild to moderate acute hepatitis in adults. The incubation period is approximately 4 weeks and the acute illness lasts 2 to 3 weeks. The virus is present in the stool of patients from the prodromal or pre-icteric phase to about two weeks after the onset of jaundice (Figure 1). Person to person, oral-fecal spread can occur during this time. There is a brief period of viremia during the acute phase of infection, and thus parenteral transmission can occur in intravenous drug users sharing needles during this phase. During acute infection, patients have flu-like symptoms such as malaise, fatigue, anorexia, and fever. Mild to moderate jaundice usually is evident. There may be a cholestatic presentation with intense pruritus and jaundice. The liver enzymes ALT and AST are moderately elevated. In addition, there may be relapsing (biphasic) hepatitis.

Fulminant liver failure causing death or requiring liver transplantation has occurred infrequently: in the elderly and in those with underlying chronic liver disease. The advent of fulminant liver failure necessitates hospital admission for supportive care and preparation for liver transplantation. The mortality rate, usually from fulminant hepatitis, is very low (0.1%); rarely is liver transplantation required. Recovery follows acute hepatitis and patients develop lifelong immunity to HAV. There is no evidence for a chronic carrier state or the development of chronic liver disease.

2.3. Diagnosis

Both IgM and IgG antibodies to the virus (anti-HAV) are detectable in hepatitis A infection. The presence of an elevated IgM antibody indicates recent infection; this clinical test diagnoses an acute infection. The IgM response usually becomes undetectable at 6 months, but the IgG response persists for life and provides lifelong immunity against the virus (Figure 1).

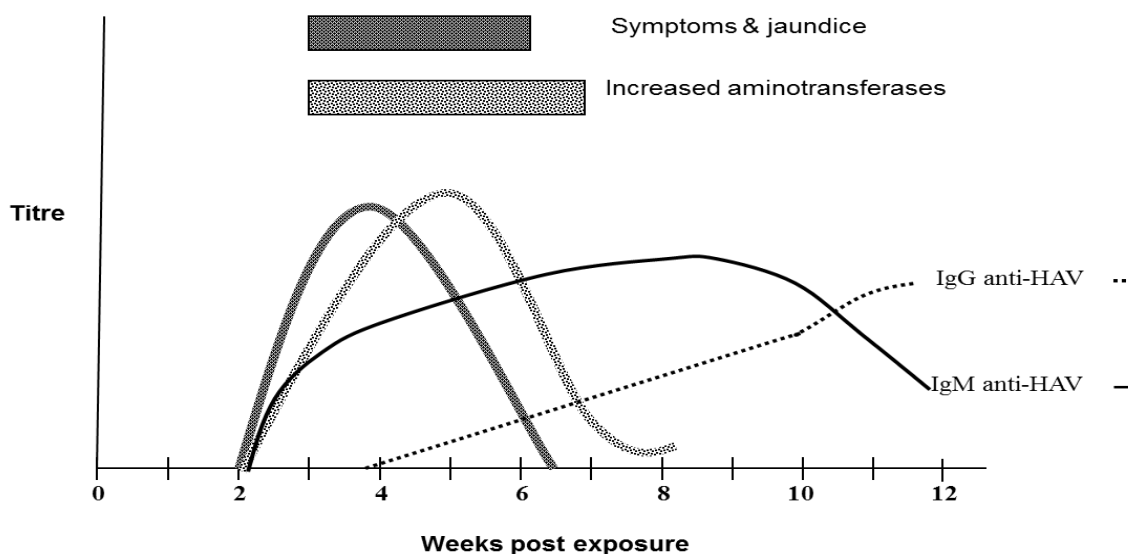


Figure 1. Clinical and serological course of infection with acute hepatitis A virus



2.4. Treatment

The illness is usually self-limited and there is no specific anti-viral therapy for acute hepatitis A. Management is therefore supportive. Patients can maintain their routine activities; strict bed rest is not necessary. Strenuous exercise has not been associated with adverse outcome during mild to moderately acute HAV infection. Diet can be liberal, encouraging a high calorie intake but excluding alcohol. Fatty foods are poorly tolerated and are best avoided. All unnecessary drugs, especially tranquilizers and sedatives, should be shunned. The patient's symptoms are the best guide for activity and return to work. Patient education helps alleviate anxiety. Referral to a specialist is not usually required.

2.5. Prevention

In the community, the prevention of hepatitis A is dependent on good sanitation and hygiene. At the time of outbreak, information regarding hygienic measures and immunoprophylaxis should be provided to family members or persons in close contact with the infected individual. This public health intervention is important to prevent the spread of hepatitis A infection. Two biologic agents can prevent disease: passive immunization with intramuscular polyclonal serum immune globulin and the hepatitis A vaccine.

Regular immune globulin preparation is effective in preventing hepatitis A, best used for passive immunoprophylaxis. The preparation consists of concentrated antibodies from pooled human plasma. The immune globulin has an efficacy of 80 to 90 percent when it is given before or immediately after exposure to HAV. Hence, it can be used for pre-exposure prophylaxis in travelers to endemic countries requiring short-term, immediate protection, and also in post-exposure prophylaxis of household and sexual contacts of an affected individual. The preparation is safe for short-term prophylaxis in children under the age of two and in pregnant women traveling to endemic areas. The current recommended dose of immune globulin is 0.02 mL/kg IM within 2 weeks of exposure.

Hepatitis A vaccines contain either purified, formalin-inactivated vaccine or live attenuated virus. These vaccines are safe and effectively provide immunity against hepatitis A virus. Administered in two doses, the current vaccines are recommended in patients above the age of two who are inhabitants of communities with high rates of hepatitis A, are at risk of occupational exposure, or are traveling to endemic countries. Intravenous drug users (IVDU), those living in institutions, or those with chronic liver disease or hemophilia should also be vaccinated (Table 3). Because of the high efficacy of the vaccine, post-treatment testing for the development of antibodies is not routinely required. Although the vaccine is very safe, there are no data regarding the safety of the vaccines in children less than 2 years of age, or in pregnant women. The most common side effect of vaccination is pain at the site of injection (18-39%). The vaccine and immunoglobulins can be given together for post-exposure prophylaxis. In this situation, there is some inhibition of antibody production, but the titre of anti-HAV is more than adequate to prevent hepatitis A infection.



3. Hepatitis B Virus (HBV)

3.1. Epidemiology and Risk Factors

HBV is a unique DNA virus that replicates through reverse transcription of its mRNA. It behaves more like a retrovirus than a DNA virus. It accounts for 40% of acute viral hepatitis in the U.S. In North America, HBV infection occurs primarily in adolescents and adults because of sexual activity and intravenous drug use (Table 4). In endemic countries, HBV infection occurs in infants and children through maternal newborn transmission or child-to-child transmission by contaminated vaccination needles or other means. This vertical transmission of HBV from mother to newborn results in the vast majority of chronic carriers worldwide. Hepatitis B infection from blood transfusion has decreased dramatically since the implementation of routine screening and the use of volunteer blood donors. Nevertheless, HBV infection through blood transfusion still represents a high risk at 1 per 72,000 units transfused in comparison to other blood borne viruses (Table 5).

Table 4. Risk factors associated with reported cases of acute HBV in the U.S.

Risk factors	Percentage (%)
➤ Heterosexual activity	48
➤ IV Drug use	11
➤ Homosexual activity	7
➤ Health-care employment	2
➤ Household contact	1
➤ Transfusion, dialysis	1
➤ Unknown	30

Source: Data from Centers for Disease Control and Prevention, 1992

Table 5. Risk of Transfusion Transmitted Infection

➤ Hepatitis B	1/72,000
➤ Hepatitis C	1/3 million
➤ HIV	1/10 million
➤ HTLV	1/1.1 million

Source: Database from CMAJ – Canadian Blood Services 1990-2000

3.2. Clinical Course

HBV is a highly contagious virus. Percutaneous or mucous membrane exposure to infectious blood or body fluid can lead to acute infection in any person lacking immunity against the virus. The infectivity of the blood or body fluid correlates to the concentration HBV DNA or the presence of HB_eAg. The higher the HBV DNA concentration in blood or fluids, the greater is the risk of transmission. The incubation



period ranges from 60-110 days. The clinical presentation of acute hepatitis B ranges from subclinical to the rare case of fulminant hepatitis (0.1-0.5%). Clinical jaundice develops in approximately 30% of patients at presentation. Relapsing (biphasic) hepatitis is uncommon. From 5% to 10% of persons with HBV will experience a serum-sickness-like syndrome (immune complex disease) characterized by skin rash, angioedema and arthritis. The outcome of HBV infection is frequently age-dependent. Perinatal transmission is associated with a 90% likelihood of chronic infection. Conversely, when acquired as an adult, HBV infection is usually self-limited; less than 5% progress to chronic hepatitis (persistent presence of HBV after 6 months of infection). Lower rates of viral clearance occur in immune-compromised persons.

3.3. *Diagnosis*

The clinical course of acute HBV infection, appearance and clearance of viral antigens, and host immune response are shown in Figure 2. The components of the HBV virus help clarify the multiple serological tests that evaluate HBV infection (Table 6A). The hepatitis B virus consists of a 28 nm central core containing the genome (a single molecule of partially double-stranded DNA) and a specific DNA polymerase. Hepatitis B core antigen (HBcAg) is an intracellular antigen that is expressed in infected hepatocytes, but is not detectable in serum. This core antigen is structurally distinct from the surface antigen (HBsAg), which packages the core in the cytoplasm of the hepatocyte. HBsAg appears in serum and represents the serologic hallmark of HBV infection. Hepatitis Be antigen (HBeAg), another viral antigen, is a secretory protein, a subunit of HBcAg that is processed from the precore protein. Released into the serum, HBeAg is a general marker for HBV replication and infectivity. HBeAg positivity thus implies viral replication, and is an indicator of high infectivity. There are also viral mutants that do not produce HBeAg; these “pre-core mutants” as a cause of severe acute hepatitis would not be evident by HBeAg. The HBV DNA is the most sensitive marker for detecting the presence of the virus. The HBV DNA as a routine test will clarify the viral replication status, guide therapy in patients with chronic hepatitis B, detect pre-core mutant virus, assess treatment response, and monitor the development of treatment-resistant HBV.



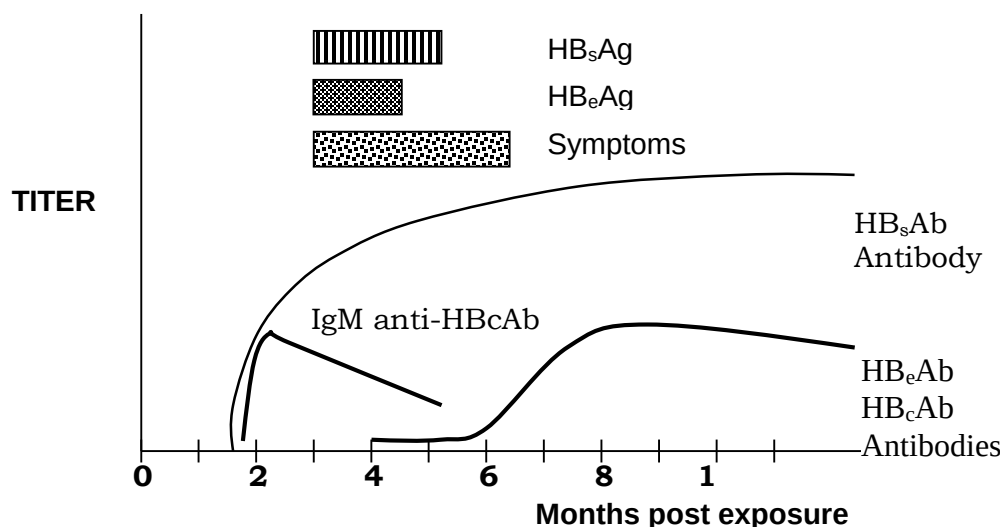


Figure 2. Typical clinical and serologic features of acute hepatitis B

Acute infection becomes evident by the appearance of HB_sAg, HB_eAg and HBV DNA in the circulation, beginning in the preclinical phase. IgM anti-HB_c (hepatitis B core antigen) soon follows, early in the clinical phase. Hence, presence of this IgM anti-HB_c antibody plus HB_sAg provides the diagnosis of acute HBV infection. With resolution of the acute infection, serum ALT falls to normal, HB_sAg clears, seroconversion develops and certain antibodies arise: HB_sAb (as HB_sAg disappears), anti-HB_c (IgM switches to IgG), and HB_eAb (replacing HB_eAg). HBV DNA disappears. IgM anti-HB_c however can recur in HBV carriers who have a flare of hepatitis. Only the persistence of anti-HB_s and IgG anti-HB_c indicate a prior HBV infection.

In chronic infection, HB_sAg, HB_eAg (for at least 6 months), and HBV DNA persist in blood. There is no recovery, normalization of ALT and no seroconversion. Anti-HB_s does become evident although ~20% may experience a non-neutralizing form of anti-HB_s.

The significance of HBV markers and their importance in the interpretation are summarized in Table 6B.

Table 6A. Interpretation of hepatitis B markers

Marker	Interpretation
➤ HB _s Ag	○ HBV infection; may be acute or chronic
➤ HB _s Ab	○ Immune to HBV (as natural immunity or after HBV vaccination)
➤ HB _c Ab-IgM	○ Acute HBV infection (newer and more sensitive assays may also be positive during reactivation of chronic infections)
➤ HB _e Ag	○ High infectivity/viral replication (precore mutant viruses lack HB _e Ag)
➤ HB _e Ab	○ Low or no infectivity, or precore mutant virus infection
➤ HBV-DNA	○ Measure of infectivity or replicative state.



Table 6B. Seromarkers of HBV infection and vaccination

	Acute Infection	Chronic infection			Previous infection	Vaccinatio n
		Active (eAg +ve)	Inactive (eAg +ve)	Pre-core mutant (eAg -ve)		
➤ HB _s Ag	+	+	+	+	-	-
➤ Anti-HB _s	-	-	-	-	+	+
➤ IgM anti-HB _c	+	-/+	-	-	-	-
➤ IgG anti-HB _c	-	+	+	+	+	-
➤ HB _e Ag	+	+	-	-	-	-
➤ Anti-HB _e	-	-	+	+	+/-	-
➤ HBV DNA	+	+	-/low	+	-	-

3.4. Treatment

For acute hepatitis B infection in adults, supportive care suffices. There is no need for antiviral therapy. Most acute infections clear completely and patients develop immunity against the virus. The rare occurrence of fulminant liver failure requires intensive support and consideration for liver transplantation. For the < 5% of HBV-infected persons who develop chronic hepatitis B infection, anti-viral agents employing pegylated interferon or oral nucleosides/nucleotides (like Lamivudine, Entecavir, Telbivudine, Emtricitabine, Adefovir, Tenofovir) are important to prevent the progression of disease to cirrhosis and liver failure. These generally are indicated in those with: acute liver failure, cirrhosis with clinical complications, cirrhosis (or advanced fibrosis) with a high serum HBV DNA, or reactivation of chronic HBV following chemotherapy or immunosuppression.

3.5. Prevention

Active immunization against the HBV is available. It has successfully changed the epidemiology of HBV infection in many parts of the world. The hepatitis B vaccine contains HB_sAg that is synthesized by recombinant DNA technology. The commercially available vaccines are safe and effective. After completing a course of vaccination, 95–99% of immunocompetent individuals develop a high titer of anti-HB_s the protective antibody that prevents HBV infection. The side effects are minimal. Many countries have a universal vaccination program for infants or children. Vaccination is recommended for high-risk groups such as health-care workers, homosexuals, intravenous drug users, family contacts of chronic carriers, chronic transfusion recipients, and renal dialysis patients. The eventual goal is to eliminate hepatitis B infection through a successful global vaccination program.

A specific immune globulin preparation from pooled plasma has a high titer of hepatitis B surface (anti-HB_s) antibody. This hepatitis B immune globulin (HBIG) can offer protection (passive immunization) against hepatitis B infection after exposure to the virus. Administration should occur within 12 hours following a clear-cut exposure,



such as an inadvertent “needle-stick” injury or sexual contact. Frequently, the hepatitis B immune globulin is combined with HB_sAg-containing vaccine.

Routine pre-natal screening with HBsAg is essential for identifying mothers with acute or chronic hepatitis B who can transmit the virus to their newborns. To prevent this vertical infection, HBIG and hepatitis B vaccine should be administered within 24 to 48 hours of delivery to neonates at risk. Unfortunately, mothers with the highest concentration of HBV DNA can still transmit the virus in spite of passive and active immunization of their neonates. Lamivudine and tenofovir are safe for expecting mothers with high HBV DNA levels, and can minimize vertical transmission of HBV.

4. Hepatitis C Virus (HCV)

4.1. Epidemiology and Risk Factors

Hepatitis C was discovered in 1989. A single-stranded RNA virus of less than 80 nm in diameter, HCV belongs to the flavivirus family. This virus exists as different genotypes; any effect of such viral factors on the natural history of attendant liver disease is uncertain. It has a worldwide distribution and is a significant cause of chronic hepatitis. In North America, the genotypes 1, 2 and 3 account for most of the infection. The prevalence of HCV infection ranges from 1% in the general population, to as high as 90% in hemophilia patients who have received clotting factor concentrate. Though common (230,000 new cases each year in the 1980s in the US), HCV infection has fallen (incidence now about 19000 per year).

The principal mode of HCV transmission is parenteral, acquired through intravenous drug use or blood transfusions. Transfusion-related cases account for 10%, yet only 1 out of every 3 million units transfused now result in hepatitis C infection. (Table 5) Intravenous drug use is the main basis for hepatitis C infection in developed countries. The decline in HCV relates to improved screening of blood products and the concern over HIV that might have limited its spread via illicit drug use. Infection through sexual contact or mother-to-newborn (perinatal transmission) does occur, but the infectivity is low, in contrast to hepatitis B.

4.2. Clinical Course

The incubation period ranges from 5 to 10 weeks (mean 7 weeks). Acute hepatitis C commonly has a mild clinical course: most are anicteric. Those with symptoms are more likely to clear the virus. Because the acute illness can be very mild, detection of acute HCV infection is difficult. Chronic HCV infection develops in 70 to 80% of patients, who then have a significant risk of developing cirrhosis and chronic liver failure many years in the future.

Chronic hepatitis C is usually asymptomatic. Fatigue is the most frequent complaint followed by somewhat vague manifestations like nausea, anorexia, myalgia, arthralgia (some have immune complexes) and cognitive impairment.

4.3. Diagnosis

Serological tests for HCV either identify viral antibody (ELISA) or constitute molecular tests to detect the virus (HCV-RNA using polymerase chain reaction, termed PCR) and classify its genotype. The presence of anti-HCV antibody suggests viral



exposure and is not a marker of immunity. The majority of patients exposed to HCV then become carriers of the virus. The presence of anti-HCV antibody however does not necessarily indicate chronic infection. The diagnosis of chronic hepatitis C infection requires detecting the virus with the PCR test.

The antibody test (ELISA, enzyme-linked immunosorbent assay) is the primary screening test. It identifies antibodies to the nonstructural as well as the structural epitopes of the virus. Being both sensitive and specific, this ELISA test is very useful in identifying patients who had exposure to the hepatitis C virus. False-positive ELISA testing occurs with hypergammaglobulinemia. False negatives occur soon after acute hepatitis C onsets, and in association with immunosuppression or renal failure. HCV RNA PCR test is thus essential to clinch the diagnosis and assess the viral load. This information guides the management of chronic hepatitis C infection including the response to treatment. Genotypes assist in understanding the epidemiology, the natural course of HCV and importantly, the response to therapy.

4.4. Treatment

Acute hepatitis C infection may be clinically self-limited but commonly leads to chronic infection and liver damage. Once established, chronic HCV becomes difficult to treat. The goal of treatment in chronic HCV hepatitis seeks to eradicate the virus, best predicted by a sustained virologic response: absence of HCV-RNA 6 months after stopping treatment. A combination of antiviral agents is necessary: pegylated interferon plus ribavirin. Genotype 1, being the most difficult HCV to treat, requires the addition of a direct antiviral agent: a protease inhibitor like telaprevir or boceprevir, boosting the response rate to 70-80%. These antiviral therapies are undergoing further evaluation.

Chronic hepatitis C requires surveillance for progression to cirrhosis, liver failure and the development of hepatocellular hepatoma.

4.5. Prevention

There is no vaccine or specific immunoglobulin available for HCV. The risk of sexual transmission is extremely low. In stable, monogamous relationships, the use of condoms is unnecessary.

5. Hepatitis D Virus (HDV)

5.1. Epidemiology and Risk Factors

The delta virus, HDV, is a small defective RNA virus that requires the presence of hepatitis B surface antigen for its expression; complete virion assembly and expression. The delta virus utilizes the HB_sAg protein as its external coat to attach to and enter hepatocytes. Found worldwide, HDV may represent a co-infection in some 5% of chronic HBV carriers in many developing countries. In North America, less than 1% of HB_sAg-positive patients have evidence of HDV infection, almost exclusively among intravenous drug abusers and their sexual partners. More common in the Mediterranean basin, 14-50% of HB_sAg-positive patients also harbor HDV in parts of Italy.



5.2. Clinical Course

Hepatitis D infection produces a spectrum of manifestations, from being asymptomatic to developing fulminant liver failure, as a super-infection in a person who is already a chronic HBV carrier. Super-infection tends to result in a more severe hepatitis than hepatitis B alone; further, 80% go on to chronic infection. Co-infection with both B and D viruses causes chronic hepatitis D infection in less than 5% of persons. Hepatitis D infection has the highest morbidity and mortality rate of all the hepatitis infections. The presentation is that of acute hepatitis or a flare of hepatitis, and the disease can rapidly evolve into cirrhosis, liver failure or hepatocellular carcinoma.

5.3. Diagnosis

The hepatitis D antigen (HDAg), associated with HDV, is detectable only during the early phases of the acute infection. The antibody to delta antigen (anti-HDV), providing the serologic marker for acute and chronic hepatitis D infection, in contrast appears late in the course of acute delta infection. Such timing would miss the HDV infection, and so might erroneously diagnose acute hepatitis B alone. The anti-HDV antibody disappears within months after hepatitis recovery. In chronic hepatitis D infection, the IgM anti-HD antibody and IgG anti-HD antibody persist. HDV-RNA, using reverse transcriptase-polymerase chain reaction (RT-PCR), detects the HDV genome indicating ongoing infection. Hence, the HDAg, anti-HDV and HDV-RNA assays will differentiate the 3 HDV-related clinical entities:

1. Acute HBV/HDV co-infection – serum HDAg appears early and then disappears; IgM anti-HDV appears early, then disappears, being replaced by IgG anti-HDV;
2. Acute HDV super-infection of a chronic HBV carrier (HBsAg and IgM anti-HBc positive), and
3. Chronic HDV (and HBV) infection – HDV-RNA persists

5.4. Treatment

There is no proven treatment for acute co-infection of HDV and hepatitis B virus, or for super infection of HDV in the chronic hepatitis B carrier. Treatment is supportive for acute co-infection. If fulminant liver failure develops, consider liver transplantation.

5.5. Prevention

Persons who are at risk for HBV infection are also at risk for HDV infection. Hepatitis B vaccination protects against hepatitis D. Hepatitis B carriers should be counseled about avoiding high-risk behaviors in order to reduce becoming super-infected with HDV.

6. Hepatitis E Virus (HEV)

6.1. Epidemiology and Risk Factors

Hepatitis E virus, a single-stranded RNA virus, causes epidemic hepatitis, is enterically transmitted and thus shares many similarities with hepatitis A. HEV infections occur primarily associated with inadequate sanitation and represent a leading cause of acute viral hepatitis in developing countries. Domestic animals are a common reservoir for the hepatitis E virus; some surveys indicate infection rates exceeding 95%



among domestic pigs in endemic countries. In women infected in the third trimester of pregnancy, however, HEV carries a high mortality rate (approaching 20%) When rarely seen in North America, it is almost exclusively in travelers returning from endemic regions.

6.2. *Clinical Course*

The clinical presentation is similar to HAV infection and is commonly mild. The incubation period is 10-50 days. The HEV infection causes self-limited hepatitis and the clinical course tends to be subclinical or mild. Following the incubation, some patients develop jaundice lasting 7 to 12 days. These patients may also experience malaise, fever, nausea, vomiting, anorexia, abdomen discomfort, headaches and fatigue. Liver transaminases may be elevated for 1 to 2 months. Chronic infection does not occur.

6.3. *Diagnosis*

The diagnosis of HEV comes from a history of travel or possible exposure to contaminated water or food, as well as the exclusion of HAV, HBV or HCV infection. Serological assay anti-HEV and polymerase chain detection assay are only available from reference laboratories.

6.4. *Treatment*

Treatment of active disease is supportive. It is not clear if acquisition of an acute infection will provide lifelong immunity.

6.5. *Prevention*

There is no passive immunoprophylaxis for HEV. Travelers going to endemic countries are at risk of contracting hepatitis E. The immune globulin produced in developed countries is ineffective to prevent HEV infection, because the preparation contains little or no anti-HEV antibody. It is not clear if the immune globulin from developing countries would be more effective. Travelers to endemic countries should be advised not to consume any uncooked food or untreated water. Safe practices, such as hand washing prior to eating and no swimming in polluted water, would decrease the risk of contracting HEV. These recommendations are particularly important to the pregnant travelers because of the possibility of fulminant liver failure with HEV infection. An experimental vaccine based on recombinant viral proteins has been developed and tested in a population of military personnel working in a developing country. This vaccine appeared to be safe and effective. Unclear is if the vaccine offers long-term protection or is cost-effective for this generally mild disease.

7. **Epstein-Barr virus (EBV) and Cytomegalovirus (CMV)**

EBV and CMV are herpes viruses that can cause acute viral illness and hepatitis. EBV is widely dispersed. About 90-95% of the North American population is seropositive, most after subclinical infection. Symptomatic infections present with infectious mononucleosis characterized by fatigue, headache, pharyngitis, fever, posterior cervical chain adenopathy, splenomegaly and lymphocytosis. Mild hepatitis is a common presentation, but jaundice, hepatomegaly and severe hepatitis are rare presentations.



CMV infection in an immunocompetent host usually presents with asymptomatic elevation of serum transaminases ALT and AST. More severe CMV hepatic involvement is limited to those who are immunocompromised, such as persons with AIDS, and allograft organ recipients receiving anti-rejection therapy.

8. Other viruses

Other viruses that can cause liver injury (e.g. Herpes simplex and yellow fever) account for less than 1% of all acute viral hepatitis in North America. New hepatitis-causing viruses will likely be discovered in the future.

9. Complications of Acute Viral Hepatitis

Most patients with viral hepatitis recover completely. The most important complication is the development of chronicity, which may follow hepatitis B, C and D. Chronic hepatitis represents continued disease activity beyond 6 months. This complicates acute hepatitis B infrequently in adults but occurs in acute hepatitis C in over 70% of cases. Chronic hepatitis is suspect if symptoms and/or elevated serum aminotransferase levels persist beyond six months. Chronic hepatitis does not occur in hepatitis A or E.

9.1. Fulminant Liver Failure

Fulminant liver failure is the development of acute liver cell injury proceeding to liver failure and hepatic encephalopathy within 8 weeks in a patient without any known previous liver disease. Clinically, the patient deteriorates with development of deep jaundice, confusion and drowsiness. The encephalopathy can progress into deep coma. Because of massive liver necrosis, there is deficiency of clotting factors, and hence the INR/PT becomes progressively abnormal. At this stage, the mortality rate exceeds 50% unless a liver transplant can be performed rapidly. Death may occur from infection, hypoglycemia, increased intracranial pressure with cerebral edema, or renal failure. Massive hepatic necrosis leads to a shrunken liver in which the architecture collapses histologically. Despite this, regeneration can occur with histologic recovery. Usually a liver biopsy is not required; the procedure is associated with considerable bleeding risk unless done by the transjugular route.

9.2. Cholestasis

Occasionally, acute viral hepatitis exhibits a cholestatic phase, in which the patient becomes intensely pruritic and jaundiced. This occurs most commonly in hepatitis A. The enzyme pattern changes, with a fall in the serum aminotransferases but with an increased alkaline phosphatase and gamma-glutamyl transpeptidase (GGT). Biliary tract disease and drug toxicity must be excluded. Resolution within a few weeks is the usual course.

9.3. Relapsing (Biphasic) Hepatitis

Clinically, these patients begin improving, only to have a recurrence of the signs and symptoms of their hepatitis. Resolution is usually complete. This pattern is most characteristic of hepatitis A. In some cases of hepatitis B, the second phase is due to



acute hepatitis D. Hepatitis C is characterized by repeated and wide fluctuations in liver aminotransferase values, but a true biphasic clinical course is uncommon.

9.4. Immune Complex Disease

Immune complex disease occurs with acute viral hepatitis. This is due to circulating immune complexes of viral proteins and antibody, with complement activation. Extrahepatic manifestations in acute hepatitis A are uncommon, but include arthritis, vasculitis, thrombocytopenia and aplastic anemia.

In both hepatitis B and C, about 5-10% of cases initially develop a serum-sickness-like syndrome characterized by skin rash, angioedema and arthritis. Other immunologic manifestations include pericarditis, aplastic anemia or neurologic abnormalities such as Guillain-Barre syndrome.

The extraintestinal manifestations associated with chronic hepatitis will be discussed in the next chapter.

10. Summary

Acute viral hepatitis is usually a self-limited disease and in most cases requires supportive care only. For the few patients who develop fulminant liver failure, liver transplantation will be the only treatment option. Chronic infection can develop in patients with HBV, HCV and HDV infection.





Chapter 3: Chronic Viral Hepatitis

S. Jayakumar and V. G. Bain



1. Introduction

The term chronic hepatitis means active, ongoing inflammation of the liver that persists for more than six months, being detected by biochemical and histologic means. It does not imply an etiology. The biochemical hallmark of chronic hepatitis is an increase in the serum aminotransferases (AST and ALT), with minimal elevation of the alkaline phosphatase (AP). When the hepatitis becomes severe and/or prolonged, hepatic dysfunction may become apparent with an increase in serum bilirubin, and prothrombin time/INR, and a decrease in serum albumin concentration. Typically, biochemical tests are used to identify and follow patients with chronic hepatitis. Liver biopsies serve to define more precisely the nature of the chronic hepatitis, and to provide useful information regarding the extent of damage and prognosis.

Histologically, chronic hepatitis is characterized by infiltration of the portal tracts by inflammatory cells. These cells are predominantly mononuclear, and include lymphocytes, monocytes and plasma cells. Liver biopsy is the gold standard to evaluate the grade (degree of inflammation) and stage (degree of fibrosis/cirrhosis) of chronic viral hepatitis. The most commonly used system for grading and staging of hepatitis is the METAVIR system established in France (Table 1). Histologic or inflammatory activity (A score) is determined by an algorithm incorporating the amount of portal and lobular inflammation and necrosis into a score from A0-A3. The degree of fibrosis (F score) is evaluated separately to obtain the stage of disease and ranges from F0-F4 (Figure 1-4). There are several other histologic scoring systems in use as well.

Table 1. The METAVIR system for staging/grading chronic hepatitis
Histologic

A0 = no activity	F0 = no fibrosis
A1 = mild activity	F1 = portal fibrosis without septa
A2 = moderate activity	F2 = portal fibrosis with few septa
A3 = severe activity	F3 = numerous septa without cirrhosis
	F4 = cirrhosis

*determined by an algorithm incorporating degree of interface and lobular necrosis
Activity(A); Fibrosis (F)

The commonest cause of chronic hepatitis is a viral infection of the liver. Other causes include autoimmune hepatitis, drug-induced hepatitis, Wilson's disease, 1-antitrypsin deficiency, and steatohepatitis. Primary biliary cirrhosis and primary sclerosing cholangitis may occasionally mimic chronic hepatitis, but are not usually classified as such. Table 2 summarizes an approach to help determine the etiology of chronic hepatitis.

2. General Considerations

Only hepatitis B (HBV), hepatitis C (HCV), and hepatitis D (HDV) cause chronic liver disease. HBV and HCV comprise the vast majority of these cases, with HDV infections occurring only in persons who have concurrent or pre-existing HBV infection. A careful assessment of risk factors is helpful in determining the cause of chronic hepatitis (Table 2).



The rate of transmission via needle stick injury varies with the type of virus exposure, bore size of the needle, and whether the needle is hollow or not (Table 3). In most cases, selected laboratory tests will provide confirmation of the diagnosis.

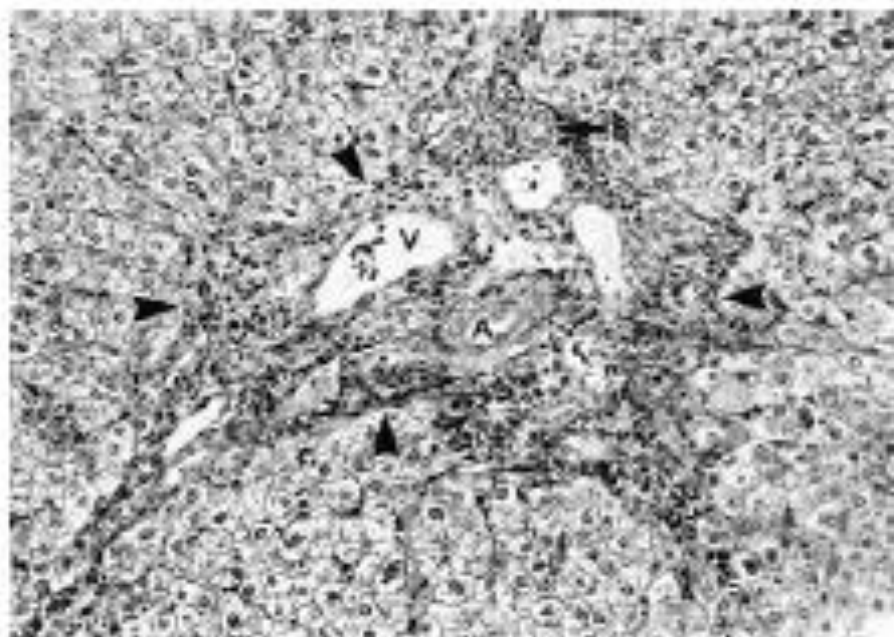


Figure 1. Mild chronic hepatitis. This portal tract contains a chronic inflammatory infiltrate that is confined to the portal triad and does not extend past the limiting plate (arrowheads).

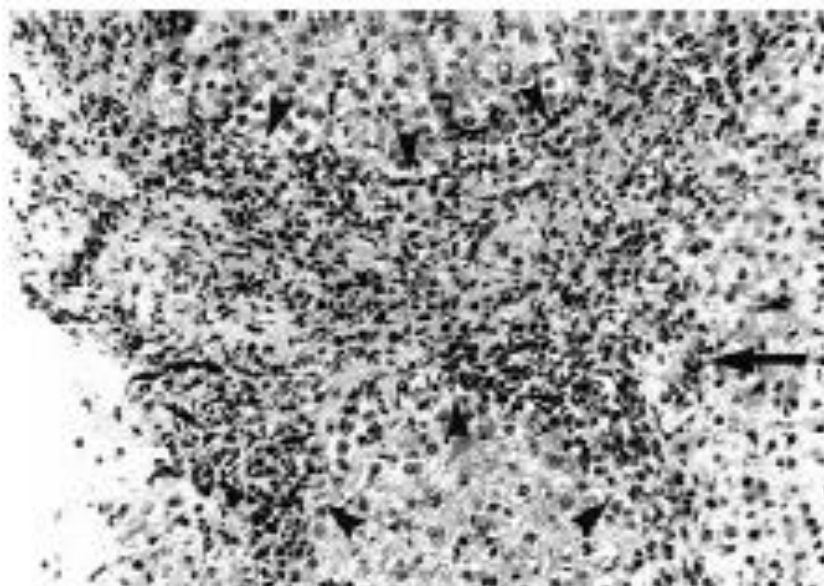


Figure 2. Moderately severe chronic hepatitis. Inflammatory cells are shown infiltrating and destroying the periportal hepatocytes (arrow) and disrupting the limiting plate (interface necrosis) (arrowheads).



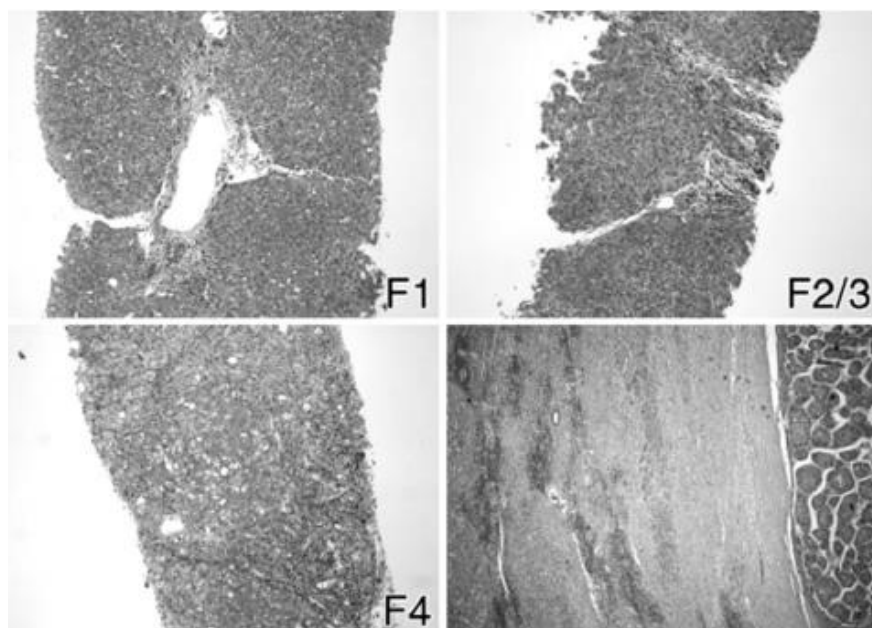


Figure 3. METAVIR staging system. F1= Minimal fibrosis without bridging; F2/3= Bridging fibrosis in which fibrous tissue connects the joining triads; F4= Cirrhosis. The slide on the bottom right represents chronic hepatitis and a hepatocellular carcinoma.

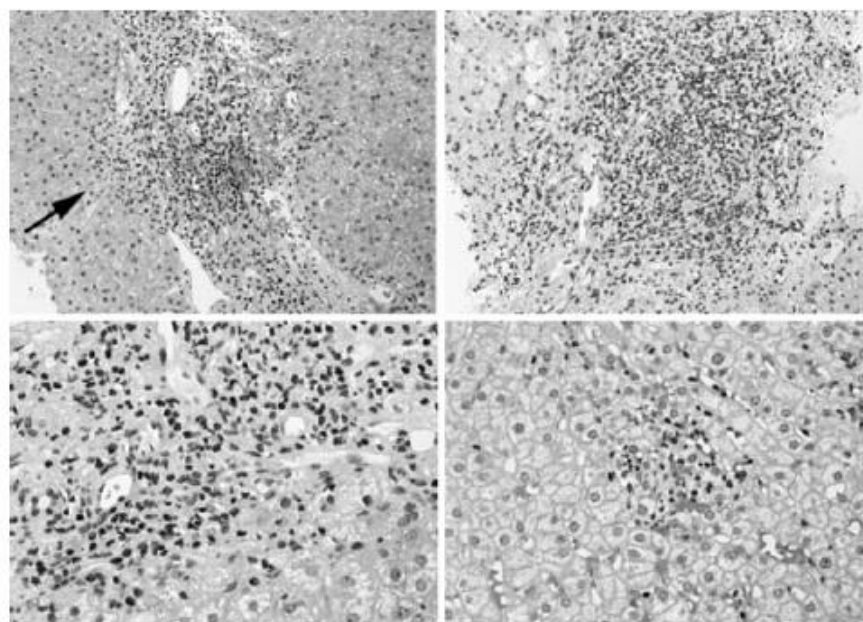


Figure 4. METAVIR grading system. The histologic activity is dependent primarily on the degree of interface necrosis but lobular necroinflammatory foci are also included in grading. Mild interface necrosis (arrow) is evident in the top left slide. A high-powered view below it demonstrates apoptotic bodies. On the top right, circumferential interface necrosis is seen. The high-powered view below it demonstrates a lobular necroinflammatory focus.



Table 2. Role of history and lab tests in the diagnosis of chronic hepatitis

Etiology	Key Points in History	Useful Lab Tests
➤ HBV	○ Sexual history (homosexuality, use of prostitutes, promiscuity) ○ Family History ○ Country of origin ○ Intravenous/intranasal drug use (IVDU/INDU)	○ HB_sAg – if positive, measure HB_eAg, HB_eAb and HBV DNA
➤ HCV	○ Blood transfusion (pre-1990), Hemophilia ○ IVDU/INDU ○ Tattoos; piercings ○ HCV positive partner ○ Incarceration	○ Anti-HCV ○ HCV RNA
➤ Drug Induced Hepatitis	○ Careful history of all drugs and herbs (commonly isoniazid, nitrofurantoin, NSAIDs, and antibiotics)	○ Liver biopsy (although not very helpful on its own)
➤ Wilson Disease	○ Family history ○ Neurologic or psychiatric symptoms in children or young adults	○ Serum ceruloplasmin ○ 24 hr urinary copper ○ Penicillamine challenge ○ Liver biopsy with hepatic copper concentration
➤ Alpha-1 Antitrypsin Deficiency	○ Family history of liver or lung disease (COPD)	○ Alpha-1-antitrypsin levels ○ Pi genetic testing
➤ Non-alcoholic Steatohepatitis (NASH)	○ Obesity ○ Recent sudden weight gain/loss ○ Diabetes mellitus ○ Use of corticosteroids ○ Bariatric surgery	○ Oral glucose tolerance test ○ HbA1c ○ Serum cholesterol profile (especially triglycerides) ○ Abdominal ultrasound



Table 3. Rate of Transmission of Viruses with Needlestick Injury

Virus	Rate of Transmission	Viral Particles/mL of Serum/Plasma
➤ Hepatitis B	30% (2-40%)	10^2 - 10^8
➤ Hepatitis C	3% (3-10%)	10^0 - 10^6
➤ HIV	0.3% (0.2-0.5%)	10^0 - 10^3

(Source: *NEJM* 1995;332 (7): 444-51)

The clinical presentation of chronic hepatitis can include no symptoms, unexplained fatigue, or complications of cirrhosis including ascites, variceal bleeding and encephalopathy.

General treatment considerations include counseling about reducing the risk of transmission, vaccination for hepatitis A and B if a patient is seronegative, and vaccination for pneumococcus and influenza in the presence of cirrhosis. Persons are screened for complications of chronic liver disease and co-existing causes of liver dysfunction. Complete abstinence or minimal alcohol intake is advised, because of the risk of accelerated progression of viral hepatitis in the person who consumes a hepatotoxin such as alcohol.

3. Hepatitis B Virus (HBV)

3.1. Evolution to chronic liver disease

A number of factors determine whether an individual will clear an acute HBV infection or progress to a chronic carrier state: the age at infection is most important. Carrier rates in vertically infected newborns are greater than 90%, as compared to less than 1% in adult-acquired infection. Statistics Canada estimates that there are approximately 600,000 persons in Canada infected with Hepatitis B, with the majority of infections occurring in immigrants (6% rate of infection in "new Canadians," 1% in Canadian born individuals, and 4% rate of infection in First Nation Canadians). Untreated chronic HBV has a liver-related mortality of 20-25%. The immunologic status of the host is also important, as immunocompromised individuals (e.g., HIV, renal failure, post-transplant) are more likely to become chronic carriers. The severity of the acute disease also correlates with outcome. In general, the milder the acute illness, the more likely that progression to chronic liver disease will occur. Presumably, individuals with mild acute disease are those with a suboptimal immunologic response to the virus, whereas persons with more severe acute disease are manifesting a prompt and effective immunologic attack on hepatocytes harbouring HBV.

The rates of progression from chronic hepatitis B infection to cirrhosis, and cirrhosis to decompensation and hepatocellular carcinoma (HCC) are given in Table 4..



Table 4. Rates of Progression over 5 years in HBV infection.

➤ Chronic HBV to cirrhosis (HBeAg positive)	17%
➤ Chronic HBV to cirrhosis (anti-HBe positive)	38%
➤ Compensated Cirrhosis to Decompensated Cirrhosis	15%
➤ Compensated Cirrhosis to HCC	10-17%
➤ Death in cirrhotics	15%

(Source: *Fattovich, J Hepatol 2008;48:336-352*)

Table 5 lists the risk factors for the development of HCC in patients infected with HBV

Table 5. Risk factors for the development of HCC with chronic HBV

➤ HBV DNA level
➤ Level of fibrosis on liver biopsy
➤ Active inflammation on liver biopsy
➤ Age>45
➤ Male
➤ Increased ALT
➤ Family history of HCC
➤ Africans > Asians >> Caucasians
➤ Both cirrhotic and non-cirrhotic patients are at risk

3.2. Hepatitis B genotypes

There are currently 8 different HBV genotypes, based upon variations in the HBV genome sequence. The different geographic distributions of the genotypes are listed in Table 6. Although different genotypes may play a role in altered natural history, disease activity and treatment efficacy, genotype testing is just beginning to have a role in treatment considerations.



Table 6. Geographic Distribution of Hepatitis B Virus Genotypes.

Genotype	Geographic Range
A	North America, Europe, Africa
B,C	East Asia, North America
D	Worldwide Distribution
E	Africa
F	South America, Alaska
G	North America
H	Central America

3.3. Hepatitis B mutations

HBV is prone to the development of mutations because of the lack of proofreading function of reverse transcriptase. Pre-core variants are encountered most frequently. The pre-core region of HBV codes for HBeAg. A mutation in the pre-core region creates a premature stop codon, so that HBeAg cannot be produced. Clinically, this presents as chronic HBeAg negative hepatitis. The patient has ongoing inflammation as suggested by elevated transaminases, as well as viremia with detectable HBV DNA in the absence of HBeAg. This mutation is associated with genotypes B and D, and found most commonly in Mediterranean countries and in Asia.

A comparison between HBeAg positive and negative cases is presented in Table 7. Clinically, confusion may arise in distinguishing an inactive hepatitis B carrier from HBeAg negative chronic hepatitis. HBeAg negative chronic hepatitis is suggested by features of active inflammation (elevated ALT, biopsy demonstrating active inflammation) and the presence of viral replication (HBV-DNA > 2000 IU/mL). Other causes of coincidental hepatitis (e.g.; drugs, HDV) must also be excluded.

Table 7. Comparison of HBeAg positive and HBeAg negative chronic hepatitis

Etiology	HBeAg positive	HBeAg negative
➤ Epidemiology	○ Most common type in North America	○ Higher incidence in Asia, Europe, and other Mediterranean countries
• Natural history	○ Lower rate of progression to cirrhosis	○ Higher rate of progression to cirrhosis
➤ Treatment	○ Seroconversion to anti-HBe associated with long term viral suppression	○ viral recurrence usual after treatment course



Etiology	HB _e Ag positive	HB _e Ag negative
➤ Monitoring of treatment response	○ Monitoring of HB_eAg seroconversion to anti-HBe positive ○ Normalization of liver enzymes ○ Marked reduction in HBV DNA	○ Normalization of liver enzymes ○ Marked reduction in HBV DNA

3.4. Presentation

The majority of persons with chronic hepatitis B are asymptomatic or have only mild fatigue. They might give a history of parenteral exposure to blood or blood products, unprotected sex, or a family history of hepatitis B infection. Liver enzyme abnormalities, even when incidentally discovered, should raise the possibility of underlying viral infection. Screening of family and sexual contacts of known cases will often reveal additional cases. Uncommonly, HBV (as well as HCV) may present with extrahepatic manifestations (Table 8) secondary to circulating antigen-antibody immune complexes.

Table 8. Extrahepatic Manifestations of HBV and HCV by Organ System

Organ System	HBV	HCV
➤ General	○ Serum sickness like syndrome (fever, skin rash, arthralgias, arthritis)	
➤ Renal	○ Glomerulonephritis esp membranous	○ Glomerulonephritis esp membranoproliferative
➤ Vascular	○ Polyarteritis nodosa ○ Polymyalgia Rheumatica	
➤ Hematological		○ Cryoglobulinemia ○ Lymphoma ○ Monoclonal gammopathies
➤ Endocrine		○ Diabetes Mellitus
➤ Dermatologica I	○ Papular acrodermatitis	○ Porphyria cutanea tarda ○ Leukocytoclastic vasculitis

3.5. Diagnosis

A summary of the interpretation of seromarkers of hepatitis B is provided in Table 9. The definition of chronic HBV requires positive HBsAg for greater than six months. There may be HB_eAg positive and HB_eAg negative disease. Viral markers are helpful to determine the phase of disease (Figure 5). HB_eAg and HBV-DNA in serum confirm active HBV replication. When HBV-DNA is > 20,000 IU/mL (note this value for HB_eAg



negative cases is 2000 IU/ml), there is a high viral load, indicating a high degree of infectivity (all physiologic fluids are potentially infectious). Although a negative HBV-DNA indicates very low or absent infectivity, the sensitive polymerase chain reaction (PCR) technique will still detect the virus. If HB_eAg is negative, there is usually lower infectivity, although as discussed this may represent a pre-core mutant. Core antibody serology is not usually required in the routine assessment of chronic hepatitis B (Table 5).

Table 9. Phases in the Course of Wild-Type Hepatitis B Infection

Phase	HBsAg	HBeAg	anti-HBe	ALT	HBV-DNA
➤ Immune Tolerant	+	+	-	N	↑↑↑↑
➤ Active Infection	+	+	-	↑↑↑	↑↑
➤ Seroconversion	+	-	+	N	<200 IU/mL
➤ Resolved Infection	-	-	+	N	negative

Abbreviation: N, normal range

Adapted from: Sherman M, et al., *Management of Chronic HBV: Consensus Guidelines. Can J Gastroenterol.* 2007 June; 21(Suppl C): 5C–24C

3.6. Phases and Natural History

The first six months of HBV infection represent the acute hepatitis phase of the infection (Figure 5). This acute phase is not often seen in chronically infected adults who have contracted the virus at birth or in early childhood. Chronic hepatitis has three phases, termed the “replicative”, “inflammatory” and “inactive” phases. As the replicative phase is most often observed after perinatal viral transmission, it is uncommon in Western countries. HB_eAg and HBV-DNA are positive indicating high levels of HBV replication. Despite this, the aminotransferases are normal, or near normal and the liver biopsy is relatively inactive. For unknown reasons, patients may then enter the inflammatory phase in which their immune system now recognizes those hepatocytes harboring HBV, and begins to attack them. Accordingly, the aminotransferases become elevated and the biopsy shows chronic hepatitis, often of a severe degree. The level of viral replication as measured by the HBV-DNA will decline. If the patient successfully clears HBV, they will enter an inactive phase characterized by normalization of the aminotransferases and relative inactivity on the liver biopsy. HB_eAg will clear and anti-HB_e will form (seroconversion).



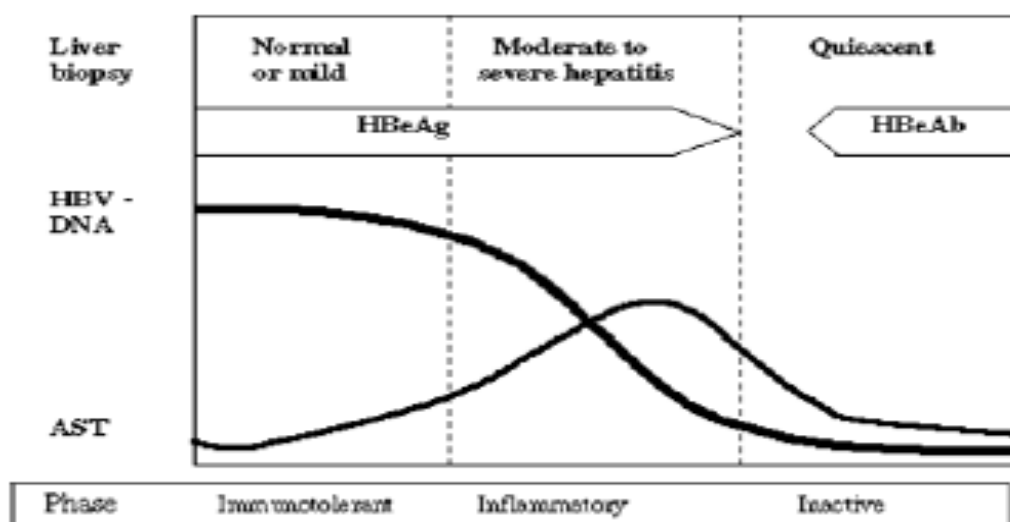


Figure 5. Phases of Chronic Hepatitis B

Seroconversion is associated with histologic and biochemical remission in most persons. Predictors of seroconversion are a high ALT, low HBV DNA titres, age less than 40, and the absence of cirrhosis. Spontaneous seroconversion occurs in 10-15% of persons per year. This number is reduced in perinatally acquired infection. HBeAg negative patients (i.e., pre-core mutants) do not meet criteria for eAg seroconversion, as they are eAg negative at baseline. Patients who have converted their HBeAg and have a negative viral load may still have HBsAg for many years after they clear the HBV.

The natural history of hepatitis B is outlined in Table 9. Patients are at variable risk of developing cirrhosis and hepatocellular carcinoma (HCC):

a) Cirrhosis - The severity and duration of the inflammatory phase of HBV is one of the main factors that determine whether a patient will develop cirrhosis. The progression of chronic hepatitis to cirrhosis occurs in 20 - 30% of all chronic hepatitis B patients. Progression is more likely in those with replicative HBeAg negative pre-core mutant than in those with HBeAg positive chronic hepatitis.

b) Hepatocellular cancer - Although patients with cirrhosis are at the highest risk of developing HCC, non-cirrhotic HBsAg carriers patients are also at risk (see Table 5 for other high risk predictors). The risk of HCC in HBV chronically infected patients is 100 times higher than that for non-carriers. The five year rate of progression of compensated cirrhosis to HCC is estimated at 6-15%.

Surveillance for HCC in chronic carriers requires performing a serum α -fetoprotein and more importantly, an abdominal ultrasound, every six to 12 months.

3.7. Treatment Indications

The workup for chronic HBV patients prior to treatment is summarized in Table 10. Factors which must be taken into account when considering initiating treatment of HBV are HBeAg status, viral load, patient age, and evidence of hepatic damage from the virus (Canadian Consensus Guidelines). Hepatic damage may be implied from elevated liver



enzymes (indicative of ongoing inflammation), or histologic or radiographic evidence of fibrosis/cirrhosis. The HB_eAg status affects the accepted level of viral load, above which treatment should be considered; in patients who are HB_eAg positive, this level is >20,000IU/mL. In those who are HB_eAg negative, this level is >2,000IU/mL. Any evidence of fibrosis increases the likely need for treatment. Similarly, any patient with evidence of hepatic decompensation should be considered for initiation of treatment. In the latter group, both lamivudine and adefovir reduce the need for liver transplantation, and should be initiated.

Table 10. Laboratory assessment prior to therapy

Hepatitis B	Hepatitis C
○ ALT, AST, ALP, Bilirubin, Albumin, PT/INR ○ CBC, Electrolytes, Cr, glucose, TSH ○ HBsAg, HB_eAg, anti-HB_eAg, HIV ○ serum HBV DNA titres ○ anti HDV (if risk factors or unexplained ↑ ALT) ○ Consider liver Biopsy if raised ALT ○ Abdominal Ultrasound ○ Fundoscopy if >50 yrs or history of diabetes ○ AFP (selected pts)	○ ALT, AST, ALP, Bilirubin, Albumin, PT/INR ○ CBC, Electrolytes, Cr, glucose, TSH anti-HCV, HCV genotyping ○ Serum HCV RNA levels ○ TSH, ANA, ASMA, B-hCG ○ ECG if older than 50 yrs, or cardiac disease ○ Liver Biopsy recommended but not mandatory ○ Abdominal Ultrasound or hypertension

Adapted from: Sherman M, et al., Management of Chronic HBV and HCV: *Consensus Guidelines Canadian J Gastroenterol* 2007; June; 21(Suppl C): 5C–24C.

If a patient does not meet criteria for treatment at the time of assessment (normal ALT or HBV DNA negative), their liver enzymes should be checked every six to 12 months. If elevated liver enzymes develop, HBV DNA should be checked to confirm reactivation. A complete virologic response is defined as the sustained loss of HBsAg. This occurs in a small minority of patients, and therefore other endpoints are used to define treatment success, i.e.; partial virologic response.

Seroconversion (HB_eAg to HB_eAb) correlates with improved long-term outcome including a reduced risk of liver decompensation and development of HCC. The durability of seroconversion may be lower in perinatally acquired HBV infection. In HB_eAg negative persons, successful response to treatment is measured by a) normalization of AST and ALT, and b) HBV DNA becoming undetectable.



3.8. Treatment Medications

Interferon- α and nucleoside analogues are available to treat chronic hepatitis B. The advantages of interferon- α are that it has a finite treatment duration (24 weeks in HBeAg positive patients, 48 weeks in HBeAg negative patients), as well as a durable treatment response in HBeAg positive patients. However, it costs more, has more side effects than lamivudine and requires subcutaneous injection. Furthermore, interferon- α is less effective in patients with a viral load $> 10^7$, low ALT levels, males, patients older than 40 years, and in patients with cirrhosis.

Lamivudine is a nucleoside analogue with antiviral effects against HBV. Administered orally, it has less adverse effects than interferon- α , and may be used in patients with decompensated cirrhosis. The optimal treatment duration is unknown, although it is dependent upon the HBeAg status; many patients will have recurrence of HBV infection when lamivudine is stopped. Unfortunately, long term use of lamivudine results in high rates of resistance mutations, approaching 70% at 4 years.

Adefovir is a phosphonate nucleotide analog of AMP that has anti-viral activity against HBV. It is not as potent as some of the newer medications discussed below for treatment of HBV, but it does have a higher generic barrier to resistance than lamivudine.

Entecavir is a selective guanosine analogue, and is one of the most potent inhibitors of HBV DNA replication of all the current medications used today. The side effect profile is similar to that of lamivudine, and is therefore well tolerated. In treatment naive patients, resistance rates are quite low (1% after 3 years of entecavir therapy), whereas resistance rates are much higher in patients with prior resistance to lamivudine (32% after three years of treatment with entecavir).

Telbivudine is a pyrimidine analogue which is more potent than lamivudine and therefore can be used in patients with high HBV DNA levels. It is less potent than entecavir or tenofovir.

Tenofovir is a purine analogue that was initially used as part of the treatment regimen for HIV, and is now used for treatment of chronic HBV, both in the setting of HBV-HIV coinfection as well as chronic HBV mono-infection. Tenofovir is much more potent than adefovir in suppression of HBV DNA. Resistance to tenofovir is rare, and when it occurs, it is attributed to noncompliance. Uncommon side effects include renal dysfunction and Fanconi syndrome. As the drug is excreted via the kidneys, patients with renal dysfunction need dose adjustment or preferably, use of a different anti-viral agent.

Drug efficacy and resistance profiles for the various drugs are listed in Table 11. Asians often have a poorer response, likely because most have perinatally acquired HBV infection with normal or minimally elevated transaminases. Since the development of resistance mutations have been associated with flares of hepatitis or hepatic decompensation, those drugs with the lowest rates of resistance are preferred in patients who have more advanced liver disease.



Table 11. Drugs Used in the Treatment of HBV - Efficacy and Resistance Levels

Drug	Efficacy	Resistance Level
➤ PEG-IFN	↑↑↑	Nil
➤ Lamivudine	↑	↑↑↑
➤ Adefovir	↑↑	↑↑
➤ Entecavir	↑↑↑↑	↑*
➤ Tenofovir	↑↑↑↑	Minimal
➤ Telbivudine	↑↑	↑↑

* Resistance rates are increased in patients with a history of lamivudine resistance.

Table 12. Factors predictive of a response to treatment of HBV infection

- Low HBV-DNA level
- Immunocompetent
- Adult-acquired infection
- Active liver disease - ALT > 5x upper limit of normal, active hepatitis on biopsy
- Female
- Absence of HDV or HIV co-infection HBeAg +ve

3.9. Prevention

Active immunization is important to prevent transmission of HBV infection from a chronic carrier to family and sexual contacts. Condoms should be used to prevent infection in persons with multiple sexual partners. The safety of the HBV vaccine is well established. Universal vaccination is recommended in Canada, either neonatally or as a pre-adolescent. The eventual goal of vaccination is total eradication of hepatitis B. On a global scale, there have been many barriers to this goal but its realization would have profoundly positive effects in many countries. Information regarding hepatitis B prophylaxis recommendations is found in the acute hepatitis chapter.

4. Hepatitis C Virus (HCV)

Chronic hepatitis C has become the most common cause of chronic hepatitis in most countries, including Canada. The identified cases of HCV may represent only the “tip of the iceberg,” with most cases still undiagnosed. Many cases are identified after investigation of raised liver enzymes in asymptomatic individuals, or after screening of blood donors. Other persons with HCV infection present to physicians with fatigue,



malaise, or less commonly, with manifestations of advanced liver disease, or extrahepatic manifestations of chronic hepatitis C (Table 8).

Treatment of HCV may result in improvement of selected extrahepatic manifestations.

4.1. HCV genotype

As a result of RNA mutations, HCV has evolved different genotypes over time. Six HCV genotypes and 50 subtypes have been identified. Genotype 1 is the most common in North America, accounting for approximately 75% of cases. Genotype 2 and 3 each account for 10-15%. Although genotype does not affect the severity of HCV infection or its progression, it has significant therapeutic implications.

4.2. Epidemiology

HCV infection can be transmitted by the same routes as HBV infection, but the majority of cases (60-70%) are related to intravenous drug abuse, and 10% of patients will have had a previous blood transfusion. Patients receiving blood products prior to 1990 are at highest risk. With current screening of blood donors, the risk of transmission of HCV with a blood transfusion is only one in 3 million units transfused. In the remaining persons a source of HCV infection is often difficult to find. Non-parenteral transmission through sexual or intimate contact and maternal-infant exposure occur much less often than with HBV. Other factors associated with a low rate of viral transmission are needlestick injuries, and intranasal cocaine use.

4.3. Natural History

Anti-HCV serologic testing has revealed that 60-85% of patients with acute HCV will remain chronically infected. Of those with chronic hepatitis, as many as 20% will be cirrhotic by 25 years. Thereafter, an additional 1% per year develops cirrhosis. Accelerated progression of HCV to cirrhosis is seen in persons with heavy alcohol use, obesity, and co-infection with HIV or HBV. In those under 40 years of age, significantly lower (2-8%) rates of cirrhosis at 20 years.

Chronic hepatitis C is a risk factor for the development of HCC. The increased risk is mostly limited to patients with cirrhosis and is estimated at 1-4% per year after the development of cirrhosis. Risk factors for the development of HCC in the presence of HCV are listed in Table 13. The current screening practice is abdominal ultrasound and serum α -fetoprotein (AFP) every six to 12 months.

Table 13. Risk factors for the development of HCC with Hepatitis C Cirrhosis

-
- Male
 - Age > 50 years
 - Hepatitis B co-infection
 - Heavy alcohol intake
 - *Risk significant only with cirrhosis
-



4.4. Treatment

The workup of a person with chronic HCV prior to therapy is summarized in Table 10. Before discussing the treatment of hepatitis C, one must understand various terminology used to interpret response to treatment (Table 14): RVR (rapid virological response), EVR (early virological response), SVR (sustained virological response), and EOT (end of treatment) response. EVR can be further categorized as either viremic or aviremic.

Table 14. Treatment Response Abbreviation Terms

Term	Definition
➤ RVR	○ HCV RNA negative (<50 IU/mL) at week 4
➤ EVR	○ Negative or > 2 log decrease in HCV RNA at week 12
➤ SVR	○ HCV RNA negative 24 weeks after end of treatment

If EVR (65% of patients with HCV genotype 1) is achieved on therapy, the viral load should be rechecked at 24 weeks. If it remains detectable, treatment should be terminated at that point (Figure 6), whereas if the HCV viral load is negative, treatment should continue for 48 weeks. If EVR is not achieved, treatment may be stopped at 12 weeks, because the chance of a SVR is now remote. It is not necessary to test for EVR in Genotype 2 and 3 patients, because of the high rate of treatment success. The monitoring of these patients on treatment is therefore much simplified. Predictors of a sustained virological response are listed in Table 15.

Table 15. Predictors of sustained response to interferon treatment in HCV infection

- Genotype 2 or 3
- HCV RNA < 800,000 IU/mL
- RVR
- Age < 40
- Short duration of infection
- Absence of bridging fibrosis/cirrhosis
- Female
- Ethnicity other than African-American
- <33% steatosis on histology
- Absence of diabetes mellitus
- Certain IL28B polymorphisms



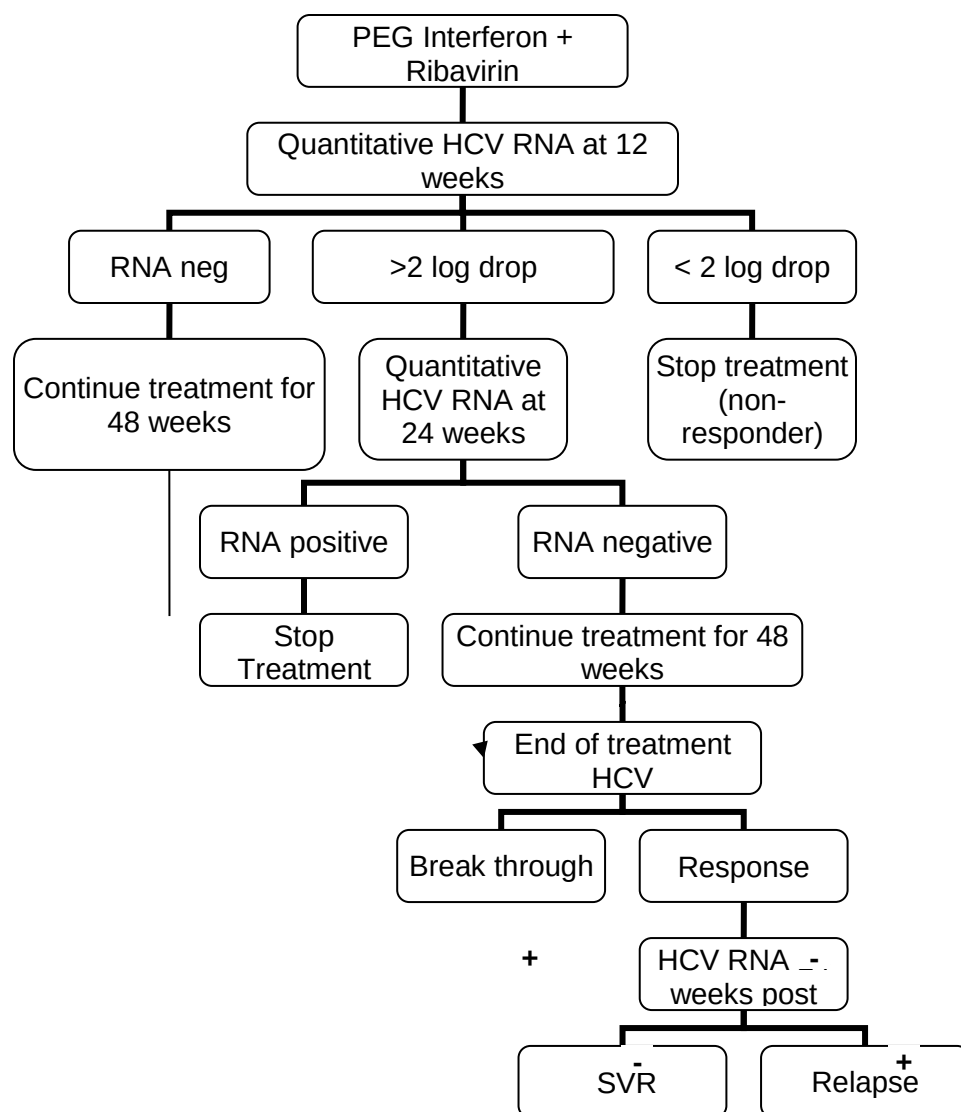


Figure 6. Monitoring treatment response in genotype 1 HCV patients on PEG-.

Treatment of chronic hepatitis C should be considered in all patients without contraindications. The decision to initiate treatment is complex and needs to be individualized on the basis of virologic features as well as patient factors that influence the risk for disease progression and likelihood of treatment response. Patient motivation is essential for treatment adherence. In general, hepatic inflammation (elevated transaminases and active inflammation on liver biopsy), degree of hepatic fibrosis as well as virologic evidence of infection (positive HCV RNA), are considerations in the decision to start treatment initiation. Patients with normal liver enzymes, cytopenias, cirrhosis and HIV-HCV co-infection may also be considered for treatment by experienced practitioners.

Since a liver biopsy is the most sensitive way to determine the level of hepatic inflammation and fibrosis, it is recommended but not mandatory prior to initiating therapy (Canadian Consensus guidelines, 2007). Patients with genotype 2 and 3 infection may



not need liver biopsy because of their high likelihood of cure with treatment.

The therapeutic agents available to treat chronic hepatitis C have evolved in the last 15 years. Current therapy is a combination of pegylated interferon and ribavirin, an oral nucleoside analog. There are two pegylated -IFN preparations available in Canada (PEGASYS (α -2a) and PEGINTRON (α -2b)). The IDEAL trial found that both had similar efficacy, ie. similar SVR rates.

The combination of PEG-IFN and ribavirin has achieved SVR of 42-60% in genotype 1 patients, and 70-90% in genotype 2 and 3 patients. Genotype 1 patients are generally treated for 48 weeks, and genotype 2 and 3 for 24 weeks. Contraindications to treatment are included in Table 16, and adverse effects and monitoring of therapy in Table 17. New HCV-specific protease inhibitors such as telaprevir and bocepravir, used in combination with current standard of care will elevate SVR in genotype 1 to the 65-70% range.

Table 16. Contraindications to IFN and ribavirin therapy

○ Pregnancy	○ Solid Organ Transplantation (other than liver)
○ Alcohol or other substance abuse	○ Uncontrolled Depression/Psychosis
○ Hepatic Decompensation	○ Autoimmune Disease
○ Ischemic Heart Disease	○ Chronic renal failure

Adapted from the *Canadian Consensus Guidelines*, 2007

Table 17. Adverse effects and monitoring requirements with IFN and Ribavirin

PEG IFN α (2a,2b)		Ribavirin	
○ Flu-like symptoms (headache, nausea, fatigue, fever)	-CBC week 1,2,3,4,6,8,10, then q monthly	○ Hemolytic anemia	-CBC as per IFN
○ Thrombocytopenia, Leukopenia	-TSH q 3 monthly	○ Rash	-Pregnancy tests regularly
○ Weight Loss	-Weight q 3 monthly	○ Anorexia, nausea	
○ Depression, Anxiety, Insomnia	-ALT, bili, glucose, U/A q monthly	○ Cough, dyspnea	
○ Worsening of autoimmune diseases (thyroid, psoriasis, autoimmune hepatitis)		○ Teratogenicity	
○ Reversible alopecia			
○ Retinopathy			



No vaccine for HCV yet exists. Newer nucleoside analogues, such as bocepravir or telapravir used in conjunction with PEG-IFN and Ribavirin are still in clinical trial but promise significantly higher rates of SVR, even in genotype 1 infection.

Condoms should be used during the acute phase of HCV illness and indefinitely for those who are immunocompromised. After being advised of the risks of HCV, couples in whom one is chronically infected with hepatitis C must make their own decision with regards to condom use. The risk of spread to regular sexual partners is estimated at 2-5%. In clinical practice, most couples choose not to use condoms, as the risk of spread may only be increased in acts of intercourse where there is exposure to blood of the infected partner.

Vertical transmission of HCV from a mother to newborn is rare, but, the risk of HCV vertical transmission is much higher if the infected mother is also co-infected with HIV (15%). Breast feeding by HCV-infected mothers is considered to be safe.

5. Hepatitis D Virus (HDV)

Chronic hepatitis D usually results from HDV super-infection of an HBV carrier. Less commonly, acute HBV/HDV co-infection leads to chronic infection. Either way, chronic hepatitis D is usually aggressive and severe with rapid progression to cirrhosis. HDV is rare in North America.

The diagnosis is made by testing for anti-HDV in the serum of HBV carriers who have risk factors for HDV infection. HDV antigen and HDV-RNA in serum or liver can also be measured, but only in a limited number of laboratories. In North America this virus is most often transmitted by intravenous drug abuse, and possibly also through the sexual route. In Mediterranean countries intra-familial transmission has been reported. Treatment with interferon for HDV infection has been disappointing. Similarly, the use of lamivudine either alone or in combination with interferon has also been ineffective. Because of the dependency of HDV on HBV, the prevention of HBV infection with vaccination can prevent HDV infection.





Chapter 4: Non-Alcoholic Fatty Liver Disease

S. Jayakumar, E. Shaffer



1. Introduction

Non-alcoholic fatty liver disease (NAFLD) is an umbrella term encapsulating anything from simple hepatic steatosis (SS) to steatohepatitis to cirrhosis. When there is steatosis and hepatocyte inflammation, it is termed non-alcoholic steatohepatitis (NASH) (See Figure 1). Simple steatosis refers to the presence of fat accumulation within the hepatocytes in the form of fat droplets, but without any associated inflammation or fibrosis. Simple steatosis is a benign process, with a low likelihood of progression and complications, whereas the presence of either inflammation or fibrosis carries a worse prognosis.

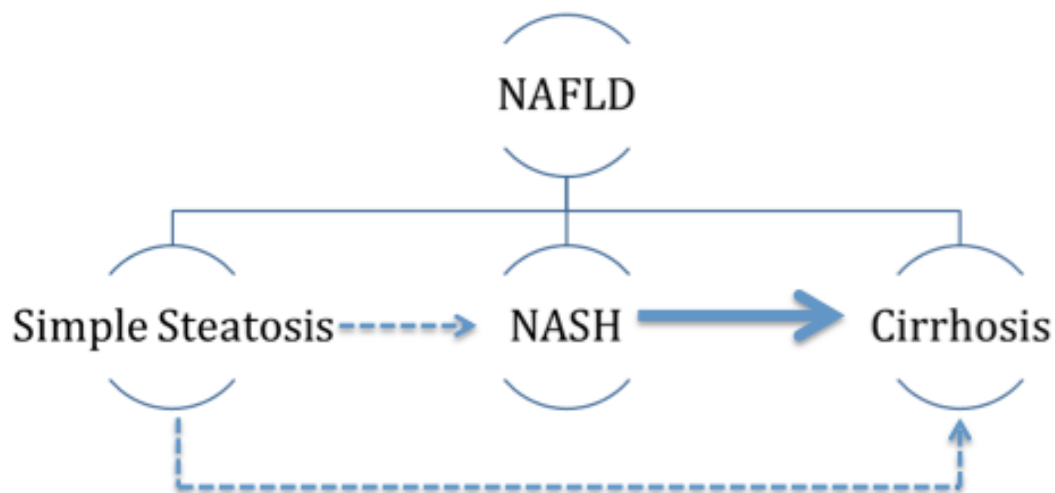


Figure 1. Natural history of non-alcoholic fatty liver disease (NAFLD) progressing to non-alcoholic steatohepatitis (NASH) and then to cirrhosis. The direct progression from simple steatosis to cirrhosis has not been documented, but estimated rates are very low. There is strong evidence for the progression of NASH to cirrhosis.

Large fat droplets, as are seen with NAFLD and alcoholic fatty liver disease, are termed as “macrovesicular”, whereas small lipid droplets within the cytoplasm are termed “microvascular”. (See figure 2) Causes of hepatic fat accumulation, in both the microvascular and macrovascular form, are listed in Table 1.



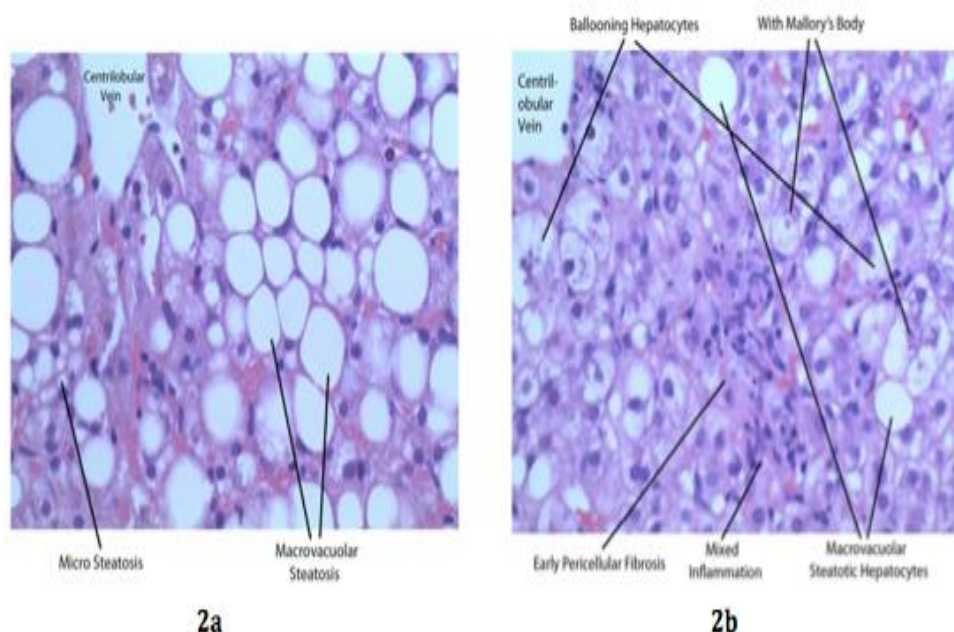


Figure 2. Steatosis and steatohepatitis (H & E 40x photomicrographs). Figure 2a shows simple steatosis with both micro- and macrovascular steatosis, without any features of inflammation or fibrosis. Figure 2b shows features diagnostic of NASH, such as

an inflammatory infiltrate (primarily lymphocytic), in addition to steatosis.

Table 1: Causes of Microvesicular and Macrovesicular Hepatic Steatosis

	Macrovesicular Steatosis	Macrovesicular Steatosis
Drugs	Steroids	ASA (Reye's Syndrome)
	Vitamin A	Tetracycline
	Methotrexate	Valproate
	Amiodarone	
	TPN	
Toxins	Alcohol	Uncooked Ackee fruit
Systemic Disorders	IBD	Acute Fatty Liver of Pregnancy
	Intestinal Bypass, Short Gut	Urea Cycle Defect
	Starvation	Defects in fatty acid beta-oxidation

NAFLD is currently the leading cause of liver disease in North America, with its prevalence ranging up to 45% in the general population. This number is an underestimate. The majority of individuals who harbor simple steatosis, or even NASH, are often asymptomatic, and therefore remain undiagnosed.

NAFLD can be classified into primary and secondary forms. The most common primary cause of NAFLD is due to insulin resistance, as is seen in patients with obesity, Type 2 Diabetes Mellitus (DM II), and the metabolic syndrome. Secondary causes of NAFLD vary from such culprits as drugs, toxins, nutritional, and systemic diseases (including metabolic abnormalities, infections and surgeries). Table 2 lists the common secondary causes of NAFLD.



Table 2: Secondary Causes of NAFLD

CATEGORY	SPECIFIC CAUSE
Nutritional	Protein calorie malnutrition
	Rapid Weight Loss
	TPN
	Starvation
Drugs - Hormones	Steroids
	Estrogen
	Tamoxifen
Drugs - Other	Amiodarone, Methotrexate, Valproate, Tetracycline, HAART, ASA (Reye's)
	Cocaine
Metabolic	A/Dys/Hypo-betalipoproteinemia
	Hypopituitarism
	Hypothyroidism
	Glycogen Storage Disorder
	Inborn Errors of Metabolism (LCAT Deficiency, Wolman disease)
	Lipodystrophy
	Familial Combined Hyperlipidemia
	Polycystic Ovarian Syndrome (PCOS)
	Celiac Disease
	Wilson Disease
Toxins	Amanita phalloides
	Phosphorus poisoning
	B.cereus toxin
Infection	HIV
	HCV
	Small Bowel Bacterial Overgrowth

Abbreviations: TPN, total parenteral nutrition; HAART, highly active antiretrovirals; ASA, acetylsalicylic acid; HCV, hepatitis C virus; HIV, human immunodeficiency virus

2. Pathogenesis of NAFLD and NASH

Although the pathogenesis of NAFLD and NASH has not yet been fully explained, the most accepted model for the development of the disease is the “two-hit model”. This is based on the observation that patients with only simple hepatic steatosis rarely develop cirrhosis (rates of 1-2% over 20 years), whereas 8-20% of those with NASH progress to cirrhosis over a mean of 12 years.

The initial “hit” is the development of hepatic steatosis, which is a manifestation of triglyceride accumulation in the hepatocyte. Since the major source of hepatic triglycerides is from fatty acids either stored in adipose tissue or newly synthesized by the liver, excess fatty acids within the liver can lead to hepatic steatosis. In simplistic



terms, this can be due to increased intake/import of dietary fats (specifically free fatty acids), increased hepatic production of triglycerides, decreased hepatic excretion of fat, or abnormal metabolism of the hepatic fat.

Increased import of free fatty acids (FFA) can occur due to increased intake of dietary fat, as is seen in obesity or poor dietary habits, or increased transfer from adipose tissue, which is seen in rapid weight loss. Increased hepatic synthesis of triglycerides (hepatic lipogenesis) occurs in insulin resistant states. Hepatic steatosis can also be seen in individuals who have genetic causes of hypertriglyceridemia. Normally, hepatic triglycerides are repackaged as very low-density lipoproteins (VLDLs), which are then excreted. This synthesis and excretion of VLDLs can be impaired through genetic means (e.g. abetalipoproteinemia, choline deficiency), or by various medications.

The second hit is the development of inflammation, which in turn leads to fibrosis. It is at this stage that the disease is termed NASH. There are multiple proposed mechanisms for the development of inflammation in the steatotic hepatocyte, including insulin resistance, mitochondrial dysfunction, and oxidative stress. (See figure 3)

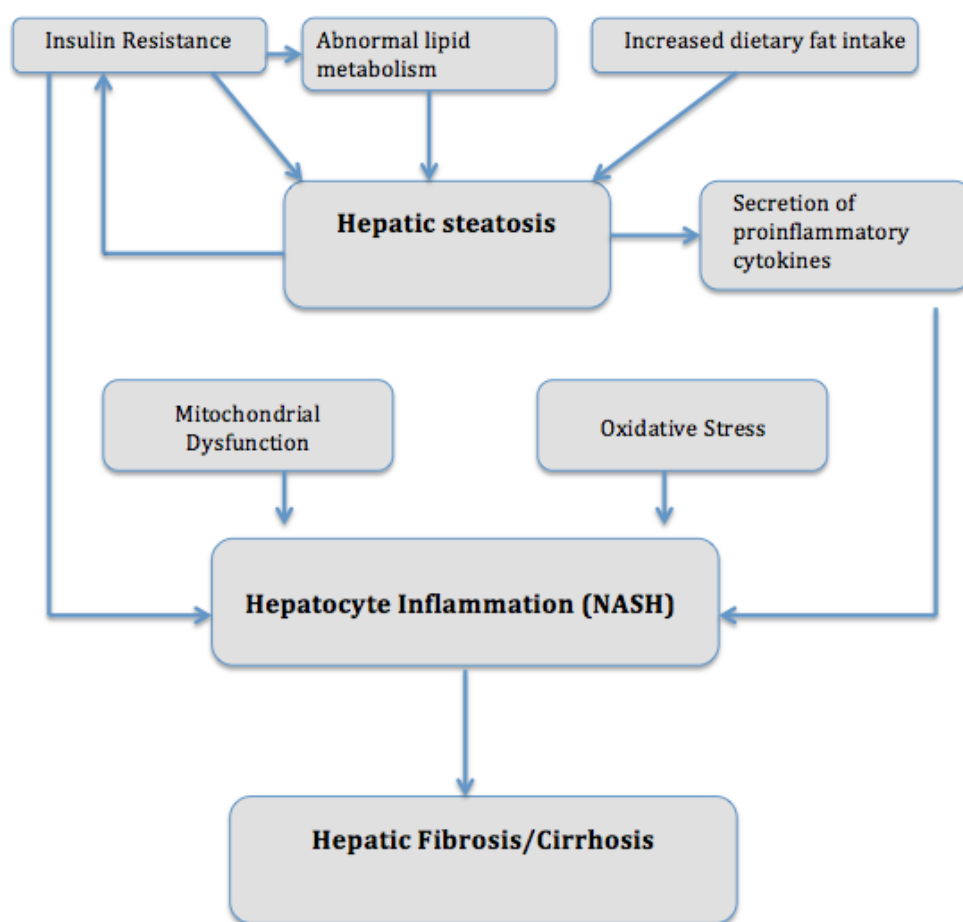


Figure 3. Pathophysiology of NAFLD showing the various mechanisms that result in the development of both hepatic steatosis and steatohepatitis.

Since the biggest risk factors for the development of NAFLD and NASH are insulin resistance, obesity (specifically truncal obesity), and hyperlipidemia, NAFLD is considered the hepatic

manifestation of the metabolic syndrome. Insulin resistance has a substantial role in the



development of both hepatic steatosis and steatohepatitis. Insulin resistance is a result of an abnormal metabolic mutual relationship between the adipose tissue, and the skeletal muscles, which utilize most of the plasma glucose. The effect of insulin, which is released in the fed state, is to inhibit lipolysis. In the setting of excess caloric intake, adipocyte hypertrophy, and subsequently obesity, emerge. Adipocyte hypertrophy in turn has many effects, including increased gluconeogenesis, increased serum free fatty acids, and insulin resistance, as well as increasing hepatic lipogenesis. Insulin resistance, while stimulating peripheral lipolysis, simultaneously causes increased synthesis of triglycerides and increased uptake of FFA by the liver; hepatic steatosis ensues.

Dietary fructose, usually highly concentrated in corn syrup/sugar, soft drinks and juices, also may lead to the development of hepatic steatosis and insulin resistance, more so than other carbohydrates and sugars.

Increased hepatic steatosis results in the secretion of pro-inflammatory cytokines such as IL-6, IL-1 β , NF- κ β , and TNF- α . These cytokines not only result in hepatocyte inflammation, but also promote hepatic and peripheral insulin resistance. There are two categories of adipose tissue – subcutaneous and visceral. Insulin resistance and NAFLD are more commonly observed in the setting of increased visceral adipose tissue (VAT). Patients with increased VAT have also been observed to have higher rates of hepatocyte inflammation and fibrosis, with higher levels of the pro-inflammatory cytokine IL-6. Currently, the only way to accurately measure VAT is through cross-sectional imaging techniques, such as CT or MRI. Neither is a realistic or feasible option for most patients. The waist circumference, as well as the waist: hip ratio (WHR) is a more accurate measure of VAT than the BMI, although the WHR has not been a widely adopted standard.

Some of the proposed mechanisms behind hepatocyte inflammation are mitochondrial dysfunction and oxidative stress. Increased hepatic steatosis, representing enlarged stores of hepatic triglyceride, results in a shift from carbohydrates as a primary fuel to the beta-oxidation of FFA. This, along with lipid peroxidation, places stress on the mitochondria, and thus produces reactive oxygen species, ultimately resulting in hepatocyte inflammation.

3. NAFLD Epidemiology

Since NAFLD is so closely tied to obesity, diabetes, and the metabolic syndrome, countries where these conditions are highest are also where prevalence of NAFLD is also high.

The prevalence of NAFLD in the general population in North America ranges from 10-46%, with rates increasing to close to 90% in severe obese, which is defined as a BMI¹ >35kg/m². Worldwide, the prevalence of NAFLD ranges from 6-35%. The

¹ Body mass index (BMI) is used to express weight adjusted for height, as kilograms divided by height in meters squared (kg/m²). The normal range of BMI is 20-25. *Overweight* is a BMI of 25-30. *Obesity* (>30) may be further divided into: *severe* (>35-39), or *extreme* (“morbid”) when BMI>35 accompanied by co-morbid conditions like diabetes or cardiovascular disease (metabolic syndrome) or when the BMI >40. Overweight for children and adolescents is a BMI for age at or above the 95th percentile of a specified reference population.



prevalence of NASH is 2-5% in the general population, and increases to about 30% in the obese. The rates of NAFLD in the US have been steadily increasing, concordant with rises in the rates of obesity, DM II, and metabolic syndrome. There are many different definitions for the metabolic syndrome, but the majority require at least 3 of the criteria listed in Table 3. The rationale for waist circumference is based on its role as a surrogate marker of VAT.

Table 3: Metabolic Syndrome (American Heart Association definition)

Parameter	Value (Men and Women)
Diabetes mellitus/insulin resistance	Fasting glucose > 5.6mmol/L OR use of hypoglycemic medications
Hypertension ($\geq 140/90$)	130/85, OR use of antihypertensive medications
Hypertriglyceridemia	TG>1.7mmol/L
Low HDL	$\leq 1.03/L$ (M) ≤ 1.29 mmol/L (F)
Central Obesity (Waist Circumference)	>102cm (M) > 88cm (F)

The frequency of NAFLD is equal between men and women. Men, however, seem to have higher rates of progression to advanced liver disease, as do those of Hispanic descent. Caucasians also have relatively high prevalence rates of NAFLD, although less than Hispanics, whereas African Americans tend to have the lowest rates of NAFLD. NASH rates and likelihood of NAFLD progressing are also increased in patients with DM II and obesity.

4. Clinical Presentation and Natural History of NAFLD and NASH

Most with fatty liver disease are asymptomatic. Hence, the detection of NAFLD most commonly occurs incidentally, through elevated liver enzymes uncovered during routine blood tests. The majority of patients are in their fifth and sixth decades.

Any symptoms are due either to hepatomegaly and RUQ pain from stretching of the capsule, or from features of decompensated cirrhosis. Patients may express non-specific complaints like fatigue and malaise. NAFLD is also associated with a number of other diseases, including diabetes mellitus, dyslipidemia (especially hypertriglyceridemia), obesity, and the metabolic syndrome. Obstructive sleep apnea is associated with higher rates of NASH, perhaps due to the intermittent periods of hypoxemia.

On physical exam, there are few findings that are unique to NAFLD. The majority exhibit obesity, especially truncal obesity; a small subset is lean yet still develop NAFLD. Hepatomegaly may be evident, secondary to fatty infiltration of the liver. The



advent of cirrhosis can lead to stigmata of chronic liver disease, such as palmar erythema, spider nevi, jaundice, edema, ascites, and other signs of portal hypertension.

The most common laboratory manifestation of NAFLD are elevated liver enzymes, or the presence of steatosis detected on abdominal imaging. The serum aminotransaminases (ALT and AST) are often elevated, although they are usually <200 IU/L. The ratio of AST: ALT is less than 2, unlike that seen in alcohol-related liver injury. Occasionally, cholestatic enzymes are also elevated, especially gamma-glutamyl transpeptidase (GGT). Normal liver enzymes however do not exclude NAFLD or NASH. Ferritin and transferrin saturation are often elevated in NAFLD; a significantly elevated ferritin (greater than 1.5x the upper limit of normal) portends worse histologic features (i.e.; increased inflammation and/or fibrosis). Markers of liver synthetic function (e.g.; bilirubin, INR, and albumin) are typically normal in the absence of liver failure or concomitant Gilbert's disease.

Steatosis is most readily detected as hyperechogenicity on ultrasound of the liver. For this ultrasound finding to be evident, the liver must have at least 30% steatosis (sensitivity and specificity of 85% and 94%, respectively).

8-20% of patients with NASH progress to cirrhosis, especially in comparison to those with simple steatosis. Risk factors for progression are diabetes, the presence of inflammation or fibrosis on the baseline liver biopsy, older age, obesity, and increased visceral adipose tissue (VAT). As with other liver diseases, the presence of a second liver disease (viral hepatitis, hemochromatosis, alcoholic liver disease) heightens the progression to cirrhosis.

Hepatocellular cancer (HCC) can complicate NAFLD, both in the cirrhotic and the non-cirrhotic stages. The frequency of HCC developing in NAFLD ranges from 2.4% to 12.8%. Although important, this complication is lower than that seen with HCV cirrhosis, HBV or even hemochromatosis. In the non-cirrhotic patient, there is an increased rate of adenoma formation and subsequent malignant transformation of the adenoma to HCC in NAFLD. This is thought to be due to multiple factors, including: diabetes, obesity, and the proinflammatory cytokines secreted by the liver in the setting of NAFLD and NASH. Although there are currently well-established guidelines for screening of HCC in the setting of cirrhosis, none yet exist for NAFLD/NASH in the absence of cirrhosis.

Patients with NAFLD have an increased rate of cardiovascular events when compared to those without NAFLD, even after controlling for diabetes, metabolic syndrome, and other CV risk factors. In fact, the leading causes of death for patients with NASH are, in order, cardiovascular disease, extrahepatic malignancy, and then liver disease. This increase in cardiac risk is associated with the degree of inflammation and fibrosis seen on biopsy, meaning that patients with NASH have a higher risk of developing cardiac disease, diabetes, and malignancy when compared to patients who have simple steatosis on their baseline liver biopsy. NAFLD places patients at high risk for developing diabetes, even if diabetes was not evident at the time of diagnosis, undoubtedly from hepatic steatosis causing peripheral insulin resistance.



5. Diagnosis of NAFLD

The diagnosis of NAFLD requires that there is: a) radiographic or histologic confirmation of hepatic steatosis, b) a lack of significant alcohol consumption (ie <40g/wk), and c) exclusion of other, secondary, causes of hepatic steatosis. Other causes of liver disease must be ruled out before securing the diagnosis of NAFLD.

The exact cut-off for alcohol consumption is controversial; there is no universally agreed-upon quantity imbibed on a regular basis. Fatty liver will not develop with alcohol consumption <20g/d. Significant alcohol consumption is best defined as >21 drinks/wk for men, and >14 drinks/wk for women.

Patients with elevated ferritin and transferrin saturation should undergo testing for hereditary hemochromatosis. Since mutations in the HFE gene occur at variable rates in NAFLD, and can be associated with a more severe course of the disease, a liver biopsy should be considered for diagnostic confirmation and for staging. Others may exhibit elevated autoantibodies, likely representing an epiphenomenon and are not being associated with more severe disease.

The most cost-effective method of diagnosing hepatic steatosis is through ultrasound, often used to screen for suspected NAFLD. Other imaging modalities to diagnose hepatic steatosis are CT and MRI. MR Spectroscopy (MRS) quantifies the liver fat. Its values closely correlate with histological assessment. MRS is useful in patients with small amounts of fat. Another possible method to evaluate both hepatic steatosis and fibrosis is the Fibroscan™, which is a non-invasive measure of the elasticity of the liver. This, in combination with a special measure called the Controlled Attenuation Parameter (CAP™), can be used to measure both hepatic steatosis and hepatic stiffness. A higher reading is consistent with both increased hepatic steatosis and hepatic stiffness, which may be from fibrosis.

Simple steatosis is often a benign process, whereas NASH carries a worse prognosis. Unfortunately, there is no definitive way to differentiate between these two processes in the clinical setting other than through a liver biopsy. Currently, a liver biopsy is the gold standard for diagnosing NAFLD and NASH, although it is only indicated either when the diagnosis is unclear after all other tests have been performed, or to differentiate between steatosis and NASH.

Histological findings in NAFLD are: steatosis, inflammation (both portal and lobular), fibrosis, Mallory-Denk bodies, and, occasionally, glycogenated nuclei and megamitochondria. Steatosis is the most important finding in making the diagnosis of NAFLD – there are often macrovesicular lipid droplets, which often push the nucleus to the periphery of the hepatocyte. The severity of the steatosis is based upon how much of the hepatocyte is affected by the steatosis. In order to make a diagnosis of NAFLD, there must be at least 5% steatosis in the hepatocyte. In order to diagnose NASH, there must be features of inflammation or fibrosis. Such signs are ballooning degeneration of the hepatocyte, and inflammatory infiltrate, or fibrosis (Figure 3). Scoring systems are being developed to grade the fat content of the liver, primarily for research purposes at this time.



6. Treatment of NAFLD and NASH

The pathogenesis of NAFLD is not completely clear. The two major risk factors to develop NAFLD are obesity and insulin resistance. Development of NAFL, progression to NASH, cirrhosis and in some cases hepatocellular carcinoma can take 20-40 years. The advanced part of this process may be genetic, with the early part initiated by environmental factors. The two-hit hypothesis is now the widely accepted theory of the pathogenesis of NAFLD and its progression. The concept is based on the observation that only some 10% of patients with NAFLD progress to NASH, and only some 15% of these will develop cirrhosis (Lazo 2008, Preiss 2008, Jou 2008).

How obesity leads to insulin resistance and later to NAFL is the first basic question.

Insulin resistance is a result of an abnormal metabolic mutual relationship between the adipose tissue, and the skeletal muscles which utilize most of the plasma glucose. In the normal subject, following a meal, the skeletal muscle cell utilizes glucose which is inserted into the cell following insulin attachment to its receptor. The receptor activates a cascade of proteins by a series of phosphorylation reactions, which stimulate the translocation of the glucose transporter 4 (Glut4) from intracellular vesicles to the plasma membrane (Choi 2010). Insulin inhibits lipolysis in adipocytes. However, in the fasting state when the level of insulin is low, lipolysis starts in the adipose tissue. Plasma free fatty acids (FFAs) become the principal fuel source of skeletal muscle. Excess of caloric intake leads to adipocyte hypertrophy, which in turn leads to the secretion of large amounts of adipokines such as monocyte chemoattractant protein-1 (MCP-1). MCP-1 enhances macrophage infiltration and secretion of TNF- α , IL-1 β and others cytokines. High TNF- α level results in decreased fatty acid esterification and enhanced lipolysis (14). Elevation of plasma FFA concentration in insulin sensitive individuals leads to an increase in the intramyocellular fat content. High concentrations of FFAs lead to malfunction of the insulin signaling pathway (Choi 2010, Guilherme 2008) and significant reduction in both the quality and quantity of the mitochondrial density in skeletal muscle cells. These in turn lead to an insulin resistant state.

Normal FFAs metabolism in the liver depends upon balances of hepatocyte uptake and *de novo* synthesis of FFAs on one hand, and disposal of FFAs by *de novo* triglyceride synthesis of the other, which then leads to export of FFA's as VLDL, and their oxidation. Thus, obesity is a chronic inflammatory state which causes lipolysis in the adipose tissue, as well as significant increases in circulating nonesterified FFAs. A high insulin level activates transcription factors, such as sterol responsive element binding protein-1c (SREBP-1c) and carbohydrate response element binding protein (ChREBP). These transcription factors increase *de novo* lipogenesis, and lead to the accumulation of triglycerides into histologically visible macrovesicles in the liver (Cheung 2008)). In the hepatocytes, FFA oxidation occurs in subcellular organelles.

Further, a high-fat diet may produce changes in the intestinal microflora, increase plasma LPS levels, and lead to the development of a "metabolic endotoxemia," which progresses to NAFLD, at least in animal models (Serino 2009).



7. Treatment of Fatty Liver

7.1. Calorie Restriction

Therapy of fatty liver begins with recognition of the condition. The epidemic of obesity besides the increasing prevalence of fatty liver is also driving an increased incidence of the metabolic syndrome, type 2 diabetes, and consequent cardiovascular effects. It is expected and hoped that the best treatments for NAFLD and NASH would also treat other aspects related to fatty liver. In this respect global treatment with regular [not fads] diet, exercise and lifestyle would fit this requirement the best. Within this paradigm the role of bariatric surgery, the most extreme form of forced weight loss supports the notion of ideal therapy.

Musso and co-workers summarized randomized controlled trials of various treatment modalities in fatty liver (diet, lifestyle, specific dietary components and pharmaceutical interventions) (Musso 2010). A total of 10 trials addressing either NAFLD or NASH were reviewed, dealing with weight reduction without or with lifestyle changes (including exercise) or addition of dietary aids. These dietary aids included a carbohydrate or lipid absorption inhibitor or antioxidant vitamins. In studies reporting diabetics their proportion included ranged from 10-100%. The mean duration of studies was 7.9 months, with a range 1-24 months.

Three studies which evaluated weight reduction alone suggested that a minimum of 7% loss is needed to result in some improvement in NASH, including loss of fat and NASH activity score. Intense life style changes over one year also resulted in improvement in two trials. Importantly the institution of physical exercise alone independently improved NAFLD parameters in three trials. A study that was not included in the systematic review supported an interesting observation that cardiovascular fitness, (independent of MRI assessment of adiposity) was related to liver fat (Kantartzis 2009).

The last area of diet reported was the role of specific dietary components especially carbohydrates. Evaluation of carbohydrate restricted diet in obese diabetics resulted in improved insulin sensitivity although again the effect of minimum 8% weight loss was evident in improving hepatic fat (Musso 2010).

The proof of principle that calorie restriction improves metabolic syndrome and its complications, including NAFLD and NASH, is provided by bariatric surgery. In a meta-analysis of 15 studies on this type of surgery, Mummadi found that of over 750 patients with paired liver biopsies had substantial improvements (Mummadi 2008). Body mass index was reduced from 19-42% by a variety of types of bariatric surgery. These operations included Roux-en-Y gastric bypass [8 studies], laparoscopic adjustable gastric band [Lazo 2008], gastropasty [Diehl 2005], biliopancreatic diversion [Lazo 2008], vertical band gastropasty [Lazo 2008], sleeve gastrectomy and bilio-intestinal bypass in combinations [Diehl 2005]. Repeat liver biopsies were performed between 2-111 months. The results were impressive, with 69.5% (95% CI 42.4 - 90.8 %) of patients showing complete resolution of NASH. Individual histologic features evaluated before and after surgery revealed 91.6% (95% CI, 82.4- 97.6 %) improvement or resolution of steatosis, 81.3 % (95% CI, 61.9 - 94.9 %) improvement in inflammation, and 65.5 % (95% CI, 38.2- 88.1 %) in fibrosis (20). Surgical intervention to alter



anatomy should be the last resort, after life-style changes have been extensively and sincerely tried and failed.

The conclusion to be drawn from analyses of these studies is that even mild (7%) weight loss improves fatty liver. Rather than “fad” diets, total caloric restriction should be the goal of dietary therapy in persons with NAFLD. In addition, the restriction of total fat and carbohydrates may be beneficial. Because saturated fatty acids increase oxidative stress, these should likely also be curtailed. In addition, simple sugars and high fructose containing foods should be specifically avoided since these are thought to aggravate obesity. Finally, alcohol consumption should be restricted in individuals with risk factors (Vuppalanchi 2009). In general, rapid weight loss of more than 2 pounds (1 kg) per week is not recommended, because there is a small risk of rapid weight loss aggravating liver function. Secondly, physical activity even independently from diet may improve the liver through improved insulin sensitivity. The recommended time of physical activity is about 30 to 45 minutes a day. This could include a brisk walk or aerobic exercises.

Unfortunately, our current environment with an abundance of calories and the economic push to consume more is difficult to overcome.

7.2 Pharmaceutical Agents

When lifestyle modification and diet fails the longterm prognosis of NASH in particular is associated with an increased liver related mortality (Rafiq 2009). Furthermore, not all these patients are willing or represent good surgical candidates. Nevertheless it is important to reduce NASH and its complications. Unfortunately, at this time, no drug is approved for use.

There have been numerous specific dietary or pharmacological agents with or without addition of dietary components [mainly vitamin E or C] which have been tried to improve either fatty liver or the more advanced NASH. Therapies are generally aimed at reversing insulin resistance with the hope that this also reverses fatty acid accumulation and its consequences. Therapy is also aimed at preventing or reversing the hypothesized second hit phenomenon of increased oxidative stress. Most information is based on randomized controlled studies (RCT).

An interesting publication by Loomba et al. evaluated the expected outcome of placebo in randomized control trials (RCTs) in NAFLD/ NASH. In a meta-analysis of 5 trials encompassing some 162 patients, the authors concluded that improvement in ALT is to be expected, but does not accurately reflect hepatic events. However, only a 1 point improvement is expected overall in histologic NASH scores (Loomba 2008). Not all studies evaluate results from these perspectives.

Table 4 lists agents used in clinical trials or only in animal models, with the rationale of their use. Because insulin resistance is a major pathogenic component of fatty liver, drugs used in treatment of diabetes have been used extensively in this condition. Recall, however, that the relationship between insulin resistance and liver histology is poor (Ratziu 2010). Other agents affect lipid transport, while still others have been used to concentrate on reducing oxidative damage and mitochondrial injury. Also, because the second hit is accompanied by inflammatory cytokines, inhibitors of tumor necrosis alfa have been studied, with varying success. Several “natural “ products also



have been tried. These include both herbal products and the currently popular probiotics [exogenous bacteria which bypass digestion and confer health benefits to the host]. These bacteria affect many gut functions and improve gut barrier permeability, which could decrease bacterial translocations limiting hepatic second hit injury.

Table 4. Outline of therapeutic agents and their proposed mechanism of action for non-alcoholic steatohepatitis (NASH).

Agent	Mechanism[s]
➤Metformin	○Stimulates aerobic metabolism, reduces FFA oxidation, decreases uncoupling protein, increases IS
➤Thiazolidinediones (Glitazones)	○Stimulates PPAR- γ , Adipokine, improves IS, increased FFA oxidation
➤TNF – α inhibitors (Pentoxifyline)	○Reversal of lipid induced increase in proinflammatory cytokines
➤Ursodeoxycholic Acid	○Improves nuclear cell signaling ○Increases GLP-1 and brown fat energy expenditure
➤Statins	○Increases β – oxidation, adiponektin ○With IS, reduces AGE [which promotes NASH]
➤Fibrates	○Agonist of PPAR – γ , increases high ○Density cholesterol
➤Probucol	○Antioxidant and antiinflammatory ○Effects
➤Endocannabinoid receptor antagonist (rimonabant)	○Reduces fat mass, insulin levels and liver triglycerides; increases adiponectin
➤Angiotensin II type 1 Converting Enzyme receptor (Telmisartan)	○Improves IS via PPAR – γ partial agonist effect
➤Carnitine	○Facilitates long chain FFA transport ○Across mitochondrial membrane
➤Betaine	○Reduces lipid accumulation in liver by ○Donating methyl groups to homo-cysteine
➤Vitamin E and C	○Inhibits FFA deposition by reducing ○Oxidative stress
➤Polyunsaturated fats	○Improves serum triglycerides and IS
➤Yo Jyo Hen Shi Ko	○Antifibrotic and hepatocellular protection



- Green tea
- Probiotics
- Antioxidative effects, and lowers serum lipids
- Improves bowel permeability and reduces bacterial translocations

Abbreviations: Advanced glycation endproducts, AGE; Free Fatty Acids, FFA; Glucagon-like peptide 1, GLP-1; Insulin sensitivity, IS; Peroxisome proliferator – activated receptor gamma, PPAR – γ ; and Tumor necrosis alpha, TNF α .

Trial outcome of drugs or specific dietary agents have been variable and follow-up has been relatively short. At least three, largely overlapping meta-analyses of RCTs were published in persons with NAFLD. The first by Socha included 15 combined therapeutic studies (Socha 2009). This study showed that metformin but not pioglitazones improved serum biochemistry, as compared with vitamin E. A second meta-analysis by Rakoski et al. evaluated only those studies using either the glitazones [5 studies] or metformin [4 studies] (Rakoski 2010). In contrast, they reported that glitazones but not metformin statistically improved ALT, as well as histologically determine steatosis and ballooning of hepatocytes. Even in the NAFLD groups without diabetes, the glitazones improved inflammation and fibrosis. The most comprehensive meta-analysis by Musso et al reviewed 49 RCTs, 23 [22 NASH and 1 NAFLD study] of which included pre- and post-liver biopsies (Musso 2010). Table 5 outlines the agents, the numbers of studies analyzed, and the odds ratios with significance for outcome of trials with comparisons of pre- and post-treatment liver biopsies. Their conclusion about insulin sensitizers was that glitazones improved histological steatosis and inflammation, but increased the patient's body weight. Antioxidants had variable outcome. In 1 RCT, each pentoxifyline [TNF α inhibitor], telmisartan [Antihypertensive], and L-carnitine [facilitates lipid transport] improved liver histology.

Table 5A. Outline of studies included in meta-analyses of various agents for treatment for non-alcoholic steatohepatitis (NASH), according to histological outcome.

Agent	Number of studies	Steatosis	Inflammation	Fibrosis
Thiazolidinediones	5	4.06, p<0.00001	3.53 P<0.00001	1.4 P=0.17
Metformin	4	1.3 NS	1.08 NS	0.9 NS
Satatin (simvastatin)	1	0.56 NS	0.00 NS	0.17 NS
Ursodeoxycholic Acid	2	1.15 NS	0.78 NS	0.94 NS
Antioxidants	5	1.26 NS	1.19 NS	0.64 P=0.07
Pentoxifyline	1	1.78 NS	12 P=0.04	1/07 NS



Telmisartan	1	1.56 NS	4.13 P=0.03	3.85 P=0.02
L-Carnitine	1	23.5 P=0.03	7.2 NS	2.21 NS

Abbreviation: NS, Not Statistically Significant

Study times ranged from 1-24 months. Agents, the number of studies included in analysis summary odds ratio and statistical significance is listed. In the majority of studies a Fixed model was used. Antioxidants and metformin fit a Random model better in fat and inflammation, These results are derived from reference (Musso 2010).

Based on these analyses, the glitazones hold the best promise at this time, with Pioglitazone being the most successful. Adverse side effects are low, although body weight gain, mild congestive heart failure, and osteopenia with fractures have been described (Ratzu 2010). Studies with antioxidants, especially vitamin E, may also have some use. Single studies showing individual positive effects need to be verified. Overall changes in lifestyle should be implemented first, or also in conjunction with any pharmaceutical therapy. In properly selected candidates especially, those with BMI > 35 kg/M², bariatric surgery is a good alternative.

Table 5B. Proportion of patients (%) [with pre and post liver biopsies] improving after bariatric surgery for NASH in 3 histologic categories is shown together with 95% confidence intervals. Results based on reference (Choi 2010)

Agent	Number of studies	Steatosis	Inflammation	Fibrosis
Bariatric surgery	15	91.6% (82.4, 97.6)	81.3% (61.9, 94.9)	65.5% (42.4, 94.9)

8. Summary

NAFLD is a problem paralleling the epidemic of obesity, and could be potentially controlled by efforts which reduce weight and alter sedentary lifestyles. While there is no proven or approved pharmaceutical treatment of NASH several agents especially the “glitazones” hold promise. Several other agents with good outcomes need further verification. Surgery is a last resort for those in whom other efforts fail. With a sizeable proportion of NAFLD patients developing NASH, and some of these likely to progress to cirrhosis with all of its many complication, it is clear that the obesity epidemic may progress to another epidemic, chronic liver disease. Successful means are urgently needed to reduce this possibility.





Chapter 5: Alcoholic Liver Disease

F. Wong



1. Epidemiology

Liver disease is the fourth commonest cause of death in adults between the ages of 20 to 70 years in Canada. Alcohol is still one of the commoner causes of chronic liver disease in this country. Not all those who abuse alcohol develop liver damage. The incidence of cirrhosis amongst alcoholics is approximately 10 to 20%. The mechanism for the predisposition of certain people to develop cirrhosis is still unknown. The amount of alcohol ingested has been shown in epidemiological studies to be the most important factor in determining the development of cirrhosis. Males drinking in excess of 60 gm and females in excess of 40 gm of alcohol per day for 10 years are at a high risk of developing cirrhosis. The alcohol content rather than the type of beverage is important and binge drinking is less injurious to the liver than continued daily drinking. Women are more susceptible to liver damage than men. They are likely to develop cirrhosis at an earlier age, present at a later stage and have more severe liver disease with more complications. Genetics may play a role in the development of alcoholic liver disease. Patterns of alcohol drinking behaviour are inherited. Social factors such as the availability of alcohol and social acceptance of alcohol use can also encourage the liberal use of alcohol, thereby increasing the risk for the development of alcoholic liver disease in susceptible individuals

2. Alcohol Metabolism

Alcohol is metabolized to acetaldehyde by alcohol dehydrogenase in the hepatocyte cytosol, and then to acetate by acetaldehyde dehydrogenase in the mitochondria. Cytochrome P-450 2E1 enzymes also convert alcohol to acetaldehyde. Genetic pleomorphism of these enzyme systems can lead to different rates of alcohol elimination, and contributes to the individual's susceptibility to alcohol damage. Some studies have reported an increased frequency of the gene that encodes for alcohol dehydrogenase in patients with alcoholic liver disease, leading to increased production of acetaldehyde. Alcoholics with decreased acetaldehyde dehydrogenase activity also develop alcoholic liver disease at a lower cumulative intake of alcohol than others. Alcohol has a direct hepatotoxic effect and does not require pre-existing malnutrition, but malnutrition may play a permissive role in producing alcohol hepatotoxicity. There is a threshold of alcohol toxicity beyond which no dietary supplements can offer protection. Obesity may also be an independent risk factor for the development of alcoholic liver disease. Finally, viral hepatitis, whether hepatitis B or hepatitis C infection, appears to play a role in the development of advanced alcoholic liver disease. Patients with alcoholic liver disease and viral hepatitis infection tend to develop their disease at a younger age, have more severe histological features and decreased survival. In addition, the presence of viral hepatitis is a major risk factor for the development of hepatocellular carcinoma in patients with alcoholic cirrhosis.

The spectrum of liver disease covers the relatively benign steatosis to the potentially fatal alcoholic hepatitis and cirrhosis (Figure 1).



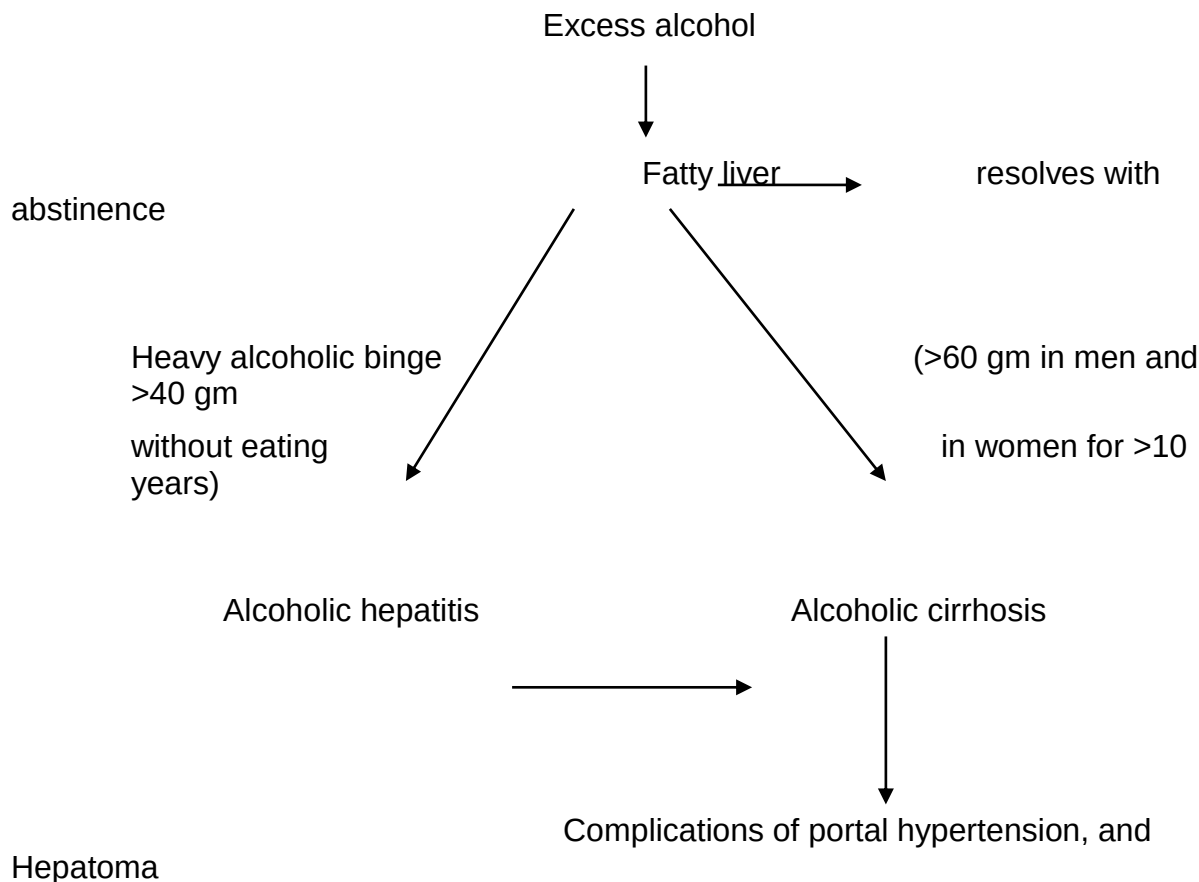


Figure 1. Schematic representation of the progression of the different stages of alcoholic liver disease

3. Alcoholic Fatty Liver

This is the most frequent hepatic abnormality found in alcoholics. It is a toxic manifestation of alcohol ingestion, appearing within three to seven days of excess alcohol intake. Alcohol dehydrogenase and acetaldehyde dehydrogenase cause the reduction of nicotinamide adenine dinucleotide (NAD) to NADH (reduced form of NAD). Metabolic changes associated with ethanol ingestion leads to altered ratio of NAD/NADH, which promotes increased triglyceride synthesis through the inhibition of gluconeogenesis and fatty acid oxidation. There is also impaired lipid secretion by the liver. This results in the accumulation of triglyceride in the hepatocytes, mainly in the terminal hepatic venular zone. In more severe cases, the fatty change may be diffuse. The fat may be macrovesicular (large droplets) or microvesicular (small droplets), which represents more active lipid synthesis by the hepatocytes. Fatty liver may occur alone or be part of the picture of alcoholic hepatitis or cirrhosis.

Clinically, the patient is usually asymptomatic and examination reveals firm smooth hepatomegaly. Occasionally the fatty liver may be so severe that the patient is anorexic, nauseated and has right upper quadrant pain or discomfort. Fatty liver is not specific to alcohol ingestion. The differential diagnoses include obesity, insulin



resistance, hyperlipidemia, malnutrition, and various medications. Attribution of fatty liver to alcohol use therefore requires a detailed and accurate patient history. In the case that the fatty liver is related to excess alcohol intake, this usually follows a prolonged heavy alcoholic binge. Liver function tests are frequently normal, although the γ -GT is invariably elevated whilst the aminotransferases and alkaline phosphatase may be slightly increased. The patient is never jaundiced and hepatic synthetic function (albumin and International Normalized Ratio or INR) is preserved. In the absence of a super-imposed hepatic process, stigmata of chronic liver disease such as spider angiomas, ascites, or asterixis should be absent. A fatty liver is usually detected by ultrasound. Liver biopsy is required to make a definitive diagnosis and to exclude the presence of steatohepatitis. When fatty liver is not associated with alcoholic hepatitis, the prognosis is excellent. Complete abstinence from alcohol and a nutritious diet will lead to disappearance of the fat over four to six weeks.

4. Alcoholic Hepatitis

Alcoholic hepatitis may occur separately or in combination with cirrhosis. There are all grades of severity. It is a condition characterized by liver cell necrosis and inflammatory reaction. Pathophysiologically, chronic alcohol exposure activates hepatic macrophages, which then produce tumor necrosis factor- α (TNF- α). TNF- α induces mitochondria to increase the production of reactive oxygen species. This oxidative stress promotes hepatocyte necrosis and apoptosis, which is exaggerated in the alcoholic individual who is deficient in antioxidants such as glutathione and vitamin E. Free radicals then initiate lipid peroxidation, which causes inflammation and fibrosis. Inflammation is also incited by acetaldehyde that, when bound covalently to cellular proteins, forms adducts that are antigenic. Alcohol is known to cause an exaggerated gradient of hypoxia from the portal vein to the central vein, suggesting that the hypoxia induced by chronic alcohol use may also contribute to hepatic damage.

Histologically, hepatocytes are swollen due to an increase in intracellular water secondary to increase in cytosolic proteins (Table 1). Steatosis, often of the macrovesicular type, is present. Alcoholic hyaline or Mallory bodies are purplish red intra-cytoplasmic inclusions consisting of clumped organelles, intermediate microfilaments (Figure 2). Polymorphs are seen surrounding Mallory containing cells and also within damaged hepatocytes. Neither fatty infiltration nor Mallory bodies are specific for alcoholic hepatitis nor are they necessary for diagnosis. Collagen deposition is usually present. It is maximal in zone 3 and extends in a perisinusoidal pattern to enclose hepatocytes, giving it a "chicken wiring" effect. Changes in the portal triad are inconspicuous. Marked portal inflammation suggests an associated viral hepatitis such as hepatitis C, whereas fibrosis suggests complicating chronic hepatitis (Table 2). When the acute inflammation settles, a varying degree of fibrosis is seen which may eventually lead to cirrhosis.



Table 1. Histopathological changes of Alcoholic Hepatitis

-
- Perisinusoidal—maximal changes
 - Hepatocytes—swollen (diffuse, pericentral changes)
 - Intrahepatocyte inclusions—Mallory bodies
 - Fat—macrovesicular steatosis (zone 3)
 - Perihepatocyte—polymorphs
 - Collagen (zone 3)—perisinusoidal pattern to enclose hepatocytes (“chicken wiring” affect)
 - Portal—minimal changes
-

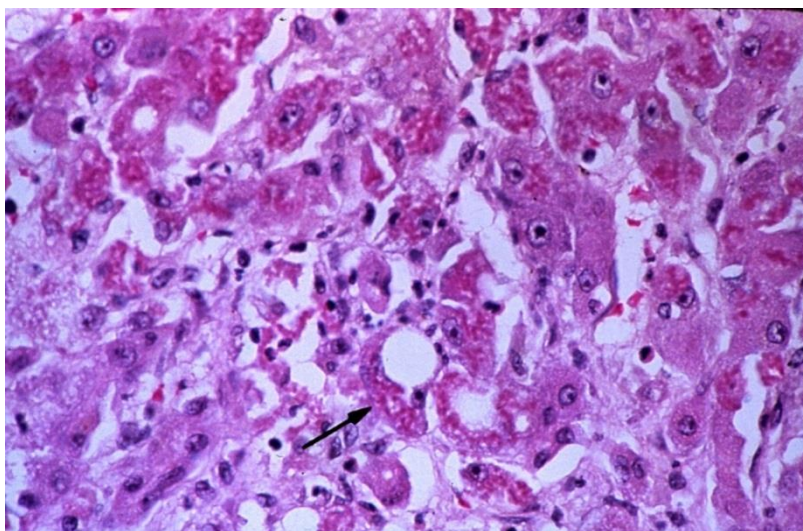


Figure 2. Photomicrograph showing Mallory bodies (arrow) and inflammatory cells, especially polymorphs, in a patient with acute alcoholic hepatitis.

Clinically, mild cases of alcoholic hepatitis are only recognized on liver biopsy in patients who present with a history of alcohol abuse and abnormal liver function tests. In the moderately severe case, the patient is usually malnourished and presents with a two to three week prodrome of fatigue, abdominal pain, anorexia, nausea and weight loss. Clinical signs include a fever of $<40^{\circ}\text{C}$, jaundice and tender hepatomegaly. In the most severe case, which usually follows a period of heavy drinking without eating, the patient is gravely ill with fever, marked jaundice, ascites, evidence of a hyperdynamic circulation, such as systemic hypotension, and tachycardia. Florid palmer erythema and spider nevi are present with or without gynecomastia. Hepatic decompensation can be precipitated by vomiting, diarrhea or intercurrent infection leading to encephalopathy. Hypoglycemia occurs often and can precipitate coma. Gastrointestinal bleeding is common, due to the combination of a bleeding tendency and portal hypertension. Signs of malnutrition and vitamin deficiencies are frequently present. When alcoholic hepatitis is severe, the differential diagnoses include autoimmune hepatitis, acute viral hepatitis,



acute Budd-Chiari syndrome, acute manifestation of Wilson's disease in a younger individual, severe drug-induced liver injury, or a combination of alcohol and acetaminophen. Acetaminophen is a hepatotoxin when taken in large quantity. Alcohol increases the patient's susceptibility to liver damage by acetaminophen due to induction of the metabolizing enzymes and smaller doses of acetaminophen in an alcoholic may precipitate liver failure.

Laboratory abnormalities include elevations of aminotransferases, bilirubin, alkaline phosphatase and γ GT (Table 2). The aminotransferase levels rarely exceed 300U/L, except in association with acetaminophen ingestion, with the AST/ALT ratio >2. Hyperbilirubinemia can be quite marked, with levels reaching 300 to 500 μ mol/L, and is a reflection of the severity of the illness. The increase in γ GT is proportionally greater than that of alkaline phosphatase. There is also mild anemia, leukocytosis of up to 20 to 25 $\times 10^9$ /L, and prolongation of the INR, which does not respond to vitamin K. The serum albumin falls. Serum IgA is markedly increased with IgG and IgM raised to a lesser extent.

Table 2- Laboratory abnormalities commonly seen in persons with alcoholic hepatitis.

-
- Hematology
 - Macrocytic anemia (increased MCV)
 - $\uparrow$ WBC
 - $\downarrow$ platelets
 - General chemistry
 - $\uparrow$ blood sugar
 - $\uparrow$ uric acid
 - $\uparrow$ triglycerides
 - Ketosis
 - Tests of liver function and injury
 - $\downarrow$ albumin
 - $\uparrow\uparrow$ bilirubin
 - $\uparrow$ INR
 - $\uparrow$ AST/ALT (ratio of 1.5 to 2.5 and total increase <10-fold)
 - $\uparrow\uparrow$ γ GT
 - $\uparrow$ alkaline phosphatase (mild)
 - Others
 - $\uparrow\uparrow$ IgA
 - $\uparrow$ IgG, IgM
-

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; γ GT, γ -glu- tamyltransferase; MCV, mean corpuscular volume.



Modified from: Shah VH. *Mayo Clinic Gastroenterology and Hepatology Board Review* 2008: page 331 with permission.

Patients with acute alcoholic hepatitis often deteriorate during the first few weeks in hospital, with a mortality rate of 20-50%. The condition may take one to six months to resolve even with complete abstinence. Alcoholic hepatitis progresses to cirrhosis in 40% of clinical episodes. Bad prognostic indicators include spontaneous encephalopathy, markedly prolonged INR unresponsive to vitamin K and severe hyperbilirubinemia of greater than 350 μ mol/L. Both the discriminant function (see below) and the model for end-stage liver disease (MELD) score (Appendix 1) can be used to predict short-term mortality in patients with alcoholic hepatitis. Long-term survival in patients with alcoholic hepatitis who discontinue alcohol is significantly better than in those who continue to drink, although it remains considerably below that of an age-matched population. Three-year survival approaches 90% in abstainers, whereas it is less than 70% in active drinkers.

Table 3. Comparison of viral hepatitis and alcoholic hepatitis based on history and physical examination, laboratory tests and liver histology.

	Viral Hepatitis	Alcoholic Hepatitis
➤ History	○ Risk factors	○ Significant alcoholic intake
➤ Physical Examination	○ Mild hepatomegaly ○ Extrahepatic stigmata not prominent	○ Moderate to marked hepatomegaly ○ Flurid stigmata
➤ Laboratory tests	○ AST variable ○ ALT usually > AST	○ AST <3 00 ○ often AST: ALT 2: 1 or more
➤ Liver histology	○ Mononuclear cells ○ Portal tract centered ○ Ground glass cells (HBV) ○ Special stains (HBV) ○ Fat, esp. HCV	○ Polymorphs ○ Pericentral, diffuse ○ Mallory's hyaline ○ Macrovesicular fat

5. Alcoholic Cirrhosis

Established cirrhosis is usually a disease of middle age after the patient has had many years of drinking. Although there may be a history of alcoholic hepatitis, cirrhosis can develop in apparently well-nourished, asymptomatic patients. Occasionally, the patient may present with end-stage liver disease with malnutrition, ascites, encephalopathy and a bleeding tendency. A history of alcohol abuse usually points to the etiology. Clinically, the patient is wasted. There may be bilateral parotid



enlargement, palmer erythema, Dupuytren's contractures and multiple spider nevi. Males develop gynecomastia and small testes. Hepatomegaly is often present, affecting predominantly the left lobe due to marked hypertrophy and there are signs of portal hypertension including splenomegaly, ascites and distended abdominal wall veins. At the late stage, the liver may become shrunken and impalpable. There may be signs of alcohol damage in other organ systems such as peripheral neuropathy and memory loss from cerebral atrophy. Alcoholic cirrhosis is also associated with several renal problems. These include IgA nephropathy, renal tubular acidosis and the development of hepatorenal syndrome. There is an association between viral hepatitis B & C and alcoholic cirrhosis.

The diagnosis of alcoholic cirrhosis rests on finding the classical signs and symptoms of end-stage liver disease in a patient with a history of significant alcohol intake. Liver biopsy is encouraged, especially when the diagnosis is in question, since patients usually under report the amount of alcohol consumed. In addition to confirming the diagnosis, liver biopsy is also useful for ruling out other unsuspected causes of liver disease, better characterizing the extent of the damage, providing prognosis, and guiding therapeutic decision making.

Histologically, the cirrhosis is micronodular. The degree of steatosis is variable and alcoholic hepatitis may or may not be present. Pericellular fibrosis around hepatocytes is widespread. Portal fibrosis contributes to the development of portal hypertension. There may be increased parenchymal iron deposition. When marked, genetic hemochromatosis has to be excluded. With continued cell necrosis and regeneration, the cirrhosis may progress to a macronodular pattern.

Biochemical abnormalities include a low serum albumin, elevated bilirubin and aminotransferases. AST and ALT levels rarely exceed 300U/L and the AST/ALT ratio usually exceeds 2. γ GT is disproportionately raised with recent alcohol ingestion and is a widely used screening test for alcohol abuse. With severe disease, the INR may be prolonged. Portal hypertension results in hypersplenism leading to thrombocytopenia, anemia and leukopenia. Other non-specific serum changes in acute and chronic alcoholics include elevations in uric acid, lactate and triglyceride, as well as reductions in glucose, potassium, phosphate and magnesium.

The prognosis of alcoholic cirrhosis depends on whether the patient can abstain from alcohol, this in turn is related to family support, financial resources and socio-economic state. The presence of hepatitis also influences prognosis. Patients who abstain have a five-year survival rate of 60 to 70%, which falls to 40% in those who continue to drink. Women have a shorter survival than men. Bad prognostic indicators include low serum albumin concentration, increased INR, low hemoglobin, encephalopathy, persistent jaundice and azotemia. Zone 3 fibrosis and perivenular sclerosis are also unfavourable features. Complete abstinence may not improve prognosis when portal hypertension is severe, although at the earlier stage of cirrhosis, the portal pressure may actually fall with abstinence. Hepatocellular carcinoma occurs in 10% of stable cirrhotics and the incidence is higher in patients who also have viral hepatitis infection. This usually develops after a period of abstinence and macronodular cirrhosis is present. Treatment strategies can be instituted if detected early (see below), therefore long-term follow-up and periodic screening is advisable.



5.1. Management

Early recognition of alcoholism is important (Table 4). Physicians should have a high index of suspicion when a patient presents with anorexia, nausea, diarrhea, right upper quadrant tenderness and an elevated γ GT. The most important therapeutic measure is total abstinence from alcohol. As patients can rarely achieve complete and durable abstinence from alcohol without assistance, support groups and regular follow-up is needed to reinforce the need for abstinence. Referral to a drug dependency unit is appropriate. Withdrawal symptoms should be treated with a benzodiazepine. A nutritious well balanced diet with vitamin supplements should be instituted. In general, enteral nutrition is preferable over parenteral supplementation, and protein should be supplied to provide positive nitrogen balance. Nutritional supplementation is generally associated with an improvement in liver test results, but only rarely with a mortality benefit.

Table 4. Treatment of Alcoholic Liver Disease

-
- Early recognition and treatment of alcoholism
 - Complete alcohol abstinence
 - Nutritional support to correct any associated malnutrition
 - Treatment of liver complications—ascites, encephalopathy, esophageal varices
 - Glucocorticosteroids for severe alcoholic hepatitis complicated by hepatic encephalopathy
 - Pentoxifylline—reduces incidence of new-onset type 4 hepatorenal syndrome and 1 month mortality rate
 - No proven use for PTU, anabolic androgenic steroids, hepatotrophic agents (insulin, glucagon)
-

Alcoholic fatty liver responds to alcohol withdrawal and a nutritious diet. The histological changes will revert back to normal in approximately 6 weeks. However, with long-term follow-up, patients with fatty liver disease may develop fibrosis or even cirrhosis as the liver heals. Morphologic features predictive of progression to fibrosis, cirrhosis, or both include severe steatosis, giant mitochondria, and the presence of mixed macrovesicular/ microvesicular steatosis.

Patients with severe alcoholic hepatitis should be admitted to hospital and complications of liver failure treated appropriately. Specific treatments for alcoholic hepatitis include the use of corticosteroid (40 mg/day for 4 weeks and then taper). Recent meta-analyses of thirteen randomized controlled trials showed a significant benefit of steroids for patients with severe alcoholic hepatitis complicated by hepatic encephalopathy (HE). There is reduction of the short-term mortality of about 50% in patients with severe alcoholic hepatitis. A discriminant function of >32 is a predictor of poor prognosis and favorable response to corticosteroid therapy. Discriminant function = $4.6 \times (\text{prothrombin time} - \text{control prothrombin time}) \text{ in seconds} + \text{serum bilirubin in } \mu\text{mol/L} \div 17$. Patients with gastrointestinal hemorrhage, active infection, diabetes and acute pancreatitis tend to do worse with corticosteroid, and therefore should not be



considered for it in the setting of severe alcoholic hepatitis. A liver biopsy is needed to confirm the presence of severe alcoholic hepatitis before corticosteroid administration.

Propylthiouracil has been used to dampen the hepatic hypermetabolic state in alcoholic hepatitis. In one long-term randomized controlled trial, there was a significantly reduced two-year mortality rate in patients who continued to drink moderately. Those who were abstinent from alcohol did not derive any benefits. However, other investigators have not been able to reproduce these positive results. A systematic review of more than 700 patients from six published randomized, controlled trials has failed to show any effect of propylthiouracil on mortality, individual laboratory parameters, liver histology, or liver related complications. Therefore, current evidence cannot support the routine use of propylthiouracil in acute alcoholic hepatitis.

Testosterone and anabolic androgenic steroids have been tried with conflicting results. Intravenous amino acid supplements have been given to the severely protein malnourished with varying degrees of success. Their expense cannot justify their use in every patient with alcoholic hepatitis. Infliximab, an anti-tumor necrosis factor alpha (TNF- α) antibody, theoretically could dampen the inflammatory process in alcoholic hepatitis. Two recent trials showed that the patients with alcoholic hepatitis treated with infliximab had more infectious complications without any benefit in liver function or Maddrey scores. The only randomized controlled study to date has demonstrated a higher probability of death at 2 months in those patients randomized to steroids and infliximab.

Pentoxifylline, an anti-inflammatory agent with anti-TNF- α properties, has been shown in one study to reduce the incidence of new-onset type 1 hepatorenal syndrome and mortality at 1 month. Pentoxifylline is safe and cheap, and could be used despite the lack of a confirmatory study. Insulin and glucagons are both hepatotrophic agents. Their use in alcoholic hepatitis could theoretically improve hepatic regeneration. However, patients treated with both agents have had complications and even deaths from hypoglycemia. Therefore, these agents should not be used except in the setting of a clinical trial.

Finally, it must be stressed that a good nutritional intake is necessary to hasten recovery and improve survival. At 1 year from the time of diagnosis of alcoholic hepatitis, patients with mild malnutrition have a 14% mortality rate, compared with a 76% mortality rate in those with severe malnutrition.

Patients who have established alcoholic cirrhosis need to be monitored for complications of cirrhosis in the same way that any other patient with cirrhosis is being monitored. Periodic assessments should include a surveillance gastroscopy to check for the presence of esophageal varices and prophylactic β -blocker therapy instituted for those with large esophageal varices. The recent advent of a transjugular intrahepatic portosystemic stent shunt (TIPS) has replaced a surgical portocaval shunt as the treatment of choice for uncontrolled bleeding esophageal varices, although the mortality rate is very high in those patients with acute alcoholic hepatitis. Hepatic encephalopathy remains a complication, but usually can be controlled with prophylactic lactulose. Ascites is managed with a low sodium diet and diuretic therapy. Ascites frequently settles down in those patients who abstain from alcohol for more than 6 months. In those patients who ascites becomes refractory to diuretic therapy, TIPS should be



considered as a treatment option, especially in those patients who have been abstinent from alcohol for more than 6 months. Every effort should be made to exclude spontaneous bacterial peritonitis and prevent hepatorenal syndrome, two life threatening complications of ascites. Periodic screening for the presence of hepatoma should be made, since effective treatments are available if hepatomas are detected early. Surgical resection in the stable compensated cirrhotic patient or local ablative therapy such as intra-lesional radiofrequency ablation in the mildly decompensated patient should be offered.

Those patients who are also infected with viral hepatitis B or C should be assessed for their suitability to receive anti-viral therapy. It is preferable that patients totally abstain from alcohol during the treatment period. Untreated viral hepatitis can certainly accelerate the fibrotic process in alcoholic cirrhosis. Colchicine has been tried as an antifibrotic agent to reduce the extent of cirrhosis and hence portal pressure without much success. Liver transplantation is a treatment option for patients with end stage alcoholic cirrhosis and this is the treatment of choice in the patient with decompensated alcoholic cirrhosis. Ethical issues surrounding the use of such a scarce resource for a self inflicted disease still need to be settled, especially when it relates to liver transplantation for patients who have active alcoholic hepatitis. In the centres that transplant alcoholic cirrhosis, the results are comparable to those in patients with other forms of cirrhosis.

Appendix 1

MELD (Model for End Stage-Liver Disease) Score

MELD Score = $[0.957 \times \log(\text{serum creatinine in mg/dL}) + 0.378 \times \log(\text{serum bilirubin in mg/dL}) + 1.120 \times \log(\text{INR}) + 0.643] \times 10$

If patient is receiving dialysis, the serum creatinine is set to 4.0

Web link: www.mdcalc.com/meld-score-model-for-end-stage-liver-disease-12-and-older





Chapter 6: Autoimmune Hepatitis

A. J. Montano-Loza



1. Introduction

Autoimmune hepatitis (AIH) is a disease characterized by chronic inflammation of the liver, interface hepatitis on histologic examination, hypergammaglobulinemia, and production of autoantibodies. AIH results from the development of an immune response against normal self-antigens that disrupt the immune regulatory system (Krawitt 2006). This disease has a global occurrence, and the prevalence among Caucasian northern Europeans is 17 cases per 106 persons per year. In North America the frequency of AIH among patients with chronic liver disease is between 11% and 23% (Boberg 2002).

Two types of AIH are recognized based, on serological markers and clinical phenotypes. Type 1 AIH is the most common form worldwide, constituting 80% of all cases. It is characterized by the presence of antinuclear antibodies (ANA) and/or smooth muscle antibodies (SMA). Eighty percent of patients are female, and occurs as commonly across all age ranges. Approximately, 40% of affected individuals have concurrent immune diseases, mainly autoimmune thyroiditis, synovitis or ulcerative colitis. Type 2 AIH is characterized by the presence of antibodies to liver/kidney microsome type 1 (anti-LKM1). This disease occurs mainly in children, and concurrent immune disease are also common, especially type 1 diabetes mellitus, vitiligo, and autoimmune thyroiditis (Manns 2010).

2. Diagnosis

Early symptoms of AIH are fatigue and arthralgia, but up to a third of patients are asymptomatic at diagnosis. Acute severe or even fulminant AIH is characterized by newly developed, severe inflammation in the liver, or a spontaneous exacerbation of a previously unsuspected chronic disease. AIH is typically diagnosed by demonstrating the presence of smooth muscle antibodies (SMA), antinuclear antibodies (ANA), or antibodies to liver-kidney microsome (anti-LKM) type 1 in patients in whom other diagnoses have been excluded (Czaja 2010).

3. Histologic Features

Liver biopsy is recommended to establish the diagnosis of AIH, and to guide treatment. Figure 1. illustrates a normal portal triad and the limiting plate. Interface hepatitis is defined as “portal inflammation crossing the limiting plate” (the first line of hepatocytes surrounding the portal triad), and is the histological hallmark of AIH. Lobular lymphoplasmacytic infiltration is also typical (Figure 2) but neither histological finding is specific for AIH, the absence of plasma cells in the infiltrate does not exclude the diagnosis.



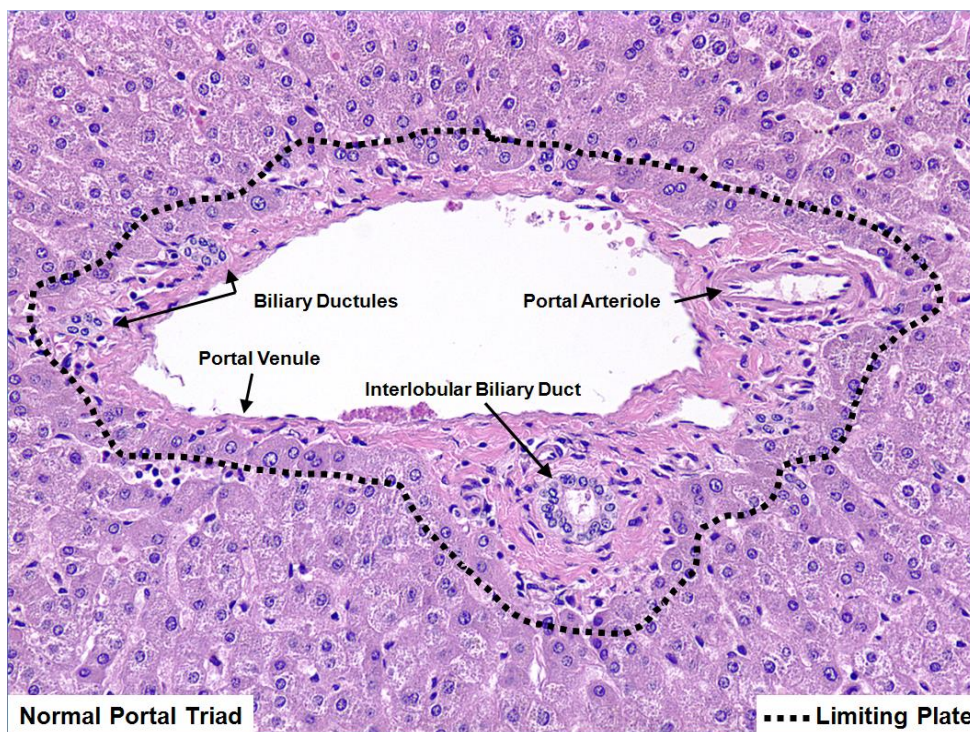


Figure 1. Normal portal triad and the limitant plate with delimitation of the first line of hepatocytes that surround the portal triad, denominated limiting plate.

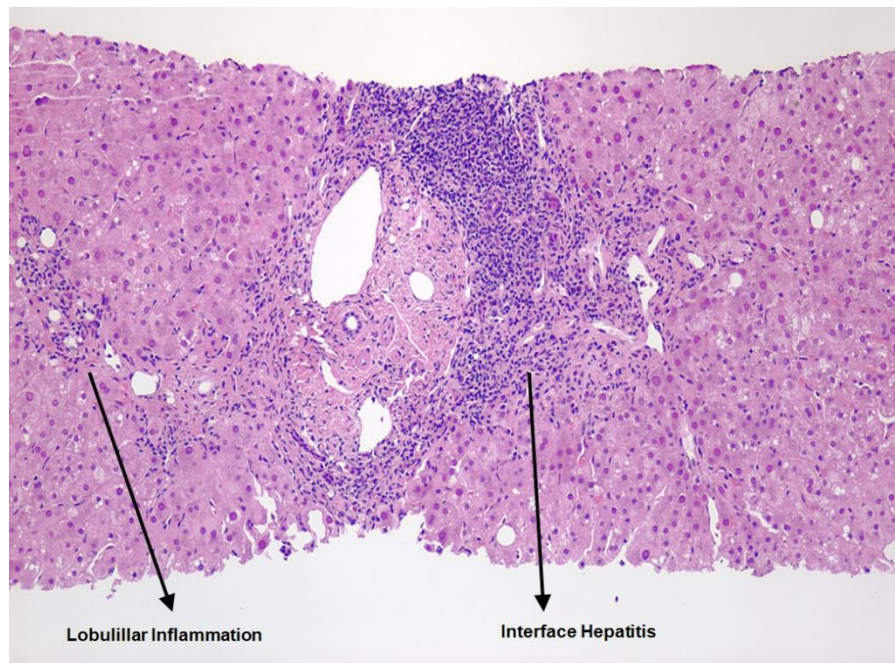


Figure 2. Characteristic liver biopsy changes in AIH, including interface hepatitis and lobular inflammation (Lymphoplasmacytic Infiltrate).



Two diagnostic scoring systems (a comprehensive system and a simplified system) have been developed by the International AIH Group that aid in the diagnosis of difficult cases. The simplified scoring system is easier to use in the clinic and assesses only 4 factors (Table 1) (Hennes 2008).

Table 1. Simplified Diagnostic Criteria for Autoimmune Hepatitis (AIH)

Variable	Cutoff	Points
○ ANA or SMA	$\geq 1:40$	1
○ ANA or SMA or LKM1	$\geq 1:80$ $\geq 1:40$	2*
○ IgG	>Upper normal limit	1
	>1.10 times upper normal limit	2
○ Liver Histology (evidence of hepatitis is a necessary condition)	Compatible with AIH (chronic hepatitis with lymphocytic infiltrate, and no other characteristic findings)	1
	Typical AIH (interface hepatitis, portal lymphocytic or lymphoplasmacytic infiltrate through the lobule, [†] emperipolesis and rosettes of hepatocytes)	2
➤ Absence of viral hepatitis	Yes	2
		≥ 6 : probable AIH ≥ 7 : definite AIH

*Addition of points achieved for all autoantibodies (maximum, 2 points).

Abbreviations: AIH= autoimmune hepatitis; ANA= antinuclear antibodies; SMA= smooth muscle antibodies.

[†]Emperipolesis: Active penetration by one cell into a larger cell, in this case when a lymphocyte penetrates a hepatocyte. (Adapted from Hennes 2008).

4. Treatment: Endpoints, Outcomes, and Liver Transplantation

The indications for treatment are based on the risk factors for disease progression, and for practical proposes can be classified as absolute, relative or uncertain indications, and no indications for treatment (Table 2) (Manns 2010). The relative contraindications for the use of prednisone or combination therapy of prednisone plus azathioprine in AIH are given Table 4. The preferred treatment schedule in adults with severe AIH is prednisone (prednisolone can be used in equivalent doses) in combination with azathioprine (50 mg/day generally used in North



America and 1-2 mg/kg/day in Europe) (Table 2). Prednisone alone in a higher dose is as effective as the combination regimen, but it is associated with a greater frequency of drug-related side effects. The dose of prednisone may be slowly tapered to the lowest individual level sufficient to maintain remission from prednisone 20 mg daily onwards, reduction should be done at the rate of 5 mg every week, until 10 mg per day is being given; an even further reduction by 2.5 mg per week may be used, down to 5 mg daily (Montano-Loza 2007).

Table 2. Treatment Indications for Adult Patients with Autoimmune Hepatitis (AIH)

Findings	Indications		
	Absolute	Relative	None
➤ Clinical	○ Incapacitating symptoms ○ Relentless clinical progression ○ Fulminant presentation	○ Mild or no symptoms	○ Asymptomatic with mild laboratory changes ○ Previous intolerance of prednisone and/or azathioprine
➤ Laboratory	○ AST≥10-fold normal ○ AST≥5-fold normal and γ-globulin≥2-fold normal	○ AST 3-9 fold normal ○ AST≥5-fold normal and γ-globulin<2-fold normal	○ AST<3-fold normal ○ Severe cytopenias ○ (White blood cell count below $2.5 \times 10^9/L$ or platelet count below $50 \times 10^9/L$)
➤ Histologic	○ Bridging necrosis ○ Multiacinar necrosis	○ Interface hepatitis	○ Inactive cirrhosis ○ Focal interface hepatitis ○ Portal hepatitis ○ Decompensated inactive cirrhosis with variceal bleeding or hepatic encephalopathy

Abbreviation: AST, serum aspartate aminotransferase level.
(Adapted from Montano-Loza 2007).

Therapy should continue until remission, treatment failure, incomplete response, or drug toxicity. The average duration of treatment required for disappearance of symptoms, normalization of laboratory indices, and histological resolution is 22 months. The ideal end point of therapy in patients with AIH is resolution of all clinical, laboratory, and histological manifestations of disease activity. Approximately 80% of treated patients achieve remission criteria within 3 years. The life expectancies of treated patients exceed 85% at 10-years, and 74% at 20 years.

Liver transplantation is an effective treatment for the decompensated patient with AIH. Patient and graft survival after liver transplantation ranges from 83% to 92%. The



actuarial 10-year survival of AIH after liver transplantation is around 75%. Recurrence of AIH in the transplanted liver occurs in 20% of patients after 5 years, especially in individuals receiving inadequate immune suppression. Adjustments in the immunosuppressive regimen are usually able to suppress recurrent AIH, and infrequently cirrhosis or graft failure occurs (Montano-Loza 2009).

Table 3. Treatment Schedules for Adults Patients with Autoimmune Hepatitis Recommended by the AASLD

Weeks Administered	Combination Therapy*			Prednisone Therapy Prednisone (mg daily)
	Prednisone (mg daily)	Azathioprine NA EU (mg daily) (mg/kg/day)		
1	30	50	1-2	60
1	20	50	1-2	40
2	15	50	1-2	30
Maintenance until end point Relative Contraindications	10	50	1-2	20

Abbreviations: AASLD: American Association for the Study of the Liver Diseases. NA: North America; EU: Europe. (*Adapted from Montano-Loza AJ 2007*).

*preferred treatment schedule for AIH.

Table 4. Relative contraindications of Prednisone or combination therapy of Prednisone plus Azathioprine for adult patients with autoimmune Hepatitis

- Cytopenias
- Pregnancy
- Active malignancy
- Short course (less than 6 months)
- Thiopurine methyltransferase deficiency
- Post-menopausal state
- Osteoporosis
- Diabetes
- Hypertension
- Obesity
- Emotional lability



Chapter 7: Primary Biliary Cirrhosis

A. L. Mason and B. Sis



1. Epidemiology

The term, primary biliary cirrhosis (PBC) was coined in 1949 but a similar condition was first described by Addison and Gull a hundred years prior in 1851. The terminology is not completely accurate, however, as the histological appearance is typically a chronic non-suppurative cholangitis (Figure 1), whereas only a proportion of patients develop cirrhosis. PBC is characterized by granulomatous destruction of 30 to 80 μm interlobular bile ducts that processes through four stages to cirrhosis. It is considered a pluriglandular disease as other organs are affected, such as the pancreas, salivary and lachrymal glands.

PBC has a worldwide distribution and has been found in all races. The prevalence of PBC ranges from 1:2,500 to 1:100,000 with an increasing prevalence moving North from the equator (Table 1).

Table 1. Demography of PBC

-
- Worldwide prevalence ranges from 1 to 2,500 to more than 1 in 100,000
 - Highest prevalence in Northern Europe and Canada
 - As high as 1 in 500 in middle aged women
 - Disease rarely reported in Sub-Saharan Africa.
 - Ten fold increased prevalence of PBC with a first degree relative with PBC
 - More prevalent in mono than dizygotic twins
 - Prevalence increases with migration from low to high prevalence areas
 - Clustering of disease in specific regions
-

In Canada, up to 1 in 700 middle-aged women develop PBC and in Northern Europe it is reported to be approximately 1 in 500 in specific locations. In British Columbia, there is an increased prevalence of disease in coastal First Nation populations, who are 3 times as likely to undergo liver transplantation for PBC compared to other Canadians. There also appears to be geographical clustering of disease in Europe and in one instance, this was related to specific water supply. It has been suggested that there is an increased prevalence of PBC near toxic waste sites suggesting a role for xenobiotics in the disease process. Generally speaking, PBC is predominantly found in the middle class population with a higher income and education status in North America, making it less likely that pollution plays a major role on disease.

Like other autoimmune disorders, PBC predominantly occurs in women with a ratio of 9 females for every male with disease. The reason for the female predilection is unknown but hormone replacement and younger age of first pregnancy are associated with increased risk of disease. These data are in keeping with the biology of one of the environmental agents linked with PBC, namely a betaretrovirus that is activated by pregnancy and female hormones in an animal model. Lesions in the X chromosome have been related to PBC as well. Notably, a higher frequency of monosomy secondary to X chromosome inactivation is found in PBC patients in general and a high prevalence of PBC has been reported in patients with Turner's syndrome.



2. Etiology

2.1. Autoimmune factors

PBC is considered an autoimmune disease because approximately 95% of patients make the diagnostic anti-mitochondrial antibodies (AMA) to pyruvate dehydrogenase E2 protein, referred to as the M2 antigen. The reason why patients make AMA is unknown but a protein resembling pyruvate dehydrogenase E2 is aberrantly expressed on the cell surface of diseased biliary epithelium and in the macrophage/monocyte population in lymphoid tissues. Normally these proteins sequestered in the inner mitochondria and are therefore not encountered by the immune system. It is thought that the exposure of the pyruvate dehydrogenase E2 complex proteins may be one of the triggers that induce a loss of tolerance to mitochondrial proteins in the setting of an inflammatory response to diseased biliary epithelium. While the mechanism that misdirects the mitochondrial proteins to the cell surface is poorly understood, there are some exciting studies that suggest an environmental factor can elicit this disease specific mitochondrial phenotype. For example, co-culture studies have shown that a transmissible agent in the lymph nodes of patients with PBC can trigger a similar mitochondrial phenotype of PBC with increased and aberrant expression of mitochondrial antigens in healthy biliary epithelium.

There are several factors that suggest an autoimmune etiology of PBC. These include the formation of a humoral and cellular immune response to self-proteins as well as the association of PBC with other autoimmune disease. For example, patients with PBC have a higher risk of developing systemic lupus erythematosus, autoimmune thyroid disease, Raynaud syndrome, Sjögren syndrome and scleroderma (Table 2). There is also an increased risk of family members developing PBC and the related autoimmune diseases. However, the role that autoimmunity plays in causing bile duct damage is unknown (Table 3). Although of diagnostic utility, AMA do not appear to directly cause PBC, as patients without AMA have comparable disease, the titers do not correlate with activity and some AMA positive individuals have no disease. Furthermore experimental criteria for the establishment of PBC as an autoimmune disease have not been met as animal models inoculated with adjuvant and the mitochondrial antigen merely develop AMA without biliary disease. With regard to disease management, the autoimmune model has not served well for PBC in contrast to other disorders. In patients with autoimmune hepatitis, for example, the use of immunosuppression improves morbidity and mortality, whereas the use of specific immunosuppressive therapies for PBC patients is not recommended due to untoward toxicity and lack of efficacy.



Table 2. Diseases Associated with PBC (Gershwin 2005)

-
- Raynaud's Disease (12%)
 - Autoimmune thyroid disease (9%)
 - Sjögren Syndrome (10%)
 - Keratoconjunctivitis sicca: > 80%
 - Systemic Lupus Erythematosus (3%)
 - Scleroderma (2%)
 - History of
 - UTI (59%) vs. controls (52%)
 - Cholecystectomy (27%) vs. controls (17%)
 - Urinary tract infection (59%) vs. controls (52%)
-

Note: The approximate frequency of associations is shown in brackets.

Table 3. Factors indicative of an infectious versus autoimmune etiology of PBC

-
- Autoimmune:
 - Personal history and family history of other autoimmune disorders
 - Demonstrable cellular and humoral autoimmune response to mitochondrial and nuclear antigens but
 - Patients without AMA have similar disease process
 - Some patients with AMA do not develop disease
 - Immunosuppression therapy of little benefit
 - Infectious:
 - Spouses, unrelated family members and care providers can develop PBC
 - PBC recurs in up to a third of patients after liver transplantation
 - Infectious agents in PBC patients' lymph nodes have been shown to trigger the mitochondrial phenotype of disease *in vitro*
-

2.2. Genetic factors

PBC is considered a complex disease as multiple factors impact on the development of disease. It is currently thought that an environmental agent triggers disease in genetically susceptible individuals. The disease is more frequently observed in monozygotic as compared to dizygotic twins and there is a ten fold increased prevalence of PBC in first degree relatives. Multiple studies have linked specific innate and adaptive immune system genes with PBC (Table 4). Three genome wide association studies involving more than 5,000 patients have confirmed an important association with the HLA class II region and the interleukin-12 (IL-12) cytokine axis with PBC. Of note, many of these genes associated with PBC have been found to confer risk to other autoimmune diseases as well (Table 4). These data suggest that PBC patients may be predisposed to a global disturbance in host response to microbial infections.



Table 4. Genetic Factors associated with PBC and other autoimmune disorders

-
- HLA class II region [DR, DQ]
 - Innate immune system
 - *MBL* (mannose-binding lectin) – receptor for bacteria, viruses and parasites
 - *VDR* (vitamin D receptor) – associated with Grave's disease and susceptibility to mycobacteria tuberculosis
 - *NRAMP-1* (natural resistance-associated macrophage protein 1) – associated with resistance to bacterial and other infections
 - *C4*Q0, C4B*2* – (Complement 4) - associated with autoimmune hepatitis
 - *IRF5* (interferon regulatory factor 5) – associated with SLE, IBD, RA
 - Adaptive immune system
 - *IL-12, IL-12 receptor* and *STAT4* (Cytokine axis stimulating T lymphocytes and natural killer cells to produce tumor necrosis factor α and interferon γ)-*STAT4* associated with SLE
 - *CTLA-4* (Cytotoxic T-lymphocyte associated antigen 4) – associated with Celiac disease, type 1 diabetes
 - *SPIB* (B-cell receptor signaling)
 - *IKZF3* (regulates B cell activation) - associated with a lupus-like syndrome.
 - *MMEL1* (membrane metallo-endopeptidase-like 1) - associated with RA and Celiac disease
-

2.3. Environmental factors

Spouses, unrelated family members and care providers have been reported to develop PBC, implicating environmental factors in disease. Moreover, migration studies show that children develop the relative incidence of their adopted host country. Observations from liver transplantation suggest that a transmissible factor is associated with the development of PBC. While 70% of recipients continue to have AMA in serum following transplantation, histological evidence for recurrent PBC is observed in up to 30% with immune destruction of bile ducts 10 years after liver transplant. Indeed, more potent immunosuppressive regimens accelerate the onset and severity of recurrent disease.

There is a controversy surrounding environmental agents that impact on the disease process. Several bacteria, xenobiotics and a betaretrovirus have been implicated in the etiology and pathogenesis of PBC but there is little direct evidence that any of these environmental factors causes PBC at this time. Cigarette smoking is the only xenobiotic clearly associated with PBC, albeit in a non-etiological role. Smoking cigarettes aggravates PBC, as the cumulative number of cigarette packs smoked is associated with advanced histological disease; however, patients with PBC tend to smoke less cigarettes and drink less alcohol as compared to the general population.



Patients with PBC are also more likely to suffer from recurrent urinary tract infection. Many bacteria have evolutionary conserved pyruvate dehydrogenase proteins that closely resemble mammalian mitochondrial proteins. As a result, it has been suggested that bacteria trigger AMA production by molecular mimicry. However, this mechanism has not been convincingly demonstrated in patients with PBC or any other human autoimmune disorder for that matter.

The identification of a betaretrovirus in patients with PBC is controversial. Two groups have been unable to confirm the preliminary findings in liver samples using different methods and the association is questionable because the virus is mainly detected in the lymphoid system. The connection of betaretrovirus with PBC is interesting because infection is associated with aberrant pyruvate dehydrogenase E2 protein expression. For example, the betaretrovirus is detected in lymph nodes of PBC patients in cells with the abnormal mitochondrial protein distribution. In addition, co-culture studies have shown that betaretrovirus can trigger the mitochondrial phenotype in healthy biliary epithelium *in vitro*.

3. Diagnosis

The diagnosis of PBC is usually established by evaluation of patients with elevated alkaline phosphatase and γ -glutamyl transferase for evidence of serum AMA reactive to M2 (Table 5). AMA are highly specific for PBC but are rarely detected in patients with SLE as well. A proportion of patients develop elevated serum IgM levels and make anti-nuclear antibodies (ANA). The ANA may be predictive of prognosis. For example, 25% of PBC patients make ANA that display a nuclear rim pattern with immunofluorescence; these antibodies react to components of the nuclear envelope and pore complex, such as Gp210. Detection of ANA to Gp210 have been consistently associated with worse prognosis and liver failure. Anti-centromere antibodies are usually found in patients with the limited cutaneous disease associated with systemic sclerosis. A variable 10%-35% of patients with PBC reportedly make anti-centromere antibodies as well, which are associated with development of CREST syndrome as well as progressive liver disease.



Table 5. Presentation and diagnostic features of PBC

-
- Elevated alkaline phosphatase (screening)
 - Symptom complex:
 - Fatigue
 - Pruritus
 - Sicca syndrome
 - Jaundice
 - Anti-mitochondrial antibody to M2, increased serum IgM and ANA
 - Liver biopsy evidence of non-suppurative granulomatous cholangitis
 - Lack of extra-hepatic disease by cholangiography
 - Differential diagnoses
 - Primary sclerosing cholangitis
 - Pericholangitis (small duct disease)
 - Sarcoidosis
 - Non-inflammatory idiopathic adulthood ductopenia
 - Transplant related ductopenia
 - Acute cellular rejection
 - Graft versus host disease
-

Liver biopsy plays less of a role in diagnosis of PBC now that specific AMA to M2 are readily available and MRCP can effectively rule out large bile duct disease. The histological appearance of granulomatous destruction of bile ducts (Figure 1) is highly suggestive of PBC but may rarely be seen in patients with viral hepatitis, primary sclerosing cholangitis or autoimmune hepatitis. The liver biopsy can also be helpful in management of disease with atypical presentation, such as AMA negative patients, or unusual biochemical profiles suggestive of a hepatitis predominant presentation with elevated serum aminotransferase levels greater than 5 times the upper limit of normal. Histological stage is predictive of survival in PBC but it should be remembered that different histological stages can be observed in the same liver (Table 1).



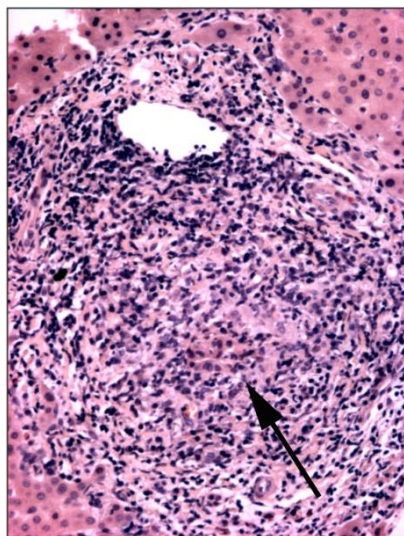


Figure 1. PBC liver biopsy showing granulomatous destruction of an interlobular bile duct (arrow).

An anatomical assessment of the liver is necessary with ultrasound or other modality and a cholangiogram with MRCP should be entertained if the diagnosis of PBC is uncertain. As discussed, the liver biopsy is necessary for establishing diagnosis of PBC in patients that lack AMA. AMA negative PBC used to be referred to as autoimmune cholangitis but now is thought to be in a diagnostic continuum with PBC. Patients presenting with the so-called “overlap syndrome” have features of both autoimmune hepatitis with markedly elevated serum aminotransferase levels and PBC. As PBC is an exclusion criteria for autoimmune hepatitis by definition, it is preferable to consider these patients as having a *forme fruste* or “hepatitis predominant” of PBC, as they usually end up with ductopenia and may also have the mitochondrial phenotype of PBC if tested. It is notable that hepatitis component may occur at presentation or remotely after diagnosis of PBC but an important diagnosis to make for management of the hepatitis component.

The differential diagnosis of PBC includes primary sclerosing cholangitis, which can be diagnosed by MRCP and pericholangitis associated with inflammatory bowel disease diagnosed by liver biopsy. Patients with sarcoidosis usually have parenchymal granuloma on biopsy and extrahepatic disease; however, the classical granulomatous destruction of bile ducts has been reported in a proportion of patients with sarcoid. The only other inflammatory ductopenic disorders of adulthood that share a histological similarity to PBC are acute cellular rejection and graft versus host disease. Otherwise, the idiopathic adulthood ductopenia syndromes lacking inflammatory disease have been reported in clusters and inbred populations attributable to genetic defects, as reported with the biliary transporter *ABCB4* gene linked with progressive familial intrahepatic cholestasis, for example.



4. Clinical presentation and management

Over the last 20 years, PBC has been diagnosed earlier in the clinical course and up to 50% of patients are asymptomatic. As the disease progresses, fatigue occurs in up to 80% of patients. Although low energy is a feature of many liver diseases, patients with PBC appear to experience additional problems such as exercise induced acidosis, autonomic neuropathy and cardiomyopathy. Pruritis occurs in a range of 20% to 70% of patients with PBC and the severity may diminish over time. Sicca syndrome with either dry eyes or dry mouth is also common. Patients with PBC and CREST may suffer from Raynaud syndrome, cutaneous calcinosis, esophageal reflux and dysphagia.

Clinical trials with methotrexate, colchicine, prednisone and other immunosuppressive agents either lacked efficacy or showed undue toxicity. Therefore, PBC specific treatment is geared towards the pathophysiology of disease, where the progressive loss of bile ducts leads to accumulation of bile within the liver causing intra-hepatic damage. Accordingly, ursodeoxycholic acid has proven helpful as a water-soluble bile salt that acts as a choleric to increase excretion of bile from the liver. Prior to the advent of UDCA therapy, the probability of progression to cirrhosis over 4 years with stage 1, stage 2 and stage 3 disease on initial biopsy was 31%, 50%, and 68%, respectively. Therefore, the average life expectancy at that time was approximately 12 years. With UDCA treatment, one third of patients normalize their liver function tests and a similar proportion develops sufficient benefit to avoid progression to liver failure. Survival rates with UDCA treatment have improved considerably and are estimated to be 85% at 10 years and 65% at 20 years.

Over a period of 15 to 20 years, the gradual loss of bile ducts results in fibrosis and then biliary cirrhosis. Variants of this clinical picture occur with severe ductopenia and repaid onset of marked cholestasis in 5% to 10% of patients. Another scenario occurs in a subgroup of PBC patients with features consistent with autoimmune hepatitis. In this case, patients experience ALT levels greater than 5-fold elevation of the upper limit of normal and have evidence of interface hepatitis on liver biopsy. Patients with this hepatitis predominant PBC have a worse prognosis compared to those with a typical course of PBC. They are an important subgroup to identify, as the hepatitis component may be responsive to immunosuppressive treatment.

Other management of PBC is directed towards symptomatic relief and prevention of other diseases as outlined on Table 7. Cholestyramine is the first line of treatment for pruritis but this should be taken at a 4-hour interval from UDCA therapy. Other measures such as opiate antagonists or rifampin are of help to patients that do not respond to cholestyramine. Furthermore, patients with severe pruritis may be candidates for plasmaphoresis or nasobiliary drainage. All patients with PBC are encouraged to take multivitamins, additional vitamin D and calcium for osteopenia.



Regular bone scans are necessary to identify patients with progressive bone disease, which should be treated with alendronate 70mg per week. Statins are well tolerated and should be given to those with hypercholesterolemia.

PBC patients with cirrhosis should be screened for esophageal varices and hepatocellular carcinoma and those with progressive PBC and liver failure should be worked up for liver transplantation. Patients with PBC account for 10% of patients requiring liver transplantation in Canada and their outcomes are excellent. Even though disease may recur in up to 30% of patients after 10 years, this does not appear to have a demonstrable effect on mortality.

Table 6. Management of PBC

-
- Licensed therapy
 - UDCA 13-15mg/kg

 - Anti-pruritic agents
 - Cholestyramine 4-8g BID, PRN
 - Rifampin 150-300mg BID, (potentially hepatotoxic)
 - Naltrexone 12.5mg slowly increased to 50mg/day, (potentially hepatotoxic)
 - Sertraline 75-100mg
 - Anti-histamines, (may cause worsening of sicca syndrome)

 - Prevention of vitamin deficiency
 - Vitamin D 1,000 – 2,000 IU and Calcium 1-1.5g
 - Multi-vitamin

 - Sicca syndrome
 - Artificial tears
 - Cyclosporine ophthalmic emulsion

 - Hypercholesterolemia
 - Statins
 - Fenofibrate

 - Liver failure
 - Liver transplantation
-



Chapter 8: Hemochromatosis and other Hepatic
Iron-Storage Disorders

P. C. Adams



1. Definition

Hemochromatosis is an iron-storage disorder in which there is an inappropriate increase in the absorption of iron from the gut. This leads to iron deposition in various organs with eventual impairment, especially of the liver, pancreas, heart and pituitary. The term hemochromatosis is preferred for genetic hemochromatosis with other diseases associated with iron overload, referred to as secondary iron overload.

2. Genetics

The gene for hemochromatosis (*HFE*) on chromosome 6 was discovered in 1996. The *HFE* protein is similar to a MHC class-I protein. A genetic test for hemochromatosis has demonstrated that more than 90% of typical hemochromatosis patients have a C282Y mutation of the *HFE* gene. The presence of a single mutation in most patients is in marked contrast to other genetic diseases in which multiple mutations were discovered (cystic fibrosis, Wilson disease, alpha-1-antitrypsin deficiency). The C282Y mutation creates a conformational change in the *HFE* protein which normally interacts with the transferrin receptor 1 and 2, bone morphogenic protein 6, hemojuvelin and hepcidin to regulate iron uptake.

A second minor mutation, H63D, was also described in the original report. Hemochromatosis is one of the most common genetic diseases, inherited as an autosomal recessive trait affecting one in 200 of the Caucasian population. Since genetic testing has been introduced, an increasing number of homozygotes have been described without iron overload. This incomplete penetrance of the gene may explain the discrepancy between the high prevalence in genetic studies and the clinical impression that hemochromatosis is an uncommon condition.

3. Clinical Manifestations

The homozygote may have continued iron accumulation leading to target organ damage. In hemochromatosis, the absorption of iron is inappropriate to the needs of the body, resulting in absorption of 4 mg/day or more. In advanced disease, the total body iron accumulation may be 40-60 g.

Most patients are asymptomatic until the 5th or 6th decade, at which time they can present with non-specific symptoms of arthritis, diabetes, fatigue or hepatomegaly (Table 1). Other symptoms include pigmentation of the skin (melanin deposition), impotence and dyspnea secondary to congestive heart failure. The classic triad of skin pigmentation, diabetes and liver disease (bronze diabetes) occurs in a minority of patients and is a late stage of the disease.



Table 1. Presentation of the Patient with Hemochromatosis

-
- Family History
 - Chronic Liver Disease
 - Hepatocellular Cancer
 - Non-specific
 - Pigmentation of skin
 - Impotence
 - Dyspnea (secondary to CHF)
 - Diabetes
-

Abbreviation: CHF, congestive heart failure

The attribution of symptoms to hemochromatosis has become increasingly difficult since studies using control subjects without *HFE* mutations have shown a similar prevalence of non-specific symptoms such as fatigue, arthralgias, and diabetes.

4. Screening

A patient with suspected hemochromatosis or unexplained liver disease can be screened for the disease with a serum ferritin and transferrin saturation (serum iron/TIBC). Transferrin saturation has significant biological variability. These iron tests increase with age and are more abnormal in males than females because of the regular menstrual blood loss in women. Serum ferritin increases with body iron stores but is commonly elevated with fatty liver, daily alcohol consumption and chronic inflammation.

5. Diagnosis

The diagnosis of hemochromatosis was previously confirmed by liver biopsy, which demonstrates marked parenchymal iron deposition with iron staining of the tissue. This hepatocyte deposition of iron is to be distinguished from secondary (non-genetic) causes of iron-overload (Table 2), by the presence of excess iron deposition in the reticuloendothelial system. The hepatic iron concentration and the hepatic iron index (hepatic iron concentration/age) can be helpful in distinguishing genetic hemochromatosis from the increased iron overload that is seen in other chronic liver diseases such as alcoholic liver disease and chronic hepatitis C.



Table 2. Classification of the acquired iron overload syndromes

➤ Hematological disorders	○ Iron-loading anemias ○ thalassemia major ○ sideroblastic anemia ○ chronic hemolytic anemia ○ ineffective erythropoiesis
➤ Chronic liver disease (end stage, cirrhosis)	○ HCV, HBV ○ HCV porphyria, (porphyria cutanea tarda) ○ Alcoholic liver disease ○ NAFLD/NASH ○ Porta-caval shunt
➤ Increased iron intake	○ Dietary iron overload (African iron syndrome)
➤ Parenteral iron overload	
➤ Longterm hemodialysis	○ Multiple blood transfusions (for example, for chronic hemolytic anemia)
➤ Acerloplasminemia	

MRI scanning can detect moderate to marked iron overload in the liver. Genetic testing has led to a re-evaluation of the role of liver biopsy in hemochromatosis and biopsy has moved from a diagnostic test done in most cases to a prognostic test done in selected cases with liver dysfunction. C282Y homozygotes, detected as young adults with a serum ferritin < 1000 µg/L, a normal AST and without hepatomegaly, will not require a liver biopsy.

Genetic testing is particularly useful in the evaluation of a patient with other risk factors for iron overload such as alcoholic liver disease or viral hepatitis (Table 3). Hepatic elastography may be a new tool to detect liver fibrosis without the need for a liver biopsy.



Table 3. Interpretation of genetic testing for hemochromatosis

C282Y homozygote – This is the classical genetic pattern that is seen in > 90% of typical cases. Expression of disease ranges from no evidence of iron overload to massive iron overload with organ dysfunction. Siblings have a one-in-four chance of being affected and should have genetic testing. For children to be affected, the other parent must be at least a heterozygote. If iron studies are normal, false positive genetic testing or a non-expressing homozygote should be considered.

C282Y / H63D – Compound heterozygote – This patient carries one copy of the major mutation and one copy of the minor mutation. Most patients with this genetic pattern have normal iron studies. A small percentage of compound heterozygotes have been found to have mild to moderate iron overload. Severe iron overload is usually seen in the setting of another concomitant risk factor (alcoholism, viral hepatitis).

C282Y heterozygote – This patient carries one copy of the major mutation. This pattern is seen in about 10% of the Caucasian population and is usually associated with normal iron studies. In rare cases the iron studies are high in the range expected in a homozygote rather than a heterozygote. These cases may carry an unknown hemochromatosis mutation and liver biopsy is helpful to determine the need for venesection therapy.

H63D homozygote – This patient carries two copies of the minor mutation. Most patients with this genetic pattern have normal iron studies. A small percentage of these cases have been found to have mild to moderate iron overload. Severe iron overload is usually seen in the setting of another concomitant risk factor (alcoholism, viral hepatitis).

H63D heterozygote – This patient carries one copy of the minor mutation. This pattern is seen in about 20% of the Caucasian population and is usually associated with normal iron studies. This pattern is so common in the general population that the presence of iron overload may be related to another risk factor. Liver biopsy may be required to determine the cause of the iron overload and the need for treatment in these cases.

No HFE mutations – There will likely be other hemochromatosis mutations discovered in the future. If iron overload is present without any *HFE* mutations, a careful history for other risk factors must be reviewed and liver biopsy may be useful to determine the cause of the iron overload and the need for treatment. Most of these cases are isolated, non-familial cases. Genetic testing for new iron mutations in ferroportin, hepcidin, or hemojuvelin is not widely available.

The heterozygote individual may have normal or minor derangements in iron metabolism that have no clinical significance. A patient that carries both the major mutation (C282Y) and the minor mutation (H63D) is called a compound heterozygote. These patients may have mild to moderate iron overload but are often normal.



6. Treatment

The treatment of hemochromatosis involves the removal of excess body iron. Iron is best removed from the body by weekly or twice weekly phlebotomy of 500 mL of blood until the body iron stores are within normal limits. The duration of treatment varies with the age and sex of the patient but older males may require weekly venesections for over three years. A serum ferritin is measured every three months to assess progress and when the serum ferritin is in the low normal range (50 µg/L), the frequency of venesections is decreased to three or four per year. Not all patients will require maintenance therapy.

The goal of therapy is to prevent any further tissue damage. Unfortunately, many of the symptoms do not improve following iron depletion. The most common cause of death is liver failure and/or hepatocellular carcinoma once cirrhosis has become established. Siblings of the patient with hemochromatosis must be screened with serum ferritin, transferrin saturation and genetic testing as the siblings have a one-in four chance of being affected. Genetic testing can now identify heterozygotes so the screening of a spouse with genetic testing can be helpful to predict the risk in children.

Screening of the general population for hemochromatosis has found many genetic mutations but not much clinical disease. Genetic screening has the potential to identify cases at birth but raises ethical issues such as genetic discrimination. Chelating agents such as desferoxamine (parenteral) and deferasirox (oral) are reserved for the patient with iron overload secondary to an iron loading anemia such as thalassemia. Future research is in progress to look for new genes that may cause iron overload, or may modify the clinical expression of hemochromatosis.



Chapter 9: Vascular Disorders in the Liver

C. S. Coffin



1. Introduction

The liver is a highly vascular organ; receiving 25% of cardiac output. Hence, it is highly vulnerable to circulatory disturbances causing diminished perfusion. There are a number of well-recognized forms of vascular injury to the liver. These include conditions related to underlying heart disease and hemodynamic instability such as congestive hepatopathy (also known as “cardiac cirrhosis”) and ischemic hepatitis (or “shock liver”). Vascular injury may be related to a predisposing hypercoagulable state, leading to portal vein thrombosis (PVT). Finally, other more rare causes include sinusoidal obstruction syndrome (SOS, previously known as “hepatic venocclusive disease”), Budd Chiari Syndrome (BCS), hereditary hemorrhagic telangiectasia, HHT, aka and Osler-Weber-Rendu [OWR] Syndrome. Table 1 provides a summary of the main clinical presentation and management of the five major vascular disorders of the liver.

Table 1. Summary of Major Vascular Disorders of the Liver

Disease	Clinical Presentation	Laboratory Tests	Diagnostic Imaging	Management
Ischemic Hepatitis	Shock, right upper quadrant abdominal pain	- ALT and AST >1000. - Jaundice is rare	Doppler US to rule out PVT and Hepatic Artery Thrombosis (HAT)	Supportive care reverse hemodynamic instability
Congestive Hepatopathy	Congestive Heart Failure, jaundice, tender hepatomegaly	- Moderate elevation in bilirubin and transaminases - High SAAG.	Abdominal Imaging (CT), showing possible hepatomegaly and ascites	Treat underlying heart disease
Portal Vein Thrombosis (PVT)	- Acute PVT - asymptomatic or sudden abdominal pain with SIRS. - Chronic - Portal hypertension, variceal bleeding	Mildly abnormal liver function tests/enzymes.	Doppler ultrasound showing reduced or absent flow. Chronic PVT – show collateral veins within main PV.	- Management of variceal bleeding and portal hypertension - Anticoagulation for 3- 6 months if acute PVT, and permanent in non-cirrhotic patients with pro-thrombotic condition



Table 1. Summary of Major Vascular Disorders of the Liver

Disease	Clinical Presentation	Laboratory Tests	Diagnostic Imaging	Management
Sinusoidal Obstruction Syndrome (SOS)	Underlying risk factor (myeloablative conditioning), portal hypertension, sudden jaundice, ascites, tender hepatomegaly	Nonspecific elevation of aminotransferases and conjugated bilirubin	- Ultrasound, rarely liver biopsy - HVPG (>10 mm Hg)	Supportive care, treatment of cause,
Budd-Chiari Syndrome (BCS)	Asymptomatic, unexplained cirrhosis, fulminant liver failure. Presence of underlying risk factor, hypercoagulable disorder	- Nonspecific abnormality liver function tests, - High SAAG	Doppler Ultrasound--absent or turbulent flow in larger hepatic vein, with hepatic venous collaterals	- Supportive care, - Manage portal hypertension, anticoagulation to prevent recurrence if underlying pro-thrombotic condition. TIPS and transplant as last resort
Osler-Weber-Rendu Syndrome (Hereditary Hemorrhagic Telangiectasia, HHT)	Family history, mucocutaneous and GI bleeding (epistaxis)	Elevation AP and GGT. Normal liver function	Doppler Ultrasound or CT showing vascular malformations. Angiography is gold standard.	Supportive care manage portal hypertension. Hepatic artery embolization in non-transplant candidates, liver transplant

Abbreviations: AP, alkaline phosphatase; HAT, hepatic artery; HVPG, hepatic vein pressure gradient; PVT, portal vein thrombosis; SAAG, serum ascites albumin gradient; SIRS, Systemic inflammatory response syndrome; thrombosis; TIPS, transjugular portosystemic shunt.

2. Ischemic Hepatitis and Congestive Hepatopathy

Ischemic hepatitis (or “shock liver”) is a condition of acute hypoperfusion of the liver, usually due to shock or hypotension, resulting in diffuse hepatocyte injury.



Ischemic hepatitis can also be due to thrombosis of the hepatic artery, such as in sickle cell crisis. The patient may present with right upper quadrant pain associated. Blood testing usually shows a profound elevation of liver transaminases from hepatocytes injury and leakage such that transaminase levels (aspartate aminotransferase, AST and alanine aminotransferase, ALT) may exceed 1000 U/L (normal limit is 60 U/L). Only acute viral hepatitis and acetaminophen injury is known to cause such a high elevation in these hepatic enzymes (reflecting hepatocellular damage). Jaundice can occur, but is rare and transient. Liver pathology is characterized by Zone 3 injury of the hepatic acinus that can extend to mid-zonal areas with severe and prolonged ischemia. There are usually few inflammatory cells.

Ischemic hepatic often co-exists with congestive hepatopathy, and many of the clinical features are similar. Congestive hepatopathy refers to hepatic injury due to passive congestion from right-sided heart failure (i.e., due to constrictive pericarditis, tricuspid regurgitation, cardiomyopathy). The diagnosis of congestive hepatopathy is suspected from the clinical presentation of right-sided heart failure, jaundice, and tender hepatomegaly. The liver biochemistries are non-specific, and show only modest abnormalities such as elevation in unconjugated hyperbilirubinemia, elevated aminotransferases (usually <2- to 3-fold), and prolonged PT/INR. The ascitic fluid (if present) has high albumin content and the serum ascites/albumin gradient (SAAG) is ($\geq$ 11 micromole/L). This liver disorder is more important as an index of the severity of heart failure than as diagnosis by itself, and management is focused on treating the underlying heart disease.

3. Acute and Chronic Portal Vein Thrombosis

Portal vein thrombosis (PVT) can be acute or chronic, and is usually caused by malignant invasion or thrombosis. Local risk factors are identified in only about one-third of patients, and include cirrhosis, cancer, focal inflammatory lesions, and injury to the portal venous system. These risk factors often occur in patients with a background history of an inherited or acquired pro-thrombotic condition. In young patients without a history of cancer or cirrhosis, acute PVT is often the first manifestation of an undiagnosed myeloproliferative disease.

Acute PVT usually presents with sudden onset abdominal pain, without peritoneal signs (except when an intra-abdominal inflammatory focus is the underlying causative event). Patients commonly manifest a marked systemic inflammatory response syndrome (SIRS), with persistent non-spiking fevers, abdominal pain and a transient rise in aminotransferases. Mesenteric thrombus progression can lead to intestinal ischemia, and if untreated can lead to severe persistent pain, bloody diarrhea, ascites and even peritonitis, shock, and multi-organ failure.

In chronic portal vein thrombosis (aka “portal cavernoma”), a network of collateral veins with hepatopetal flow connects the patent portion of the portal vein upstream from the thrombus, to the patent portion downstream. The degree of collateral flow varies from patient to patient, but complete occlusion is associated with the development of portal hypertension and portosystemic collaterals.

There are no RCTs (Randomized Controlled Trials) regarding the optimal treatment of acute PVT. Spontaneous recanalization is rare. Retrospective studies have shown that



anticoagulation therapy is associated with improved rates of recanalization. It is generally recommended that at least 3 months of anticoagulation be given, and that permanent therapy be considered in patients with permanent prothrombotic conditions.

Diagnosis of PVT is usually made after first presentation of portal hypertension and hypersplenism. Gastrointestinal variceal bleeding is better tolerated, as patients are often younger with preserved liver function. Approximately 50% of patients' hepatic encephalopathy, and 10% present with hepatopulmonary syndrome. Liver enzymes are usually normal, with only mild alteration in coagulation factors. If a patient has biliary symptoms (i.e., jaundice, cholecystitis, pancreatitis), these may be due to portal cholangiopathy from compression of the large bile ducts.

The diagnosis of acute or chronic PVT is made by abdominal imaging. Ultrasound will show obstruction of the vessel lumen, with distention of the portal vein. Chronic PVT will show replacement with serpiginous structures or collateral veins within the main portal vein. Doppler ultrasound of the vessels shows the absence or reduced flow within the vessel lumen. CT or MRI imaging with vascular contrast is recommended for assessment of thrombus extension, management since the mesenteric veins are difficult to visualize by ultrasound.

The management of chronic PVT is aimed at reducing the complications of portal hypertension such as esophageal variceal bleeding. Provided there is no major contraindication, anticoagulation should only be considered in non-cirrhotic patients with a known pro-thrombotic condition.

4. Sinusoidal Obstruction Syndrome

Sinusoidal Obstruction Syndrome (SOS) is a primary circulatory disorder due to obstruction of the hepatic sinusoids. In developed countries, SOS occurs most commonly as a complication of myeloablative conditioning regimens for hematopoietic stem cell transplantation, such as combination of high-dose chemotherapy and total body irradiation therapy. The overall incidence of SOS has declined in most centres with the use of reduced intensity conditioning regimens. SOS should be considered in persons at high risk for SOS such as those with a history previous of SOS, some forms of pre-existing liver disease (i.e., viral hepatitis and hepatic fibrosis), use of conventional dose chemotherapy, immunosuppressive agents with azathioprine, and herbal teas with pyrrolizidine alkaloids. The clinical presentation may be asymptomatic, but with increasing SOS disease severity, patients can manifest weight gain, with or without ascites, right upper quadrant pain, jaundice, and renal failure. Onset occurs from 10 up to 30 days after myeloablative therapy is started. A diagnosis of SOS can usually be made on clinical criteria, after ruling out other confounding conditions such as sepsis, drug-induced cholestasis, graft-versus-host disease, or fungal infection. The diagnostic gold standard for SOS is measurement of wedged hepatic vein pressure (HVPG) gradient by transjugular liver biopsy (HVPG > 10 mmHg has positive predictive value of > 85% for the diagnosis of SOS). Diagnostic imaging is not diagnostic by itself, but Doppler ultrasound is recommended to rule out other causes and will often demonstrate hepatomegaly and ascites in support the diagnosis.



The management of established SOS is supportive care, diuretics, abdominal paracentesis, and dialysis as needed. There are no randomized controlled trials to definitively support the Defibrotide.

5. Budd-Chiari Syndrome

Budd-Chiari syndrome (BCS) is due to “hepatic venous outflow tract obstruction”, independent of the level or mechanism of obstruction. BCS is classified according to the level of obstruction – small hepatic veins, large hepatic veins, or inferior vena cava. BCS is caused by either secondary malignant vein invasion, or due to primary venous thrombosis or phlebitis (often related to underlying myeloproliferative disease or other hypercoagulable risk factors).

The clinical presentation of BCS can vary from asymptomatic to acute liver failure. The classical symptoms include fever, abdominal pain, ascites, lower extremity edema, gastrointestinal bleeding, and hepatic encephalopathy. Jaundice is uncommon. Liver enzymes and liver function tests may be normal or abnormal. Serum ascites-albumin gradient > 11 micromole/L is supportive of BCS.

Doppler ultrasound of the abdomen may help establish the diagnosis of BCS by showing absent flow or reversed/turbulent flow in the large hepatic vein, in association with intrahepatic or subcapsular hepatic venous collaterals. A confirmatory CT and MRI study may be needed in difficult cases, or as an alternative to Doppler ultrasound. A liver biopsy is usually not required; its main yield is to show congestion, liver cell loss and centrilobular fibrosis.

The clinical strategy proposed by expert consensus treatment includes anticoagulation (usually indefinitely in persons with a permanent underlying risk factor for thrombosis), supportive care, management of portal hypertension complications, and treatment of the underlying condition if applicable. The use of stenting or angioplasty is reserved for short segment stenosis. Transjugular portosystemic shunt (TIPS) is recommended for unresponsive patients, liver transplantation is a last resort if TIPS fails, and if there is fulminant liver failure.

6. Hereditary Hemorrhagic Telangiectasia (HHT) (aka OWR [Osler-Weber-Rendu Syndrome])

HHT is a rare congenital autosomal dominant disease characterized by widespread cutaneous, mucosal and visceral arteriovenous malformations. These AVMs may involve the lung, brain and/or liver. The liver has widespread microscopic and macroscopic vascular malformation, resulting in three types of functional shunts: arteriovenous, portovenous and arteriportal. In 75% of HHT patients, the vascular malformations can be visualized by using sensitive diagnostic imaging techniques. The typical clinical presentation is a female ~age 30, with high output heart failure due to a hyperdynamic circulatory state, portal hypertension and biliary ischemia, all of which can occur simultaneously or successively. Suggestive clinical characteristics include epistaxis, mucosal telangiectasias, as well as family history of stroke or intracerebral hemorrhage (from cerebral arteriovenous malformations). The most common liver enzyme abnormalities include elevations of alkaline phosphatase (AP) and gamma-



glutamyl-transpeptidase (GGT); liver function is preserved. In difficult cases, genetic testing can be done for the most common coding sequence mutations. The gold standard for diagnosis of HHT of liver vascular malformations is angiography, but can usually be determined by non-invasive methods such as Doppler ultrasound and CT scan demonstrating heterogeneous enhancement or hypervascularization of the liver and common hepatic artery enlargement. The liver has widespread microscopic and macroscopic vascular malformations, resulting in three types of functional shunts: arteriovenous, portovenous and arterioportal. A liver biopsy is not recommended due to potential risk and frequent problems with histological misinterpretation.

No treatment is necessary for patients who have asymptomatic liver involvement with HHT. The management of symptomatic patients depends on the clinical presentation – i.e., congestive heart failure, portal hypertension complications, or abdominal pain from biliary ischemia. The experimental antiangiogenic drug VEGF (antibody to vascular endothelial growth factor) has shown promising data for symptom relief. Hepatic artery embolization is only considered for patients with intractable heart failure who have failed maximal medical therapy, and who are not candidates for liver transplantation. Liver transplantation is the only definitive curative therapy, and should be considered for acute biliary necrosis syndrome, intractable heart failure, or portal hypertension.





Chapter 10: Neoplasms of the Liver

K. W. Burak



1. Introduction

Neoplasm of the liver can be categorized as cystic or solid, benign or malignant, and primary or metastatic (Figure 1). With the frequent use of abdominal imaging such as ultrasound (US), computed tomography (CT) or magnetic resonance imaging (MRI), many benign tumours of the liver are found incidentally. Metastases from cancers of the lung, colon or breast are relatively common and the prognosis is related primarily to the underlying type of cancer. Worldwide, hepatocellular carcinoma (HCC) is a very common malignancy and is most often related to chronic hepatitis B infection. In North America, HCC is on the increase and is most often associated with cirrhosis of the liver related to chronic hepatitis C. The treatment of HCC depends on the stage of the tumour, the performance status of the patient and the underlying liver function. Cholangiocarcinoma (CCA) is a primary cancer arising from the bile ducts, often in response to chronic inflammation, and has a very poor prognosis. This chapter will review the diagnostic features and management of common benign and malignant neoplasms of the liver.

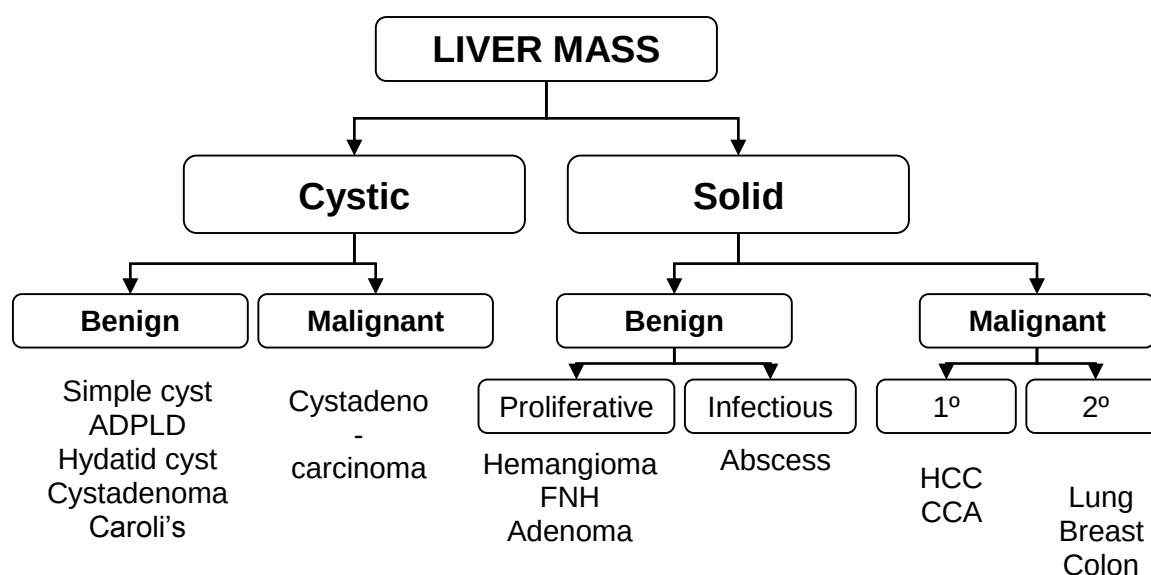


Figure 1. Approach to a Liver Mass.

Abbreviations: 1° = primary, 2° = secondary, ADPLD = autosomal dominant polycystic liver disease, FNH = focal nodular hyperplasia, HCC = hepatocellular carcinoma, CCA = cholangiocarcinoma



2. Benign Tumours of the Liver

2.1. Cystic Neoplasms of the Liver

Hepatic cysts are relatively common, especially in individuals over the age of fifty. Solitary cysts are reported to occur in 3-5% of the population and are four times more common in women. Simple cysts are easily characterized by ultrasound and further imaging is rarely required (Figure 2A). Simple cysts are usually asymptomatic, but rarely, they may present with right upper quadrant (RUQ) pain or fever if complicated by hemorrhage or infection. All other potential explanations for symptoms should be ruled out before pain, bloating or early satiety is attributed to a hepatic cyst. Treatment is rarely required unless the patient is truly symptomatic. Percutaneous aspiration is associated with a high recurrence rate unless combined with sclerotherapy. Laparoscopic surgical fenestration is usually preferred if the lesions are very large or complicated.

Multiple cysts in the liver may represent autosomal dominant polycystic liver disease (ADPLD) which often coexists with autosomal dominant polycystic kidney disease. The cysts in ADPLD can lead to painful massive hepatomegaly, abdominal distention and early satiety. Selected patients with massive hepatomegaly may have benefit from surgical resection or fenestration but this often only provides temporary relief of symptoms. Liver transplantation, with combined renal transplant if there is coexisting renal failure, is sometimes needed. A randomized placebo controlled trial has demonstrated a benefit long acting octreotide to slow the progression of liver and kidney cysts in these patients.

If a cystic lesion has internal debris, septations or daughter cysts it is considered a complex cyst and it raises the possibility of a cystadenoma or hydatid cyst disease (Figure 2B). Cystadenomas are rare cystic liver tumours which are mucin filled and often have a solid (papillary or stromal) component in the wall. Even if asymptomatic, they should be removed surgically, because rarely these benign tumours may progress to malignant cystadenocarcinoma. Hydatid disease is caused by the zoonotic parasites *Echinococcus granulosus* or *E. multilocularis*. These parasites have part of their life cycle in dogs (definitive host) and sheep (intermediate host). Humans who contact infected animals may become accidental intermediate hosts. The disease is endemic in sheep raising areas in the Middle East, Asia, Africa, South America and Australia. Immigrants from these regions with complex liver cysts should have echinococcal serology ordered. Patients should receive therapy with albendazole before surgical or percutaneous therapy is performed. Cystic fluid can result in intense anaphylactic like reactions if it is released into circulation, but PAIR therapy (Percutaneous Aspiration, Injection of hypertonic saline and Reaspiration) is associated with a low risk of allergic reactions.

Caroli's disease is a congenital abnormality of the biliary system that often presents in childhood. The cystic lesions of the liver represent dilated segments of the bile ducts and communication with the biliary system is best confirmed with MRI and magnetic resonance cholangiography (MRC). Patients may have recurrent bouts of cholangitis and may form intrahepatic biliary stones. The condition can also be associated with congenital hepatic fibrosis, which may lead to liver failure and portal hypertension.



2.2. Pyogenic Liver Abscess

Pyogenic liver abscess (PLA) is most commonly related to biliary obstruction, but can also result from intra-abdominal infections (diverticulitis, appendicitis, inflammatory bowel disease, pelvic sepsis) or from hematogenous spread (endocarditis, dental infections). It has also been reported as a complication of non-operative therapy for primary hepatocellular carcinoma (see below) after transarterial chemoembolization (TACE) or radiofrequency ablation (RFA). Diabetics and immunocompromised hosts appear to be at higher risk for the development of PLA. Patients may present with non-specific symptoms early on in the course of the infection (malaise, arthralgias, anorexia) before the onset of fever and RUQ pain. CT is more accurate than US and enhancement of abscess wall on contrast CT is diagnostic (Figure 2C), especially in a patient with fever and an elevated white blood cell count. Furthermore, a CT may elucidate the source of the PLA in many patients. Blood cultures should be drawn and broad-spectrum antibiotics should be started to cover both aerobic and anaerobic gram negative and positive bacteria. Typically, antibiotics are delivered intravenously for the first two weeks, followed by at least another 4 weeks of oral antibiotics. Percutaneous aspiration or drainage is performed by US or CT guidance and only rarely is surgical resection required.

Amoebic liver abscess usually occurs several months after returning from travel to endemic areas. The protozoan *Entameba histolytica* can cause diarrhea (amoebic colitis) and liver abscess (usually single, large, and loculated), although the two rarely present at the same time. US has a high diagnostic accuracy and serology can help with the diagnosis. Necrosis within the abscess leads to the typical “anchovy paste” appearance. Treatment is with metronidazole and patients without resolution of symptoms may need to undergo aspiration.

2.3. Hemangioma

Hemangiomas are the most common benign tumor of the liver and are seen in 5-20% of the general population. These vascular lesions are usually asymptomatic and are six times more common in women. Hemangiomas present at all ages but are most commonly seen in the third to fifth decades. Lesions larger than 4 cm are called *giant cavernous hemangiomas*, and rarely they can result in pain (from stretching the liver capsule) or a consumptive coagulopathy (Kasabach-Meritt syndrome) when they are very large. They are hyperechoic on US and doppler studies can confirm filling vessels in the periphery. Contrast enhanced CT and MRI show peripheral nodular enhancement (puddling of contrast) with progressive centripetal filling (Figure 2D). RBC-labeled nuclear medicine scans can be used for diagnosis if other imaging modalities are non-diagnostic. No treatment is needed for these lesions as they have no malignant potential and the risk of hemorrhage is extremely rare.



2.4. Focal Nodular Hyperplasia

Focal nodular hyperplasia (FNH) is the second most commonly encountered benign liver lesion, occurring in 3% of the population. It is eight times more likely to occur in women, but its association with the use of the oral contraceptive pill (OCP) is controversial. It is postulated that they form in response to micro-thrombosis of branches of the portal vein, with that area of the liver growing aberrantly because of its predominant arterial blood supply. Histologically, they are hypervascular, often with a central scar, and although they lack normal venous anatomy they contain all of the normal cells of this liver (including Kupffer cells). On US they are isoechoic and the central scar may be evident. Contrast enhanced ultrasound (CEUS) can differentiate from adenoma by a centrifugal filling pattern in the arterial phase and stellate vascularity. On CT there is transient arterial phase enhancement with the central scar being more evident on delayed imaging. The central scar can often be seen on MRI (Figure 2E) and the use of MR hepatobiliary specific contrast agents (Gd-EOB-DTPA or Primovist®) is particularly good at differentiation between FNH and adenoma. Technetium sulfur colloid scans will often show normal or increased uptake in the lesion due to the presence of the Kupffer cells. No therapy is required for FNH as these lesions have no malignant potential and they rarely bleed or cause other symptoms.

2.5. Adenoma

Hepatocellular adenoma is a rare mass lesion of the liver characterized by the benign proliferation of hepatocytes. They are eleven times more common in women and are clearly associated with the use of the OCP. In men they are often the result of anabolic steroid use. Patients can present with multiple adenomas, with hepatic adenomatosis being associated with glycogen storage disease. Many patients are asymptomatic, but up to one quarter of patients may present with pain in the epigastrium. Adenomas can rapidly grow in response to high estrogen states, such as pregnancy or ongoing use of the OCP, and they can present with shock due to a hemoperitoneum following spontaneous rupture. Although benign, it is estimated that approximately 10% of adenomas will undergo a malignant transformation, with the risk being highest for larger adenomas. Adenomas do not have specific findings on US. CT scanning typically demonstrates arterial phase enhancement which becomes isointense on later imaging. Often lesions show intralesional hyper- or hypo-densities related to necrosis or hemorrhage (Figure 2F). MRI may show the presence of microscopic fat within the lesion. Sulfur colloid studies may show the characteristic lack of uptake due to absence of Kupffer cells in the adenoma. Management includes stopping the OCP and resection of lesions larger than 5cm or symptomatic tumours.



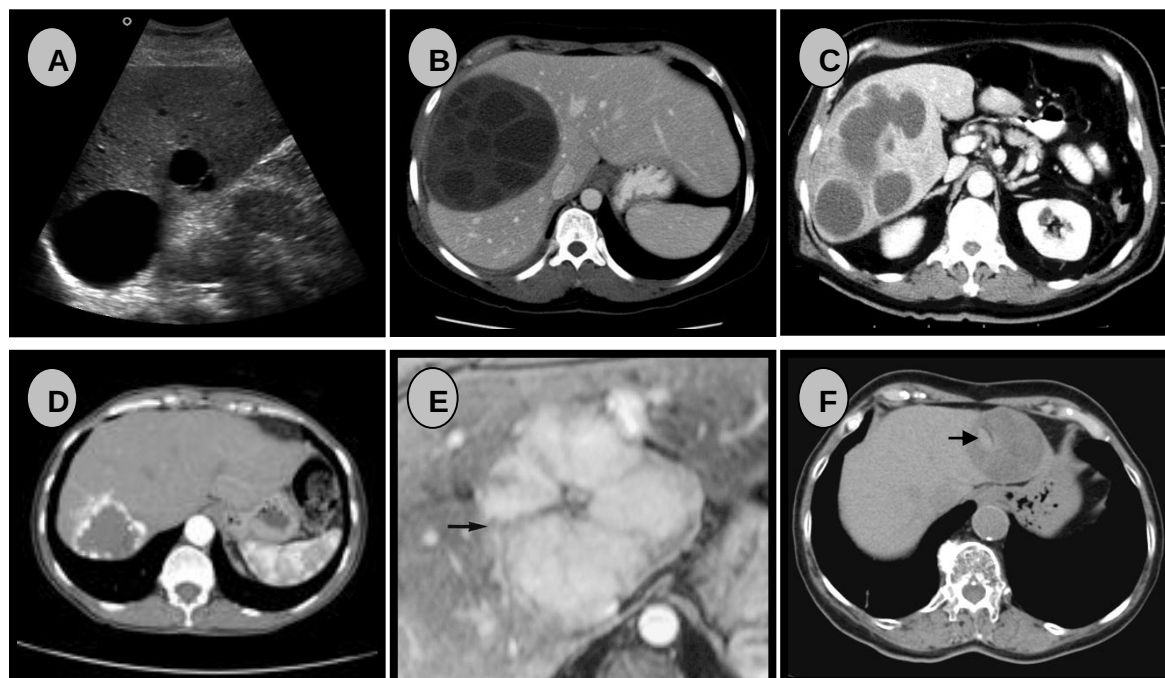


Figure 2. Radiographic findings of benign liver tumours. A) Simple cyst – hypoechoic on US with no internal septations or debris; B) Hydatid cyst – complex cystic mass on CT scan; C) Pyogenic liver abscess – note enhancement of the wall on CT scan; D) Hemangioma – CT scan demonstrates peripheral puddling of contrast; E) Focal Nodular Hyperplasia – MRI demonstrates the classic central scar (black arrow); F) Adenoma – CT scan demonstrates hyperenhancing area of recent hemorrhage (black arrow).

3. Malignant Tumours of the Liver

3.1. Hepatocellular Carcinoma

Hepatocellular carcinoma (HCC) is the fifth most common cancer globally and the third leading cause of cancer related mortality world-wide. Each year there are more than 600,000 new cases, with more than half of them occurring in China alone. Although a rare malignancy in Western countries, HCC is one of only a few cancers with an increasing incidence in North America. Globally, hepatitis B virus (HBV) infection is the leading cause of HCC. In North America, HCC occurs in the setting of cirrhosis in more than 80% of cases, with hepatitis C virus (HCV) being the leading cause. HCC is two to three times more common in men compared to women. Screening for HCC should be performed in all patients with cirrhosis and chronic carriers of HBV (Asian males over the age of 40, Asian females over the age of 50, and Africans over the age of 20). US performed every six months is the recommended screening modality. Alpha-fetoprotein (AFP) is only elevated in approximately 60% of HCC and can be falsely elevated by flares of viral hepatitis. Because it lacks sensitivity and specificity, AFP is no longer recommended as a screening test for HCC, although many clinicians still use US and AFP in combination.



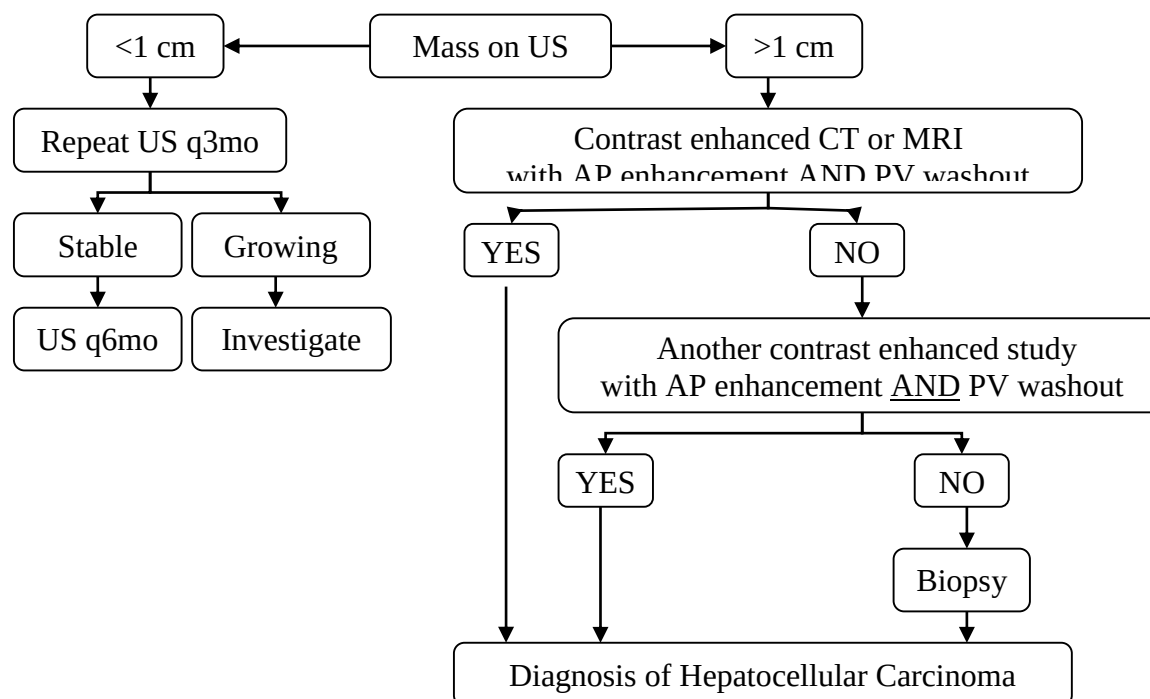


Figure 3. Diagnosis of hepatocellular carcinoma (HCC) in a cirrhotic liver.

Abbreviations: AP = arterial phase, PV = portal venous, US = ultrasound

Adapted from AASLD Practice Guidelines: Bruix J and Sherman M. Management of hepatocellular carcinoma: an update. *Hepatology* 2010. (available on-line at <http://www.aasld.org/practiceguidelines/Documents/Bookmarked%20practice%20Guidelines/Hccupdate2010.pdf>)

To establish the diagnosis of HCC, an elevation of AFP >200 ng/mL is helpful, but contrast enhanced imaging is needed. When a small (<1cm) suspicious nodule is identified on US it should be followed more closely with US every 3 months until it shows stability over time (Figure 3). If it is larger than 1 cm, the nodule should be investigated with a contrast enhanced CT, MRI or US. Because these malignant tumours derive most of their blood supply from the hepatic artery, a HCC will show enhancement in the early arterial phase (Figure 4). In later images, as the remainder of the liver is perfused with contrast arriving from the portal vein, the HCC (which has very little blood supply from the portal vein) will appear darker than the rest of the liver. This pattern is referred to as portal venous “washout” (Figure 4). Arterial phase enhancement and portal venous washout for a lesion > 1 cm in the setting of cirrhosis is highly specific for HCC. Recently, the specificity of CEUS has been questioned as intrahepatic peripheral cholangiocarcinoma (CCA) have been found to have similar vascular patterns to HCC. A biopsy is needed to confirm HCC only when the contrast CT or MRI is not classic and the AFP is <200 ng/mL. Biopsies are now rarely performed to establish the diagnosis of HCC because they are associated with a risk of bleeding, a 1-



2% chance of tumour seeding, and biopsies of small lesions can be falsely negative in more than 10%.

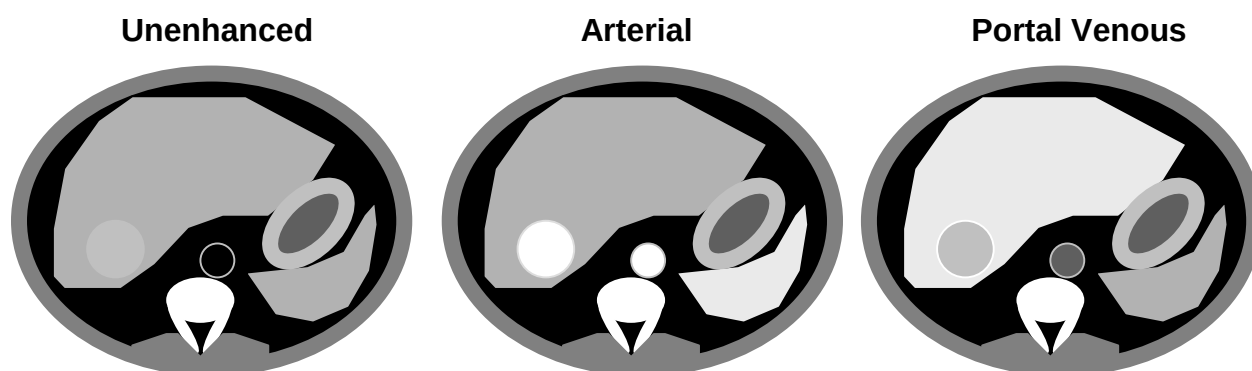


Figure 4. Diagnosis of hepatocellular carcinoma (HCC). The classic HCC, which may be barely perceptible on unenhanced CT or MRI, will be enhancing on the arterial phase and will demonstrate “washout” compared to the rest of the liver on the portal venous phase.

The management of HCC is complex and is best performed in a multi-disciplinary group, consisting of hepatologists, surgeons, oncologists, and interventional radiologists. It is important to understand the competing risks for mortality of the cirrhotic liver and the HCC. The preferred staging system for HCC is the Barcelona Clinic Liver Cancer (BCLC) system, as it takes into account the tumour stage, the liver function according to the Child-Turcotte-Pugh (CTP) system, and the patient performance status (PS) according to the Eastern Cooperative Oncology Group (ECOG). Furthermore, it has the advantage of linking these prognostic factors to recommended therapies. The Alberta HCC algorithm (Figure 5) incorporates local selection practices for the various treatment options of HCC into the BCLC staging system.



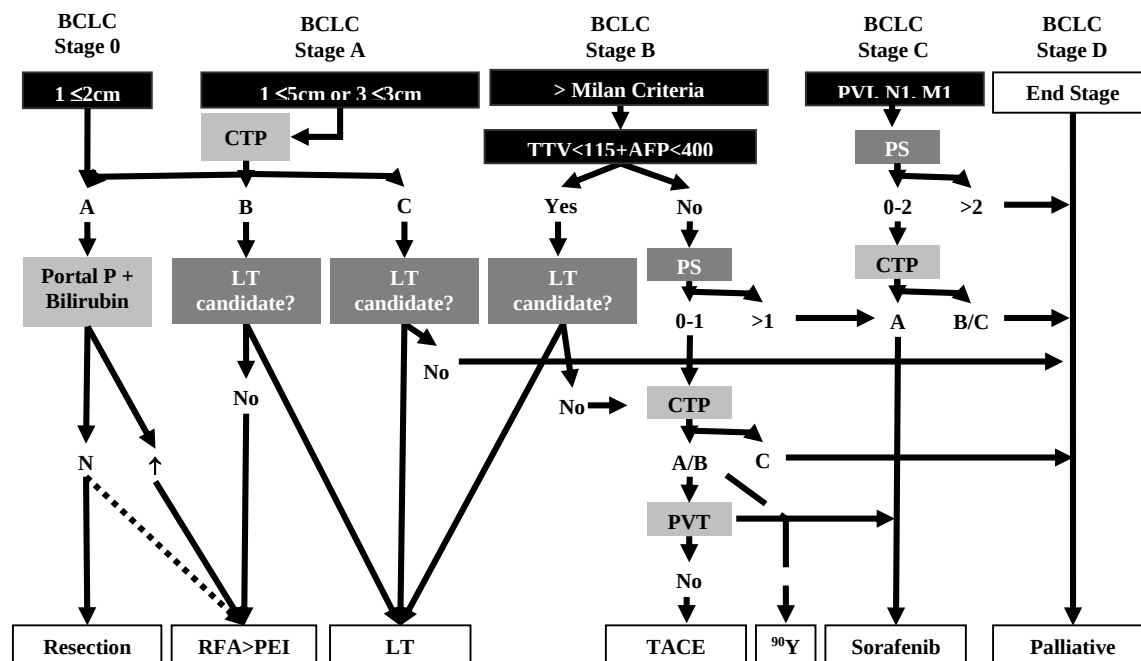


Figure 5. Management of hepatocellular carcinoma according to the Alberta HCC algorithm. The algorithm recognizes the importance of tumour properties (size, number, extra-hepatic spread and AFP) [black boxes], patient characteristics (performance status and candidacy for transplantation) [dark grey boxes], and liver function (CTP class along with elevated pressure within or thrombosis of the portal vein) [light grey boxes] and links patients to most appropriate therapy [white boxes]. Dotted line represents potential role of RFA in very early stage HCC. Dashed line recognizes potential role of ^{90}Y radioembolization, especially for patients who are not candidates for TACE because of bland portal vein thrombosis.

Abbreviations: BCLC= Barcelona Clinic Liver Cancer; PVI = portal vein invasion; N = lymph node; M = metastases; CTP = Child-Turcotte-Pugh class; TTV = total tumour volume; AFP = alpha-fetoprotein; PS = performance status; Portal P = portal pressure; LT = liver transplantation; PVT = portal vein thrombosis; RFA = radiofrequency ablation; PEI = percutaneous ethanol injection; TACE = transarterial chemoembolization; ^{90}Y = transarterial radioembolization with $^{90}\text{yttrium}$.

Adapted from: Burak KW and Kneteman NM. An Evidence-Based Multidisciplinary Approach to the Management of Hepatocellular Carcinoma (HCC): The Alberta HCC Algorithm. *Can J Gastroenterol* 2010, in press.

In North America, approximately 30% of patients have their HCC detected at an early stage where curative treatment options are possible. Patients with a small single tumour (<2cm) with good PS and well compensated cirrhosis are candidates for surgical resection (BCLC stage 0); however, recent studies have suggested similar outcomes in this patient population with radiofrequency ablation (RFA). BCLC stage A patients may



be offered surgical resection, liver transplantation (LT) or RFA depending on their liver function. In carefully selected patients 5 year survival rates of 70% have been reported with all three modalities. Surgical resection should be reserved for patients with CTP class A cirrhosis, who have a normal bilirubin and no evidence of portal hypertension (no splenomegaly, no varices, platelet count > 100) to avoid post-operative liver failure. Unfortunately, 70% of patients will have a recurrence of HCC in the remnant cirrhotic liver within 5 years of resection. Patients who are not candidates for resection should be considered for LT, as it treats both the liver failure and the liver cancer. The size of the tumour predicts microvascular invasion and subsequent risk of tumour recurrence after LT. The risk of recurrence after LT is low ($<15\%$) if the Milan criteria (single tumour $<5\text{cm}$ or 3 tumours each $<3\text{cm}$) are used to select patients. Unfortunately, long waiting times for cadaveric organs means many patients progressing beyond these criteria while awaiting LT. Many centers, including the University of Alberta in Edmonton, have tried to expand the criteria for LT beyond the Milan criteria. Currently in Alberta patients are candidates for LT if their total tumour volume (TTV, measured by $\frac{4}{3}\pi\text{radius}^3$) is less than 115cm^3 and their AFP is $<400\text{ng/mL}$, as these cutoffs result in low recurrence rates and acceptable post-LT survival. This TTV equates to a single tumour $\leq 6\text{cm}$ or many smaller tumours. If patients are not a candidate for LT they may be treated with RFA. Percutaneous RFA burns the tumour under US guidance and is associated with low complications (2% risk of bleeding, hyperbilirubinemia, damage to adjacent structures) but recurrence rates that are higher than after surgical resection, especially if the tumour is larger than 2cm . RFA has been shown to be superior to percutaneous ethanol ablation (PEI), although PEI may be used for tumours adjacent to large blood vessels where a “heat sink” effect can reduce the efficacy of RFA.

Approximately 50% of patients in North America will present with intermediate or advanced stages of HCC. Patients with large single tumours or multifocal disease, who are not candidates for curative options, can be offered transarterial chemoembolization (TACE) for palliation. TACE takes advantage of the arterialized blood supply of HCC to deliver chemotherapy and embolic particles to the tumour via the hepatic artery. Meta-analysis of randomized trials have demonstrated a survival benefit of TACE in patients with intermediate stage HCC who have preserved liver function (CTP class A or early class B cirrhosis) and good PS. With TACE median survival increases from approximately 16 months to 20 months in BCLC stage B patients. TACE is generally well tolerated but frequently causes post-embolization syndrome (fever, RUQ pain, nausea) and can result in liver failure, especially in patients with portal vein thrombosis (PVT). Transarterial radioembolization (TARE) is similar to TACE but supplies beta-emitting internal radiation with $^{90}\text{yttrium}$ (^{90}Y) microspheres. It has not been compared to TACE in randomized trials, although cohort studies suggest similar outcomes. TARE has the advantage of being performed as an outpatient and can be safely performed in patients with PVT. Advanced stage HCC (BCLC stage C) is characterized by malignant portal vein invasion (PVI) or extrahepatic spread into lymph nodes (N1) or distant organs such as the bone, lung or brain (M1). Sorafenib, a multikinase inhibitor which also blocks vascular endothelial growth factor (VEGF) and platelet derived growth factor (PDGF), has been shown in a placebo controlled trial to improve survival from approximately 8 months to 11 months. The therapy has only been carefully studied in



patients with reasonable PS and well preserved CTP class A cirrhosis. It costs approximately \$5,000 per month, and although generally well tolerated, it may result in hypertension, diarrhea and hand-and-foot reactions. Sorafenib is now also being studied as adjuvant therapy to prevent recurrence following curative intent surgical resection or RFA and in combination with TACE in intermediate stage patients. Many other multikinase inhibitors, anti-VGEF drugs and inhibitors of m-TOR (eg. sirolimus and everolimus) are currently being studied in clinical trials. Patients with CTP class C cirrhosis, and those with PS ≥ 2 (more than half of time confined to bed), who are not LT candidates, should be offered only best supportive palliative care as their prognosis is very guarded (median survival ~ 3 months in BCLC stage D patients).

3.2. Hepatoblastoma

Primary liver tumours account for only about 1% of all childhood malignancies. Hepatoblastoma is a rare malignant tumor that develops in the liver of young children. It accounts for two-thirds of all malignant liver tumours in children (others include HCC, sarcoma, and germ cell tumours). Approximately one-third of patients will present at an early stage where surgical resection can be performed. In other patients, neoadjuvant chemotherapy with cisplatin, 5-fluorouracil and vincristine can be followed by liver transplantation. The five-year survival rate is less than 35% but improves to approximately 70% in patients undergoing transplantation.

3.3. Cholangiocarcinoma

Cholangiocarcinoma (CCA) is a primary liver cancer arising from the biliary epithelial cell. CCA can present in the distal bile duct or hilum (Klatskin tumours) and these patients will often present with painless jaundice. Intrahepatic cholangiocarcinoma (ICC) arises within the liver and may present as an asymptomatic mass lesion without jaundice. ICC is the second most common primary liver cancer and accounts for 10-15% primary liver malignancies. As with HCC, the incidence of ICC is on the increase in North America. ICC is slightly more common in women and the risk increases in the elderly. Risk factors for ICC include chronic inflammation of the biliary system (primary sclerosing cholangitis, choledochal cyst, Caroli's disease, or parasitic biliary infections with *Clonorchis sinensis* or *Opisthorchis viverrini*) or cirrhosis of the liver (HBV, HCV, PBC, NAFLD, etc). Biopsy will reveal adenocarcinoma; however, this pathology within the liver will usually be metastatic (see below) and therefore a workup to rule out another primary malignancy is necessary. CT scan should be performed of the chest, abdomen and pelvis and positron emission tomography (PET) scanning may be helpful to evaluate the extent of disease. The tumour marker carbohydrate antigen 19-9 (CA19-9) has a reasonable sensitivity and specificity for CCA if the level is above 100 U/mL. Surgical resection is the only curative option for ICC but the prognosis remains guarded (5 year survival rates of 15-40%). For patients with unresectable ICC the median survival is approximately 6 months, but the combination of gemcitabine and cisplatin chemotherapy may improve survival.



3.4. Metastatic Tumors

In North America, metastases from another malignancy are the most common malignant tumor to affect the liver. Common sources include lung, breast, colorectal, gastric, pancreatic, urogenital or neuroendocrine tumors. Patients may present with vague symptoms of weight loss, anorexia, low grade fever or symptoms related to the primary malignancy (change in bowel habit, gastrointestinal bleeding, cough or hemoptysis). Metastases are more likely to be multiple small lesions, and on CT they are often described as target ring-enhancing lesions. CT or MRI of the abdomen may also help identify a primary malignancy in the pancreas, colon or urogenital system. The diagnosis is usually confirmed by needle biopsy, and immunohistochemical staining may help identify the likely primary malignancy. A work-up for an unknown primary malignancy should include tumour markers like carcinoembryonic antigen (CEA), which is elevated in colorectal cancer, as well as AFP and CA-19-9 (to exclude primary liver cancers). Women should undergo breast and pelvic exams, as well as mammography and pelvic ultrasounds. Chest X-ray or CT scan is especially important for smokers. Endoscopy and colonoscopy should be performed to rule out gastrointestinal malignancy.

For most cases, metastatic disease implies an advanced stage of cancer with a poor prognosis. However, patients with metastatic colorectal cancer (CRC) and neuroendocrine tumors may have many therapeutic options and overall these groups may have a reasonable prognosis. Nearly one-half of patients with CRC will develop a liver metastasis. The combination of chemotherapy and surgical resection can significantly prolong survival and quality of life in these patients, with 5 year survival rates of 70% being reported for patients with solitary liver metastases from CRC. Between 50-90% of neuroendocrine tumours will involve the liver. Non-operative treatment options include radioactive labeled therapy with ^{131}I -metaiodobenzylguanidine or ^{111}In -octreotide and chemotherapy. However, prolonged survival and improved quality of life can be achieved in many patients with neuroendocrine liver metastases following resection, RFA, TACE, TARE and liver transplantation.



Chapter 11: Congenital Hyperbilirubinemias

P. Paré



1. Introduction

The importance of recognizing congenital hyperbilirubinemia lies mainly in distinguishing it from other, more serious hepatobiliary diseases. Except for Crigler-Najjar syndrome, congenital hyperbilirubinemias do not impair either the quality of life or the life expectancy of affected subjects. Persons with congenital (recessive) hyperbilirubinemia have normal standard liver tests (except of course for elevated serum bilirubin concentrations). The liver histology is also normal, (except for the black pigment accumulation in centrolobular hepatocytes Dubin-Johnson syndrome). With the exception of Gilbert's syndrome, these syndromes are distinctly uncommon and are divided into two groups on the basis of the type of the serum hyperbilirubinemia (Table 1).

Practice points:

- Unconjugated hyperbilirubinemia in absence of hemolysis, is usually secondary to congenital defect in glucuronidation of bilirubin.
- Congenital hyperbilirubinemia does not impact on life expectancy or quality of life of affected individuals, except for Crigler-Najjar type I syndrome, in which patient may require a liver transplantation.

2. Unconjugated Hyperbilirubinemia

2.1. Gilbert's Syndrome

Gilbert's syndrome is the most common congenital hyperbilirubinemia syndrome. Its pathogenesis is related to a partial deficiency in hepatic uridinediphosphoglucuronate glucuronosyltransferase (UGT) enzyme. It is due to a mutation in the promoter region of the UGT1A gene, upstream to exon 1 of the gene encoding bilirubin-UGT. Approximately 9% of the general population in Western countries are homozygous for the variant promoter, and 30% are heterozygous. Other factors are probably involved in the clinical expression of the Gilbert's phenotype since not all homozygous carriers develop hyperbilitubinemia. The syndrome manifests itself only in homozygous individuals; its inheritance is therefore consistent with an autosomal recessive trait. Gilbert's syndrome is usually detected in adolescents and young adults, most commonly in males. Clinically, it does not cause symptoms, scleral icterus may be present slight, and fluctuating, and the physical examination is otherwise normal. Liver tests and hemogram (to exclude hemolysis) are normal except for unconjugated serum bilirubin which is elevated between 20 and 100 $\mu\text{Mol/L}$.

Certain conditions can increase the plasma bilirubin concentrations to higher values (usually less than 200 $\mu\text{Mol/L}$): hemolysis, fasting, a normocaloric diet without lipids, intercurrent febrile illnesses, stress, physical exertion. Hepatic enzyme inducers such as phenobarbital and clofibrate can normalize plasma bilirubin concentrations within a few weeks.

The long-term outcome of subjects with Gilbert's syndrome is similar to that of the general population. In neonates, it may be associated with increased duration or severity of normal post-partum physiological jaundice. Diagnostic tests are usually not necessary but genetic testing is available in certain laboratories. The most important aspect is to recognize the syndrome distinguishing it from other causes of elevated unconjugated hyperbilirubinemia.



Table 1. Congenital syndromes of hyperbilirubinemia

	Unconjugated Hyperbilirubinemia			Conjugated Hyperbilirubinemia	
	Gilbert's	Crigler-Najjar type 1	Crigler-Najjar type 2	Dubin-Johnson	Rotor's
➤ Prevalence	7% of population	Very rare	Uncommon	Uncommon	Rare
➤ Inheritance (all autosomal)	Recessive	Recessive	Recessive	Recessive	Recessive
➤ Serum bilirubin concentration ($\mu\text{mol/L}$)	< 100 (all unconjugated)	> 400 (all unconjugated)	< 400 (all unconjugated)	< 100 (about half conjugated)	< 100 (about half conjugated)
➤ Genetic basis	Defect in promoter region of UGT1A1 gene, reduced UGT enzyme activity	Alterations in UGT1A1 gene & absent UGT enzyme activity	Point mutations in UGT1A1 gene → reduced UGT enzyme activity	Mutations in MRP2 gene → reduced excretion of organic anions (except blue acids)	Genetic basis unknown
➤ Diagnostic features	Unconjugated Bilirubin concentration: ↑ with fasting, ↓ with phenobarbital	Unconjugated bilirubin: No response to phenobarbital	Unconjugated Bilirubin concentration: ↓ with phenobarbital	Urinary coproporphyrin excretion (isomer 1 > 80%) - Pigment in centro-lobular hepatocytes - Oral cholecystogram shows delayed or absent	Urinary Coproporphyrin excretion of isomer 1 < 80%
➤ Prognosis	Normal	Early death from kernicterus	Usually normal	Normal Excretion	Normal
➤ Treatment	None needed	Liver graft	Phenobarbital	Avoid estrogen	None available

2.2. Crigler-Najjar Syndrome

The Crigler-Najjar syndrome is a rare autosomal recessive disorder. It may present in two types. The phenotypes of the syndromes are caused by a variety of alterations in the coding sequences of the UGT1A1 gene, in contrast to Gilbert's



syndrome in which the defect is in the promoter region rather than in the gene itself. In type I, a variety of mutations leads to absent UGT enzyme activity. In type II, genetic lesions consist of point mutations resulting in the substitution of a single amino acid, leading to markedly reduced enzyme activity.

Type 1 is a serious disease characterized by unconjugated hyperbilirubinemia often greater than 400-500 $\mu\text{Mol/L}$. Jaundice occurs almost immediately after birth and may lead to kernicterus with consequent neurologic damage and mental retardation. Kernicterus involves damage to the basal ganglia and cerebral cortex because unconjugated bilirubin is able to penetrate the immature blood-brain barrier of infants. Untreated, death occurs early. Nowadays, most patients treated with phototherapy and plasmapheresis survive postpuberty without significant brain damage. Subsequently, due to thickening of the skin making phototherapy less effective, patients succumb to kernicterus later in life. Liver transplantation is the only curative treatment. Gene therapy may eventually improve the outcome.

Type 2 syndrome is a much more benign condition in which unconjugated hyperbilirubinemia usually does not exceed 400 $\mu\text{mol/L}$. Patients are much less likely to develop neurologic consequences. Specific therapy may not be necessary. If necessary, phenobarbital or clofibrate reduces bilirubin levels by at least 25% and may improve quality of life of some individuals. Prognosis is good, despite a lifelong persistent unconjugated hyperbilirubinemia.

An important research agenda explore gene therapy for Crigler -Najjar type I syndrome.

3. Conjugated Hyperbilirubinemia

Two conditions characterized by congenital conjugated hyperbilirubinemia without cholestasis have been described, Dubin-Johnson and Rotor syndrome are inherited as autosomal recessive traits. Both are uncommon, believed to result from specific defects in the hepatobiliary excretion of bilirubin. These conditions are benign, and their accurate diagnosis provides reassurance to the patient. Plasma bilirubin levels are usually in the range of 35-85 $\mu\text{mol/L}$. Plasma bilirubin may increase further in both conditions during intercurrent infection, pregnancy or use of oral contraceptives. Pruritus is absent and serum bile acid levels are normal, as are routine liver tests, except for the serum bilirubin concentration. Bilirubinuria is usually present. No treatment is necessary.

Diagnosis is made by documenting conjugated hyperbilirubinemia (where at least 50% of the total bilirubin is the direct fraction) while other liver tests are normal. Distinction of the two syndromes is made by the characteristic urinary coproporphyrin excretion (D-J, isomer 1>80%; Rotor, isomer 1<80%).

Some distinctive features allow differential diagnosis between the two syndromes.

3.1. Dubin-Johnson Syndrome

The syndrome results from mutations in the MRP2 gene. Biliary excretion of organic anions, except bile acids, is impaired. Patients have a black liver, which results from the accumulation of a melanin-like pigment in lysosomes. Visualization of the



gallbladder during oral cholecystography is usually delayed or absent. Urinary excretion of total coproporphyrin is normal, whereas the proportion of isomer 1 is higher than in normal controls (>80%).

3.2. *Rotor's Syndrome*

The genetic basis of Rotor's syndrome has not been identified. It is a disorder of hepatic storage. The appearance and histology of the liver are normal. Oral cholecystography usually visualizes the gallbladder. Total coproporphyrin excretion is greater than normal, as in other hepatobiliary disorders, and isomer 1 makes a smaller proportion (<80%) than in Dubin-Johnson patients.





Chapter 12: Drug-Induced Liver Injury

M. Gupta and A. B. R. Thomson



1. Background

Drugs are the second most common cause of acute liver failure, and are the predominant cause of liver injury in the Western world. Drugs account for about 25% of persons admitted for acute hepatitis, and about 50% of persons admitted with acute liver failure (ALF). However, fewer than 10% of drug induced liver injury (DILI) progress to ALF. Incidence has been estimated to be 1-2/million. However, 80% who develop ALF need transplantation or might die. Adverse events (AEs) can either occur secondary to escalation of drug dosing, or be an idiosyncratic reaction. Rarely do these patients have a background history of liver disease (Andrade et al., Gastro 2005; 129:512-21). The risk of an adverse event (AEs) to a drug is quoted as AEs per number of persons exposed. For example, the risk of hepatic toxicity from NSAIDs is approximately 5/10⁵ persons exposed, 1/10⁵ for amoxicillin-clavulanic acid. Drug-induced liver injury (DILI) is under recognized because the diagnosis is often based in the exclusion of other conditions. It has been estimated that the incidence of DILI is approximately 10 cases per 100,000 patient years.

When the serum ALT (Alanine Aminotransferase), AP (Alkaline Phosphatase) or bili' (bilirubin) rise to two-times the upper limit of normal or higher, it is prudent to explore the possibility of liver disease caused by drugs. If a medication is having a toxic effect on the liver, it should be stopped quickly in the hope that the liver damage will not progress. However, despite that, many cases follow a sub-acute course with progression to liver failure. This is important, because the mortality rate for the persons hospitalized for DILI (adverse hepatic drug reactions associate with an abnormal liver biopsy) is 10%, largely related to acute liver failure (such as from acetaminophen). According to the Zimmerman "Hej's rule", ALT > 8x ULN, or ALT plus bilirubin increases suggest the 10% potential for acute liver failure. Use of a web-based search for drug effects in a patients dossier will show that most drugs can result in abnormal liver enzymes tests (LEs) or liver function tests (LFTs). Hence, virtually any drug, toxin or herbal preparation may damage the liver. At least 300 agents have been targeted.

The Acute Liver Failure Study Group from 23 US academic centres reported 1400 cases of acute liver failure (ALF) over the decade ending in 2008 (Stravitz and Kramer, 2009). Excluding the cases of acetaminophen (45%) overdose, 15% of cases were idiosyncratic reactions to drugs (e.g. NSAIDs, anti-convulsants, antibiotics). Marked elevations in transaminases reflect an hepatocellular pattern in 87% of patients, while 13% had a cholestatic pattern. Hepatocellular variety has been documented to carry worse prognosis, compared to cholestatic. It is important to note that the drug-associated ALF patients are often found to have consumed the offending drug for a median of three months. So it is important to obtain an extensive list of all medications including OTC (over-the-counter), prescription drugs and herbal preparations taken in the past several months. There was a wide range of offending drugs (Table 1).



The outcome of persons with drug-induced ALF is poor: without a liver transplantation, about one third died (Table 2).

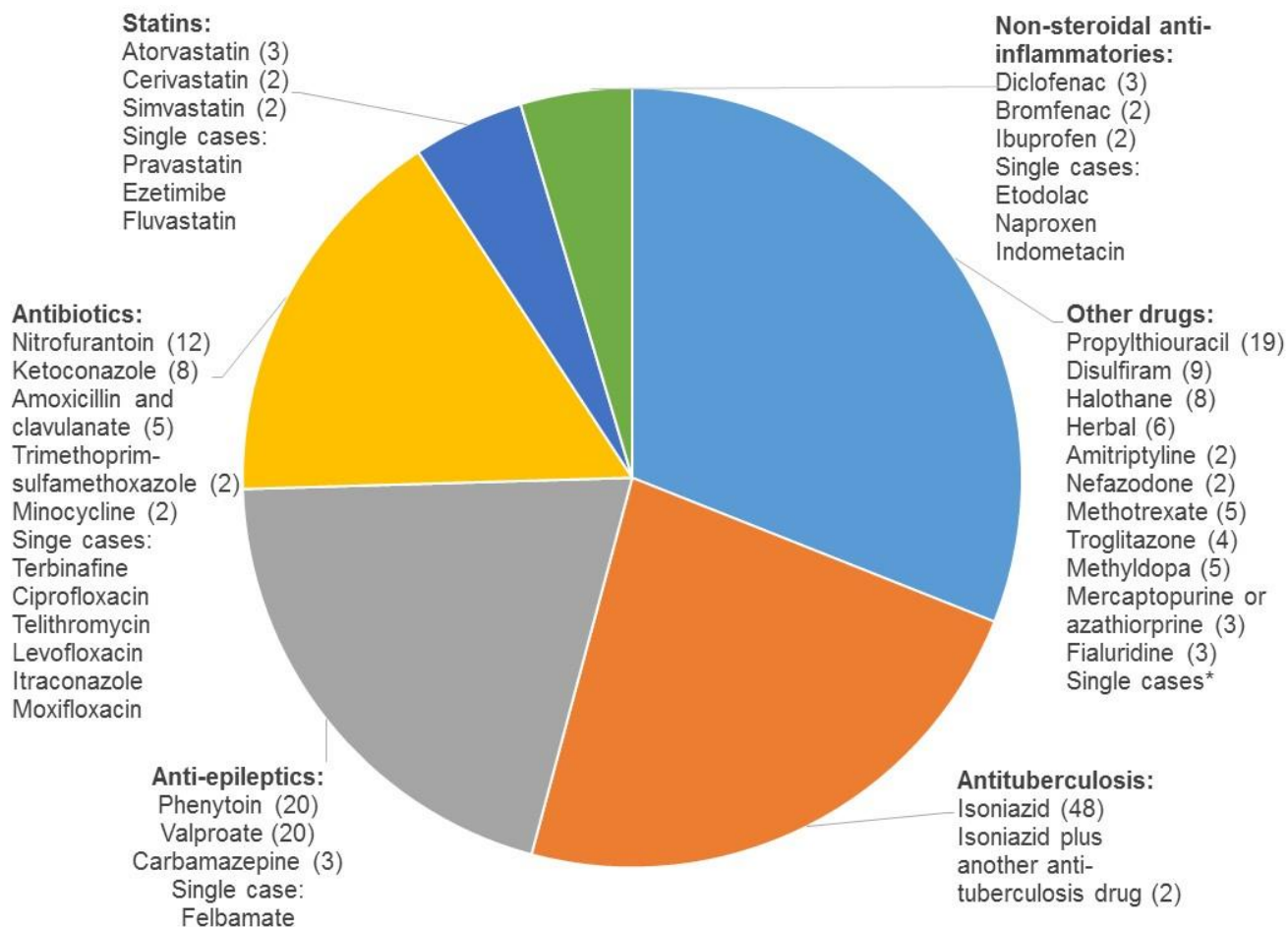


Figure 1. Non-paracetamol-based drugs causing acute liver failure in patients requiring emergency liver transplantation in USA, 1987-2006

Permission granted: Bernal et al., *Lancet* 2010; 376:190-201.



Table 1. Drugs other than acetaminophen implicated in causing acute liver failure

-
- Antibiotics
 - Isoniazid alone, or in combination with other antituberculosis drugs
 - Nitrofurantoin
 - MSK
 - NSAIDs
 - Metabolic
 - Statins
 - Propylthiouracil
 - Anti-seizure
 - Phenytoin
 - Miscellaneous
 - Complementary or alternative medications, or illicit “street” drugs
-

Source: Reuben A, et al. Drug-induced acute liver failure: Results of U.S. multicentre, prospective study. *Hepatology* 2010;52:2065.

Table 2. Outcome of non-acetaminophen-associated cases of acute liver failure (ALF)

○ Liver transplantation	42%
○ Died while waiting liver transplantation	13%
○ Not suitable for liver transplantation and died	18%
○ Spontaneous recovery	27%

It is important to remember medications used to treat various complex medical diseases may be associated with liver damage. Thus, assuming that the abnormal liver enzyme abnormality is due to the underlying disorder for which the medications are being used is not always sufficient to explain the extent of abnormal LEs (Table 3).



Table 3. Drug associations with other diseases, and genetic determinants

➤ Drug Associations with other diseases		
○ ASA (salicylates)	- Rheumatoid arthritis in adults	
○ Methotrexate (hepatic fibrosis)	- Accentuated by ALD and NAFLD, diabetes, obesity, chronic renal disease	
○ Tetracycline (fatty liver)	- Renal disease	
○ Anti-cancer drugs (sinusoidal Obstruction Syndrome)	- Bone marrow transplant, HCV	
○ Sulfonamide	- HIV/AIDS	
○ Azathioprine (vascular disease)	- Renal transplantation patients	
➤ Genetic determinants		
○ Penicillin		
○ Valproic acid (inherited mitochondrial diseases)		
○ Amoxicillin-clavulanic acid (HLA halotype associates)		

Table 4. Treatment for GI disorders commonly associated with Hepatotoxicity

➤ Esophagus	○ H ₂ -RAs, PPIs ○ Beta-blockers ○ Calcium Channel Blocker	- gastrointestinal reflux disease - portal hypertension esophageal - -- dysmotility syndromes
➤ Stomach	○ H ₂ -RAs, PPIs ○ ASA, NSAIDs, COXIBs	- peptic ulcer disease, dyspepsia, - gastroprotection - gastric damage (ulcers, upper GI bleeding; gastric or duodenum), perforation
➤ Small bowel	○ Azathioprine, methotrexate, Salazopyrine/mesalamine	- inflammatory bowel diseases
➤ Liver	○ HAART, alcohol	- HIV/AIDS

2. Risk Factors

The risk of drug AEs depends on the drug in question, and is influenced by genetic factors; age (<60 yr); gender; dose; duration of alcohol use; obesity; current nutritional status; family history; previous liver disease; previous drug reactions.

There are three inducible/adaptable hepatic pathways of drug metabolism:

I – Alter the parent drug molecule by oxidation, reduction, or cytochrome P450 enzymes via more than 20 hydrolytic reactions



- II– Conjugation with sugar, amino acid or sulphate to increase water solubility, and therefore excretion of drug (e.g. glucuronyl transferase).
- III–Energy dependant carrier-mediated excretion of drug, its metabolite or conjugate into bile by ATP-binding cassette (ABC) proteins such as MDR₁ (multidrug resistance protein 1) and MRP's (multidrug resistance-associated proteins)

Presence of deep jaundice, raised ALT/AST and increasing age are associated with a higher mortality (Bjornsson et al., *Hepatology* 2005; 42:481-9). There are numerous mechanisms of liver injury, but it is not always possible to determine which mechanism of injury is responsible for the hepatotoxicity (Table 5).

Drug-associated liver injury may have no known explanation (“idiosyncratic”) mitochondrial damage leading to features including microvascular fatty liver and inhibition of hepatic mitochondrial DNA replication. DILI may cause cholestasis resulting from impairment of the hepatobiliary system for bilirubin or bile acid uptake, as a result of the offending drug binding to transporters (eg, systems for bilirubin or bile acid uptake, as a result of the offending drug binding to transporters (eg, BSEP [ABC B11], MDR1 [ABCB1], MRP2 [ABCC2] and MDR3 [ABCB4]). Finally, drugs or drug metabolites may act as haptens and bind covalently to hepatic proteins. These drug-protein adducts may lead to an immune response involving CD4⁺, CD8⁺ t-cells, and Fas ligand mediated hepatocyte apoptosis.

Table 5. Mechanism of liver injury by drug and toxins

- Direct damage to hepatic membranes and mitochondria
- ROS (reactive oxygen species) overwhelming hepatic antioxidant systems such as the glutathione system, activating signalling by Fos, JNK (impaired assembly of microtubules and abnormal folding of protein, p53)
- Oxidation of proteins, fatty acyl groups of phospholipids (lipid peroxidation) and nucleosides
- Post-translational changes in proteins through ADP ribosylation or protease activation, activation of endogenous endonucleases and cleavage of DNA, activation of phospholipases leading to membrane damage
- Activation of hepatic stellate cells and Kupffer cells, as well as damage to endothelial cells
- Immunopathogenic mechanism such as formation of neoantigens (haptens) or drug-protein adducts, or drug-induced autoimmunity leading to drug-induced antibodies
- Hepatic drug reactions may be dose-dependent or idiosyncratic due to metabolic idiosyncrasy or immune allergy

Just as there are several mechanisms responsible for liver injury, different hepatic cell sites may be involved, giving rise to a range of clinical presentations.



Table 6. Drug induced hepatic injury may affect several different cellular sites and give rise to various presentations

Cellular Site	Type of Hepatic Injury
○ Hepatocyte	- Hepatitis: acute, chronic, granulomatous
○ Bile duct	- Cholestasis: with or without associated hepatitis or bile duct injury
	- Cholangitis: with or without cholestasis, vanishing bile ducts, or sclerosis
○ Fat cells	- Steatohepatitis
	- Acute steatosis
○ Sinusoidal cells	- Sinusoidal obstruction syndrome
	- Nodular regeneration hyperplasm
○ Tumors	- Adenoma, HCC, angiosarcoma

3. Clinical Presentation

There are a variety of presentations for the persons with drug associated hepatotoxicity, ranging from the finding of abnormal liver enzyme tests in the asymptomatic persons, to life-threatening, systemic acute liver failure (Figure 1, Table 7). A recent NIH workshop has provided a framework for making the diagnosis of DILI.



Table 7. Clinical features of acute liver failure

-
- Whole body
 - Systemic inflammatory response
 - High energy expenditure and catabolism
 - Liver
 - Loss of metabolic function
 - Decreased gluconeogenesis leading to hypoglycemia
 - Decreased lactate clearance leading to lactic acidosis
 - Decrease ammonia clearance leading to hyperammonemia
 - Decreased synthetic capacity leading to coagulopathy
 - Lungs
 - Acute lung injury
 - Adult respiratory distress syndrome
 - Adrenal gland
 - Inadequate glucocorticoid production contributing to hypotension
 - Bone marrow
 - Frequent suppression, especially in viral and seronegative disease
 - Circulating leukocytes
 - Impaired function and immunoparesis contributing to high risk of sepsis
 - Brain
 - Hepatic encephalopathy
 - Cerebral edema
 - Intracranial hypertension
 - Heart
 - High output state
 - Frequent subclinical myocardial injury
 - Pancreatitis
 - Particularly in paracetamol-related acute liver failure
 - Kidney
 - Frequent dysfunction or failure
 - Portal hypertension
 - Might be prominent in subacute disease and confused with chronic liver disease
-

Permission to reprint: Bernal et al., *Lancet* 2010; 376:190-201



Table 8. From asymptomatic to life threatening presentations

-
- Suspicion: Drug, rash, eosinophilia, organ involvement
 - Reactive metabolite syndrome (RMS) – idiosyncratic drug reactions in any organ system
 - Associated Risk factors

RMS in 1 st degree relative	1 in 4
Use of steroids, valproic acid	5-X ↑
Lupus	10-X ↑
HIV/AIDS	100X ↑
 - Acute liver failure
-

4. Example of Drugs

4.1. Acetaminophen

Acetaminophen is an effective over-the-counter analgesic, and is safe when taken in a daily dose that does not exceed 4 gm. It is an example of dose-dependant hepatotoxicity. It is the # 1 cause of ALF in the USA, UK and Western Europe. There are many risks which modify the risk of hepatotoxicity. For example the malnourished, alcoholic taking an acute dose of acetaminophen of >100mg/kg or a 10 to 20 gm dose over three days will develop: acute zone 3 necrosis, extending to bridging or panacinar (massive) necrosis. Liver failure may result from attempted suicide or therapeutic misadventure, as confirmed by a recent literature review (Larson et al., 2005). Remember the rule of “20s”. Fatal cases usually involve 20 gm acetaminophen (caution in the heavy alcohol abuser, where even 2 gm may be fatal). Over 20% develop severe liver injury, and of these, 20% die from the hepatotoxicity.

There are two mechanisms of DILI for acetaminophen. The metabolism involves the formation of the highly reactive intermediate metabolite, NAPQ1 (N-acetyl-p-benzo quinone imine). At therapeutic doses, only a small amount of acetaminophen is initially metabolized by the phase I reactions of cytochrome P450 (CYP) –mediated oxidation, followed by phase II conjugation reactions. What acetaminophen which is oxidized by the CYP2E1 and CYP3A4 isozymes produces only a small amount of NAPQ1, which is readily detoxified by binding of the small amounts of NAPQ1. In contrast, when high doses (generally > 4 gm/day) of acetaminophen are ingested, the sulfation and glucuronidation pathways are overcome, the NAPQ1 is not detoxified, the liver stores of glutathione are depleted, and the excess NAPQ1, damages the liver by binding to intracellular proteins, preventing the normal function of the nuclei and mitochondria. This in turn leads to the production of reactive oxygen species, hepatocellular apoptosis, and centrilobular necrosis. If the necrosis is sufficient, the person develops acute liver failure.

The second mechanism of acetaminophen toxicity relates to possible genetic polymorphism in the genes which encode the enzyme such as glutathione S-



transferase as well as those of the CYP family, leading to the recognized variability of person's susceptibility to develop DILI. Also, results of studies in animal models and humans suggest a role for variation in the expression of CD44 in acetaminophen hepatotoxicity.

Hyperacute injury to the liver occurs within 48 to 72 hours after acetaminophen ingestion. Characteristically, ALT and AST levels rise > 1000 u/L (often 2000 to 10,000 u/L) with associated low bilirubin. There may be nausea, vomiting, fever, malaise, pain (acute dilation of liver with stretching of pain-sensitive liver capsule membrane), with associated symptoms/signs of liver failure [such as jaundice, coagulopathy, renal failure hepatorenal syndrome or acute tubular necrosis (ATN), and hepatic encephalopathy]. Death can occur in 4 to 8 days from cerebral edema, sepsis, liver and multi-organ failure.

After 4 hours of taking an overdose, when most of the acetaminophen has been emptied from the stomach and absorbed, blood levels reflect the prognosis. The risk is assessed with the Prescott nomogram, which plots the plasma concentration of acetaminophen versus hours post-ingestion. Note that with chronic intake, blood levels of acetaminophen are not a reliable indicator of liver injury as it is with acute overdose. The use of cysteine (thiol) donors orally or IV NAC (N-acetyl cysteine) (e.g. oral dose: 140 mg/kg loading dose, then 70 mg/kg every 4 hours for 72 hours) should be administered as late as 36 h after self poisoning as it may be beneficial. If the patient cannot retain orally administered NAC, then the thiol donor may be given intravenously, although the risk of adverse events (rash, angioedema, shock and death) is slightly higher compared to oral route.

From an understanding of the metabolism of acetaminophen we can appreciate the reason for the lag interval, variable dose dependency, effects of alcohol, drugs, fasting, and malnutrition, and the potential therapeutic benefit of a cysteine donor. With acute doses of acetaminophen (> 10 g/day), and during the first 48 hours after overdose the primary pathway is overwhelmed and the secondary pathway becomes involved (Figure 2). The oxidative metabolism of acetaminophen to NAPQ₁ and subsequent oxidation of thiol injures mitochondrial function and activates pathways for all cells by the induced cytochrome P450 system (CYP 2E1 or CYP 3A4), and by competing with glucuronidation pathways. The depletion of glutathione (e.g. alcohol abuse) leads to an accumulation of oxidative toxic NAPQ₁, resulting in hepatotoxicity. Fasting reduces the cofactors needed for glucuronidation and sulfation, depletes hepatic glutathione, and induces CYP 2E1. Alcohol also increases the expression of CYP 2E1, and depletes glutathione. The administered NAC stimulates the hepatic synthesis of glutathione, providing a means to continue the metabolism of acetaminophen without its oxidation to NAPQ₁.

When the patient presents with acute liver failure and acetaminophen toxicity is suspected, it is important to start treatment (Table 9) with NAC. Even in non-acetaminophen related toxicity, there is now mounting evidence that NAC provides anti-oxidative benefits and reverses toxic effects in the body. Spontaneous resolution of acetaminophen related DILI is high at 65%, and therefore the need for transplantation in



this group is low. Comparatively, non-acetaminophen DILI is associated with 30% spontaneous survival. In patients who do not have spontaneous resolution, risk stratification for emergency liver transplantation is required (acetaminophen and non-acetaminophen toxicity) (Table 10).

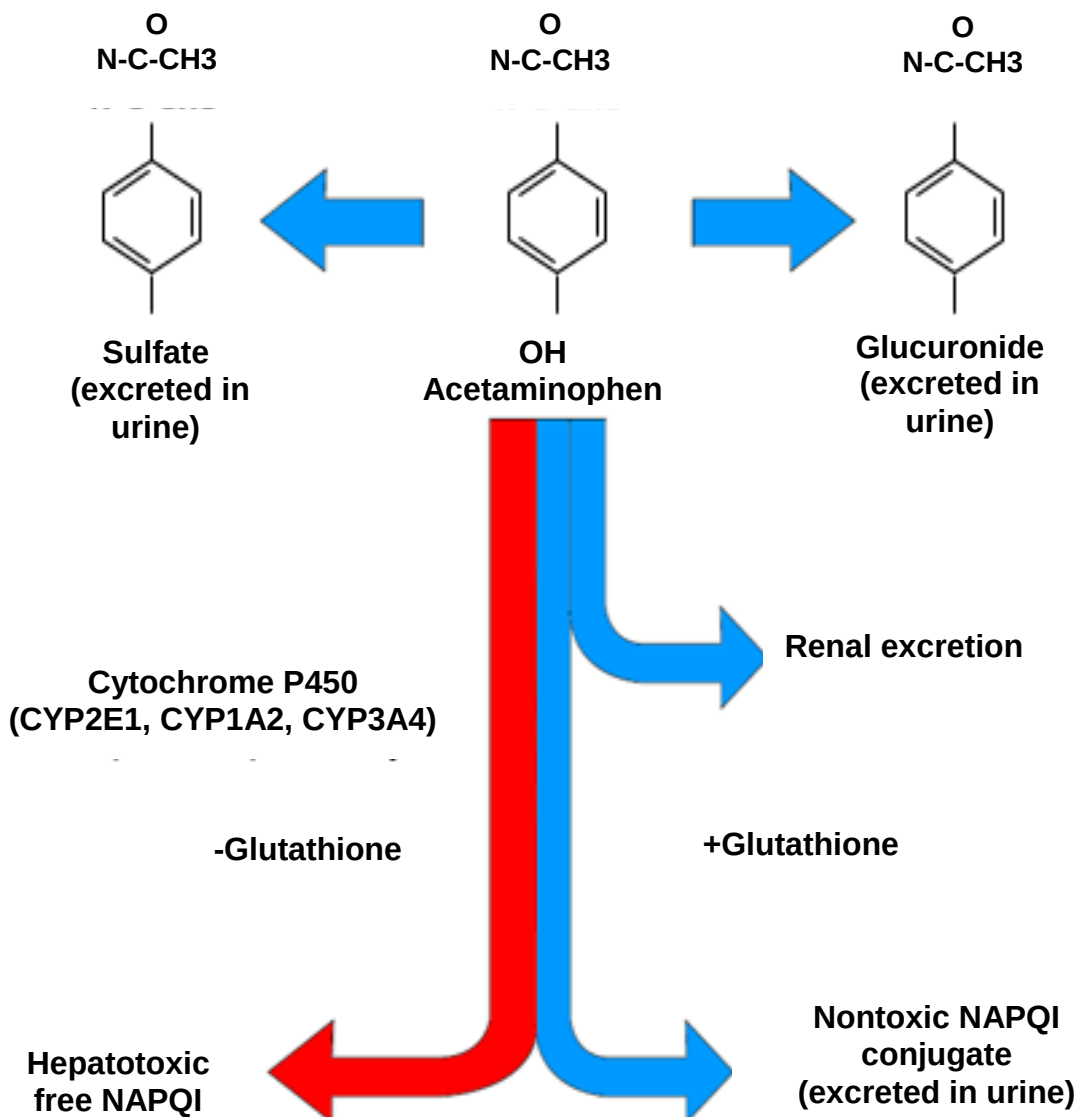


Figure 2. Pathophysiology of acetaminophen toxicity (UptoDate 2011)



Table 9. The management of patients with acetaminophen (ACM) overdose

-
- Initial measure
 - ABC's
 - Rule out other co-ingestions
 - Contact liver centre
 - Serum ACM level, urine toxicology screen, LFT's, INR, arterial lactate
 - Determine likelihood of hepatotoxicity from normal nomogram (except in non-intentional cases)
 - Within 4 hrs of ingestion of acetaminophen, charcoal may be given prior to starting NAC
 - Oral N-Acetylcysteine (NAC)
 - Loading dose: 140 mg/kg po/NG x1
 - 70 mg/kg q 4 hours x 17 doses
 - Compazine/raglan for nausea prn
 - Cimetidine (P450 inducer)
 - IV N-Acetylcysteine (NAC)
 - Dose 1. Loading dose: 140 mg/kg NAC in 200 ml D5W over 1 hr.
 - Dose 2. 50 mg/kg NAC in 500 ml D5W over 4 hours.
 - Dose 3. 125 mg/kg NAC in 1000 ml D5W over 19 hrs.
 - Dose 4. 150 mg/kg NAC in 1000 ml D5W over 24 hrs.
 - Dose 5. 150 mg/kg NAC in 1000 ml D5W over 24 hrs.
 - Caution
 - Do not administer NAC to patients with known sulfa allergy
 - Administer IV formulation of oral NAC through a leukopore filter in a monitored setting after consent obtained from patient/family.
 - IV infusion of NAC leads to anaphylactic/hypersensitive reactions in 3 to 5% most commonly during loading dose.
 - Hold and reduce infusion rate by 50% if rash/nausea occurs (rare). Administer fluids, IV Benadryl, IV steroids as needed.
 - Psychological assessment
 - Seek transplant centre assessment if hepatic failure (encephalopathy of grade 1 → 4, ATN, hepatorectal syndrome, jaundice, coagulopathy)
-



Table 10. The King's College risk stratification criteria for liver transplantation in Acute Liver Failure

-
- Acetaminophen
 - INR > 6.5 (PT > 100 sec), serum creatinine > 3.4 mg/dl, stage 3 or 4 encephalopathy
 - Arterial lactate > 3.5 4 hours after resuscitation
 - pH < 7.30 or arterial lactate > 3.0 12 hours after resuscitation; or
 - Non-acetaminophen
 - INR > 6.5 (PT > 100 sec); or
 - Any 3 of the following:
 - INR > 3.5 (PT > 50 sec)
 - Age < 10 or > 40 years
 - Bilirubin > 17.5 mg/dl
 - Duration of jaundice > 7 days
-

4.2. Antiretroviral Agents

Hepatic damage is not uncommon with nucleosides and nucleotide reverse transcriptase inhibitors, as well as protease inhibitors. Persons with HIV/AIDS may be co-infected with HBV or HCV. Immune reconstitution following HAART may activate previously inactive HBV. In addition, this person may over-use alcohol, have other types of hepatic infections, lymphoma or other hepatic tumors, HIV infection itself as well as the drugs used to treat HIV/AIDS can induce DILI. Therefore, it is important to consider all these factors, as they contribute to liver damage.

The blockers of reverse transcriptase of HIV inhibit mitochondrial DNA and reduce oxidative phosphorylation. This leads to fatty liver (micro- and/or macrovascular steatosis), insulin resistance with lactic acidosis and acute liver failure. The onset of these abnormalities will usually be about 6 months into the treatment.

Acute hepatitis occurs in 3% to 30% of persons taking the protease inhibitor ritonavir. Acute liver failure is rare; the unconjugated hyperbilirubinemia seen in 7% of persons given protease inhibitors does not forebode progression to severe cholestasis.

4.3. Aspirin (ASA)

When ASA is given in high dose (blood salicylate > 25 mg/100 ml), and especially to persons with juvenile rheumatoid arthritis or SLE (systemic lupus erythematosus), there may be marked rises in transaminase levels. Fortunately, acute liver failure is rare, and the drug hepatotoxicity resolves when ASA is stopped. The ASA damage is dose-dependent, so it is safe to restart ASA but at a lower dose.

4.4. Sulfasalazine and Mesalamines

Salazopyrine (salicylazosulfapyrine) and mesalazine (mesalazine, 5-aminosalicylate) used in persons with Crohn disease or ulcerative colitis cause an increase in serum ALT and AP, as well as rare cases of chronic hepatitis and the



formation of hepatic granulomas. Thus, possible drug toxicity must be included in the differential diagnosis of abnormal liver enzymes in persons with IBD (inflammatory bowel disease).

4.5. NSAIDs and Coxibs

Celecoxib, a COX-2 inhibitor, has a sulfa moiety that may result in a cross sensitivity reaction in persons who are intolerant of sulphonamides. NSAIDs may be associated with the development of hepatocellular injury or cholestasis. With Diclofenac, for example, hepatotoxicity occurs in about 5 persons per 10⁵ exposed, but clinical hepatitis is uncommon, and fatalities are exceedingly rare.

4.6. H₂- Receptor Antagonists (H₂-RAs) and Proton Pump Inhibitors (PPIs)

Rare cases of mild acute hepatitis, sometimes associate with cholestasis, have been reported with histamine H₂-receptor antagonists. It is not certain if the rare cases of hepaototoxicity reported in persons taking PPIs were actually drug-related.

4.7. Calcium Chanel Blockers (CCBs) and B-Adrenergic Blockers (BBs)

There have been rare case reports of acute hepatitis with calcium channel blockers. While the acute hepatitis seen with beta-blockers is rare, it may be serious.

4.8. Anti Tuberculosis Therapy

For every 100,000 persons given Isoniazid, about 2000 will develop hepatitis, and approximately 150 will die from acute liver failure. After acetaminophen, isoniazid-hepatitis is the second most common reason for the liver transplantation for drug-induced liver injury. The risk of this adverse effect increases with age; infection with HIV, HCV and possibly HBV; chronic alcohol use; malnutrition; as well as intake of acetaminophen, rifampin and pyrazinamide.

It is important to stress that the hepatotoxicity of isoniazid does not relate to the dose or blood level. Because up to one third of persons taking INH will have an elevated serum ALT within the first 10 weeks of taking the drug, and may fall even with continuation of drug, measuring serum ALT every 2 to 4 weeks may not necessarily detect severe liver damage. It is uncertain if or when blood monitoring should be done. However, for any person on INH who develops clinical symptoms of hepatitis (anorexia, nausea, vomiting, malaise, fatigue, usually within 1 to 26 weeks of staring INH), the drug must be stopped immediately, regardless of the values of LEs and LFTs.

4.9. Anti-fungals

While some 10% of persons on ketoconazole and 5% on fluconazole have abnormal ALTs, symptomatic hepatitis from ketoconazole occurs in only about 10/10⁵ exposed persons, and is usually mild. The severe hepatic necrosis from fluconazole is even less common, but it can cause derangement in all Les (ALT, AST, AP, bili).



4.10. Anti-depressants

TCAs (tricyclic antidepressants) may cause cholestatic injury which is rarely prolonged. SSRI (selective serotonin reuptake inhibitors) have a good safety profile, with only very rare cases of centrilobular necrosis which may be massive or submassive.

4.11. Immunosuppression agents

Azathioprine or methotrexate may frequently be used in persons with chronic hepatitis or inflammatory bowel disease (Crohn disease or ulcerative colitis). Azathioprine hepatitis occurs with a frequency of about $100/10^5$. The dose and duration of therapy do not predict the likelihood of hepatocellular injury, although monitoring of ALT and AP are still generally recommended. The range of possible liver damage is extensive (Table 11).

Table 11. Hepatic damage associated with the use of azathioprine

-
- Biochemical changes, asymptomatic
 - Cholestasis, cholestatic hepatitis with bile duct injury
 - Vascular injury
 - sinusoidal obstruction syndrome (hepatic venous outflow, previously called veno-occlusive disease)
 - Peliosis hepatitis
 - Nodular regeneration hyperplasia
 - Non-cirrhotic portal hypertension
 - Hepatocellular carcinoma
-

The hepatotoxicity with methotrexate can occur with both high and low dose weekly MTX, as used in IBD or RA. The reported incidence of MTX induced ALT rise is 14% and 8% for AST. The LEs tend to resolve within one month of discontinuation. Persons with pre-existing liver disease, chronic excessive use of alcohol (3-fold increase risk of hepatotoxicity with MTX intake with consumption of > 15 g alcohol/day), obesity, diabetes, chronic renal disease, use of NSAIDs or vitamin A may have an increased risk of hepatic damage. After a total intake of 5 g (maintenance MTX in Crohn disease is 25 mg/week, 1300 mg/year, so after about 4 years of MTX), the IBD patient would be at risk: about 20% will develop NASH, 3% hepatic fibrosis. However, clinically significant liver disease is rare. Regardless, all patients are recommended to be on folic acid to reduce side effect profile. Because change in LEs are neither sensitive nor specific, the clinician needs to depend instead on finding hypoalbuminemia (hyperbilirubinemia and increase INR are rare) or hepatomegaly. It remains disputed how to surveillance these patients, when or if liver biopsy should be performed to detect MTX-associated liver damage. A liver biopsy can be considered if cumulative dose of 1000-1500mg has been achieved. However, the jury is still out.



4.12. Oral Contraceptives

There is a widespread use of oral contraceptive agents in young women, and several cholestatic hepatic toxicities are recognized (Table 12).

Table 12. Hepatobiliary complications of the use of oral contraceptive agents

-
- Gallstone
 - Cholestasis
 - Unmasking cholestatic disease such as primary biliary cirrhosis
-

4.13. Herbal preparations

With the public's enthusiastic use of herbal preparations and the potential for some of these agents to cause hepatocellular injury and even acute liver failure, a careful historical inquiry into use of herbal preparations must be made in any person with abnormal LFTs or suspected liver disease, or acute liver failure.

5. Drugs causing Chronic Hepatitis

Some drugs such as nitrofurantoin, methyldopa and minocycline may cause chronic hepatitis, especially in older women who have been on the drug for a long interval. The hepatitis usually responds to stopping the offending agent. In another form of chronic drug-associated hepatotoxicity, anti-nuclear and anti-smooth muscle antibodies develop. Again, stopping the offending drug forms the basis for the recommended therapy.

In persons with known cirrhosis, there will be reduced mass of healthy liver cells capable of metabolizing drugs handled by the liver, and the dose of the drug will need to be reduced ("hepatic dosing") (Table 13). In the same token, there are drugs which are relatively contraindicated in persons with liver disease (Table 14). It is unreasonable to commit these long list to memory, but this information would be useful for you to have handy on your iPhone .



Table 13. Drugs for which lower doses are recommended in patients with cirrhosis

-
○ Acetaminophen	○ PPIs
○ Benzidiazepine	○ Repaglinide
○ Beta-blockers	○ Risperidone
○ Cetirazine	○ Sertraline
○ Fluoxetine	○ Topiramate
○ Indinavir	○ Tramadol
○ Lamotrigine	○ Valproic acid
○ Losartan	○ Venlafazine
○ Moricizine	○ Verapamil
○ Narcotics	
-

Table 14. Drugs which are relatively contraindicated, or which must be used very cautiously in persons with liver disease

-
○ Alcohol	○ Naltrexone
○ Clonazepam	○ Niacin
○ Felbarnate	○ Pemoline
○ Gemfibrozil	○ Tacrine*
○ Lovastatin and other HMG-CoA reductase inhibitors ("statins")	○ Ticlopidine
○ Methotrexate	○ Tolcapone
○ Metformin	○ Zalcitabine
-

* in persons with prior jaundice





Chapter 13: Cirrhosis and Portal Hypertension

K. S. Gutfreund and A. B. R. Thomson



1. Introduction

There are numerous causes of PHT (portal hypertension), and these can be considered anatomically as pre-hepatic, intrahepatic, and post-hepatic (Figure 7A), or may be considered on the basis of the site of involvement relating to sinusoid: pre-sinusoid, sinusoidal and post-sinusoidal (Figure 7B). In Canada, by far the most common cause of PHT is cirrhosis, ie intrahepatic and sinusoidal. A regenerating nodule will partially block the blood flow in the hepatic sinusoidal and hepatic vein (Figure 8). Note how an internal fistula (anastomosis) forms between the portal vein (PV) and the hepatic vein (HV) at the site of the pre-existing sinusoids (Figure 9A). These regenerating nodules are nourished by blood from the hepatic artery. Note the difference in the structure of the normal acinis (Figure 5), the acinis in cirrhosis (Figure 9A), and in other causes of PHT (Figure 9B). Rarely, no disease process is identified, and idiopathic (primary) PHT may occur (Figure 9C).

With PHT, the normal anatomy of the portal venous system changes dramatically (Figure 10), leading to distention and increased pressure in collaterals which may partially affect the PHT. In time however 50 mg these collaterals may burst and lead to life-threatening bleeding such as from esophageal varices. Note that the paraumbilical anterior abdominal wall veins in PHT flow both upwards and downwards (Figure 11), whereas the flow in distended veins from obstruction of the inferior vena cava do not radiate from the umbilicus, and flow only upwards.

Portal pressure is the product of the portal blood flow in the portal vein (the confluence of the superior mesenteric vein and the splenic vein, and the resistance to blood flow in the liver with PHT, collaterals form in the portal and systemic circulations in the body's attempts to decompress the elevated portal pressure. The development of the collaterals does not usually have any major clinical consequence, except for upper GI bleeding from esophageal varices, or lower GI bleeding from the hemorrhoidal veins. The classification of PHT may be based on whether the disease process is prehepatic, hepatic and posthepatic. A more physiological consideration is whether the cause is presinusoidal (prehepatic and many intrahepatic conditions), postsinusoidal (posthepatic plus two intrahepatic conditions; alcoholic terminal (central) hyaline sclerosis in zone 3, and veno-occlusive disease), or sinusoidal (alcoholic hepatitis or established cirrhosis). The major pathophysiological abnormality in PHT is high-resistance, and it is not clear why high-resistance states are associated with enhanced mesenteric and therefore portal venous flow. The resistance may rise in the liver because of mechanical pressure on the vessels from inflammation, swelling of the hepatocytes, collagen deposited in the space of the Disse, fibrosis and architectural change) or because of the activation of the hepatic stellate cells (aka myofibroblasts, fat storing or Ito cells) leading to vasoconstriction of the sinusoids and elevated microvascular pressure. Presinusoidal causes of the PHT respond well to TIPS or other shunting procedures because the liver's function are generally well-preserved because of normal hepatocellular function. Also, ascites does not usually occur with presinusoidal PHT.

The portal disease may be measured directly by the percutaneous insertion of a needle into the portal vein, liver or spleen. Wedging a catheter into the hepatic



vein gives the hepatic vein wedge pressure (HVWP), which is an accurate indirect measure of portal pressure. The exception for HVWP being a good surrogate, marker for portal vein pressure is when there is a condition such as portal vein thrombosis causing intrahepatic portal vein resistance, and there will be PHT (portal vein pressure increase, but normal HVWP).

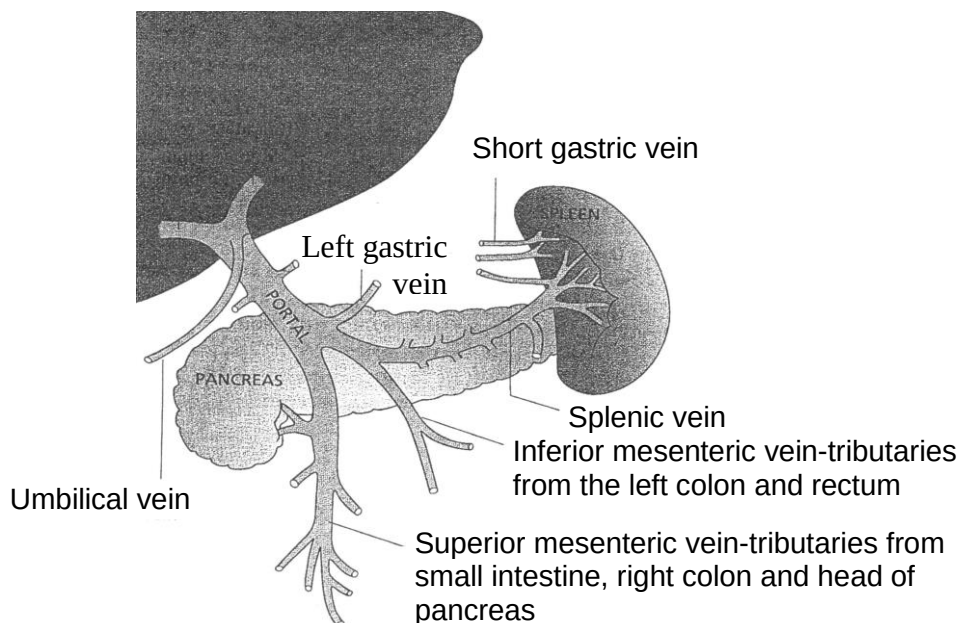
TIPS, transjugular intrahepatic portosystemic stent (shunt); a percutaneously-placed shunt between the hepatic and portal veins, reducing portal vein pressure. For prehepatic cause of PHT (eg, portal vein thrombosis), portacaval or mesocaval shunting will be necessary, in which case hepatic encephalopathy will not develop from the shunting because of the metabolic detoxification capacity of the normal liver parenchyma.

2. Normal anatomy

Before considering what happens to the patient with cirrhosis, we need to review briefly the normal gross anatomy of the liver (Figure 1), including the portal venous system (Figure 2). Blood flows into the liver from the portal vein (PV) (80%) and the hepatic artery (HA) (20%). From the portal vein (PV), blood flows through the sinusoids and into the hepatic vein (HV) (Figure 3). This structure may also be appreciated histologically (Figure 4).



A. Extrahepatic



B. Intrahepatic

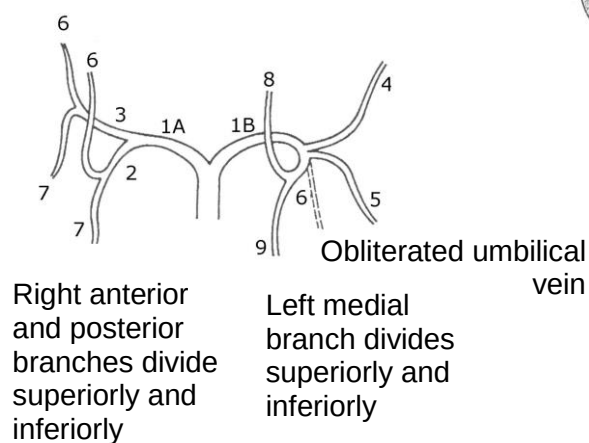
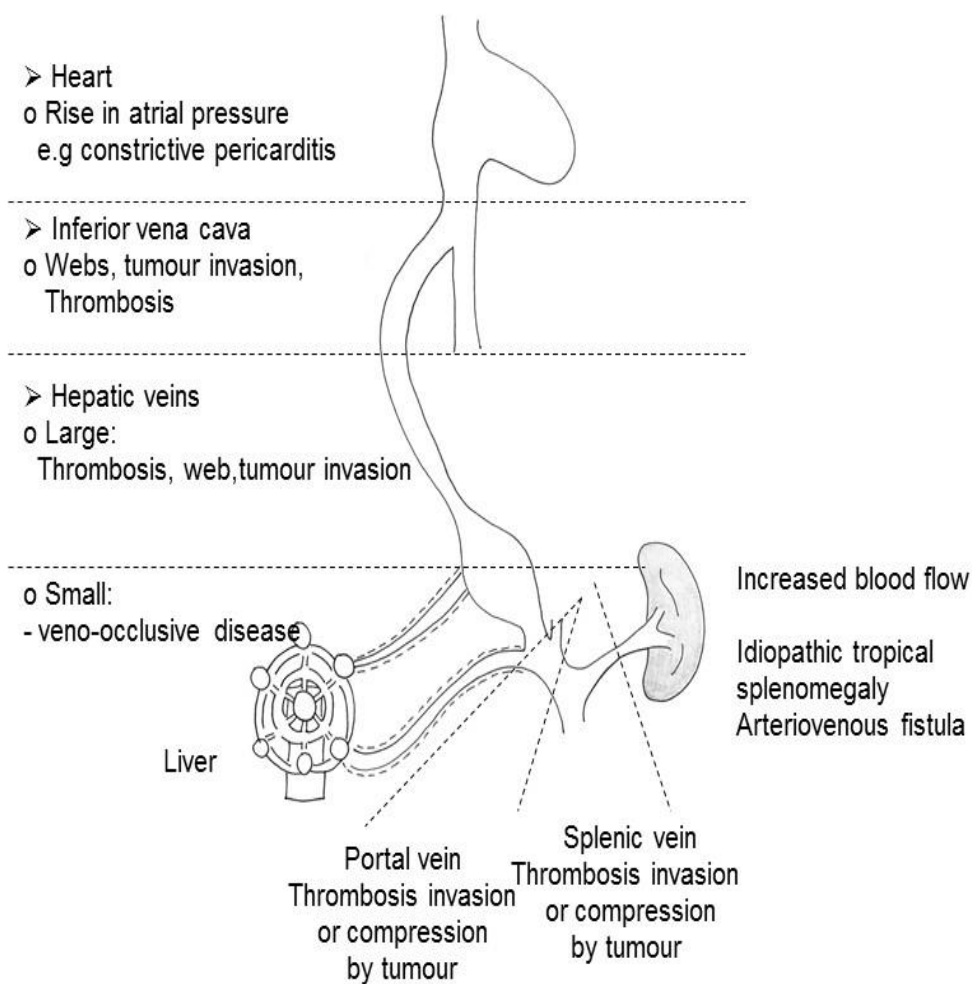


Figure 2. Portal venous system. A). Portal vein is posterior to the pancreas. B). Progressive branching of the intrahepatic portal vein and its distribution to the lobes of the liver. (a) Division into the right and left branches. (b) Division of the right branch into anterior and posterior branches and of left branch into lateral and medial branches. (c) Four segments of liver supplied by the right anterior and posterior and the left lateral and medial branches. (d) Eight final branches of the portal vein.

Adapted from: Sherlock & Dooley, Figure 10.1, page 147, Eleventh Edition, 2002.



Causes of portal hypertension

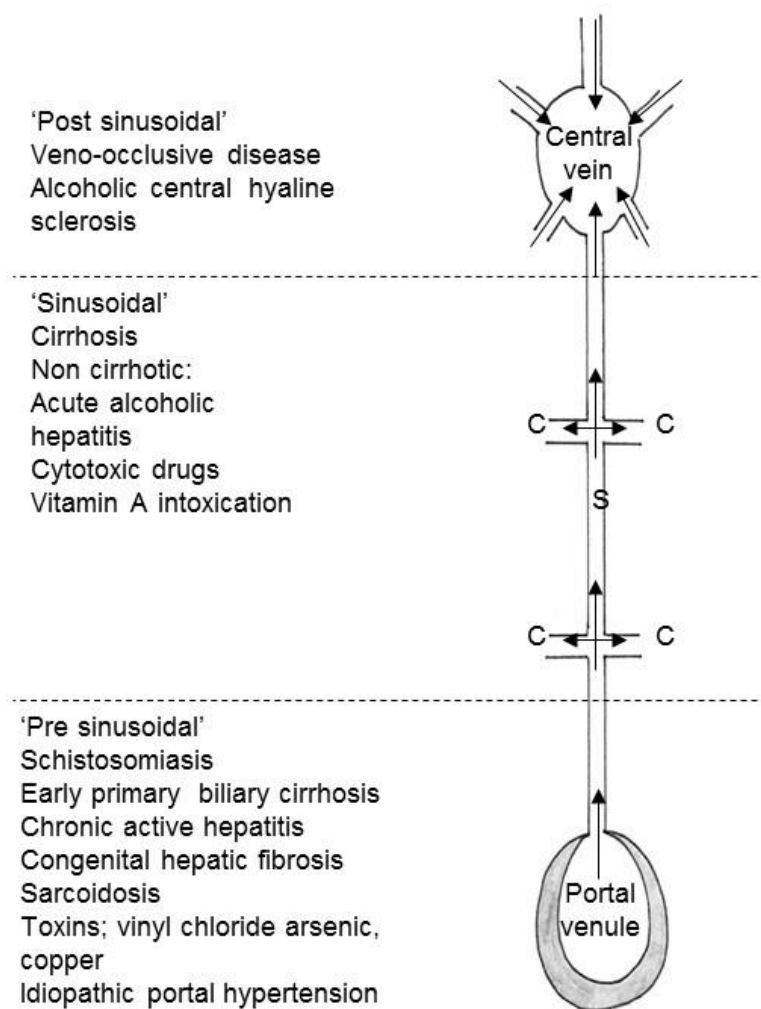


Elee.

Adapted from: Sherlock and Dooley. Figure 10.36, page 166, eleventh edition, 2002.



Causes of portal hypertension (b)



- o (a) Pre and post hepatic
- o (b) Intra hepatic (NB an overlap exists; wedge hepatic vein pressure may be high in patients with 'pre sinusoidal' causes, especially as the disease progresses, indicating sinusoidal and/or collateral involvement)
- o Some 'post sinusoidal' conditions may also have a sinusoidal component

Elee

Adapted from: Sherlock and Dooley. Figure 10.36, page 166, eleventh edition, 2002.

Figure 5a and b. Causes of portal hypertension. (a) Pre- and post- hepatic. (b) Intra-hepatic (NB an overlap exists; wedge hepatic vein pressure may be high in patients with 'pre-sinusoidal' causes, especially as the disease progresses, indicating sinusoidal and/or collateral involvement. Some 'post-sinusoidal' conditions may also have a sinusoidal component).

Adapted from: *Sherlock & Dooley*, Figure.10.36, page 166, Eleventh Edition, 2002.



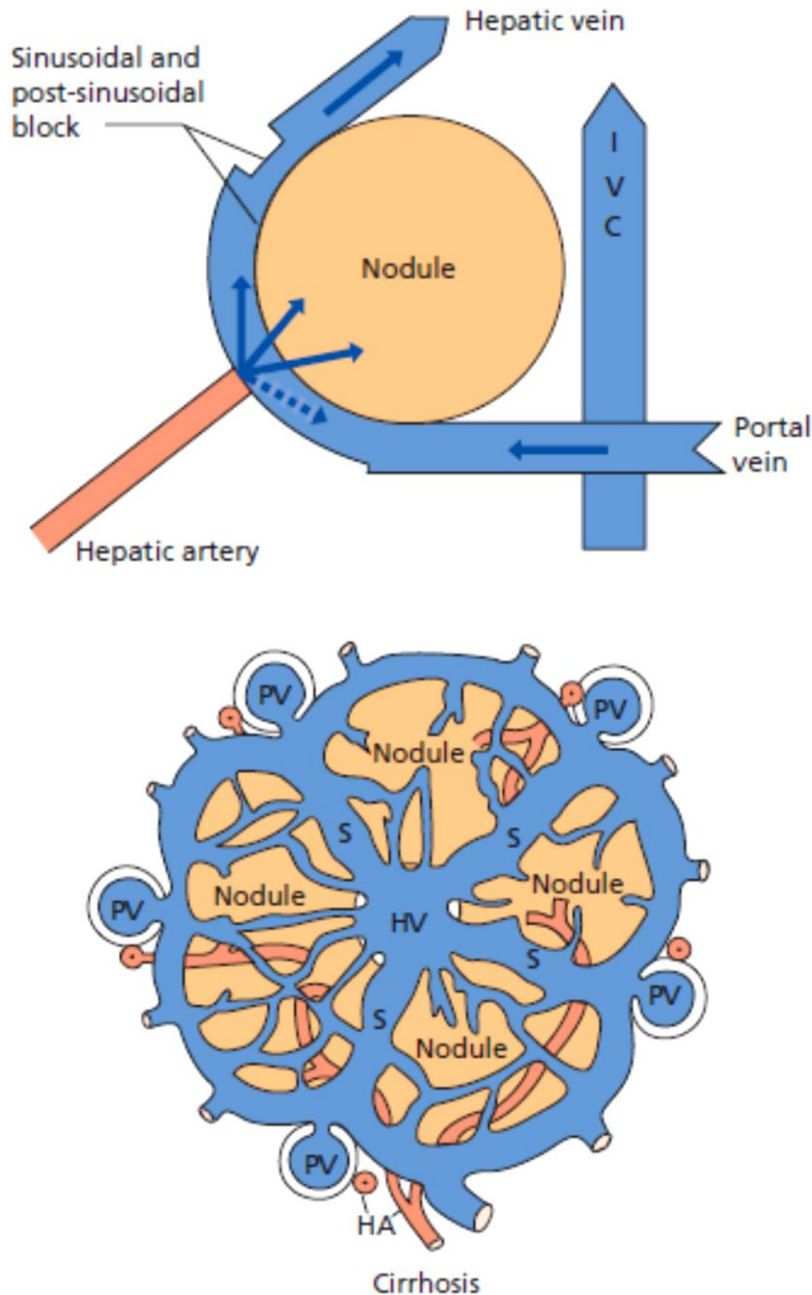


Figure 6. The intrahepatic portion of the hepatic circulation in cirrhosis. (A) A nodule obstructs the sinusoids and hepatic veins. The nodule is supplied mainly by the hepatic artery. IVC, inferior vena cava. (B) Cirrhosis of the liver showing the formation of portal vein (PV)/hepatic venous (HV) anastomoses or internal Eck fistulae at the site of pre-existing sinusoids (S). Note that the regeneration nodules are supplied by the hepatic artery (HA).

Adapted from: Sherlock & Dooley, Figure. 10.43, page 170; and Figure. 10.42, pg 170, Eleventh Edition, 2002.



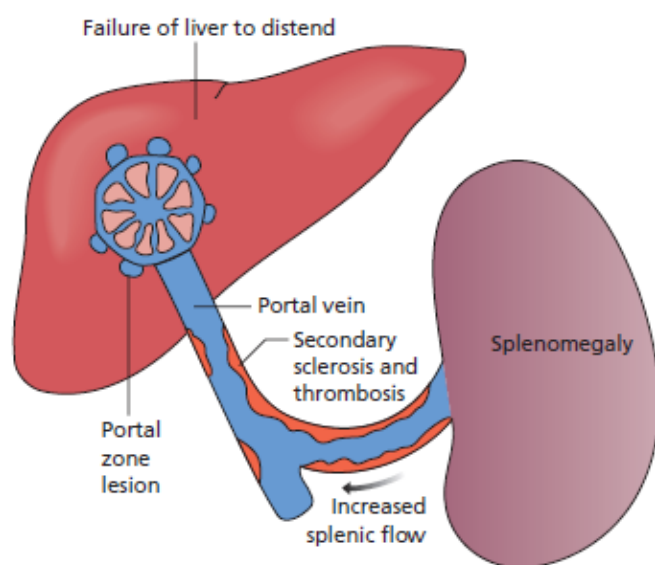
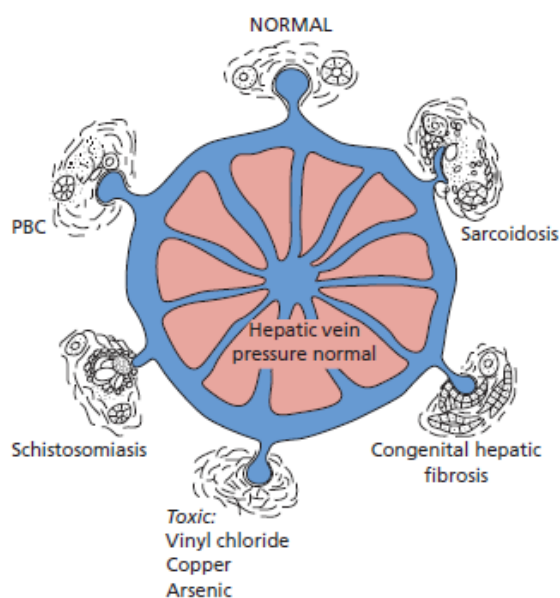


Figure 7. Non-cirrhotic pre-sinusoidal portal hypertension. (A) Idiopathic 'primary' portal hypertension. (B) the etiology of pre-sinusoidal intra-hepatic portal hypertension. PBC, primary biliary cirrhosis.



Adapted from: *Sherlock & Dooley*, Figure 10.40, page 168; and Figure 10.41, page 169, Eleventh Edition, 2002.

As a result of the portal hypertension, a collateral circulation develops between the portal and the systemic circulation (Figure 8). While some of these collaterals are a curiosity (Figure 9), life-threatening hemorrhage may develop from the collaterals that develop through the coronary to the esophageal veins, forming esophageal varices (Figure 10). The

nodules replace normal hepatic parenchymal tissue, so that with the loss of hepatocytes, there is the loss of the normal functions of the liver, synthesis, secretion and metabolism.

3. Clinical Considerations

Cirrhosis is a pathological condition referring to changes seen on biopsy of the liver in persons with any type of chronic liver disease. Portal hypertension (PHT) is a pathological condition in which the pressure in the portal circulation is elevated (>8 mm Hg), usually but not always due to cirrhosis. The clinical presentation of cirrhosis and



PHT may overlap for this reason the two conditions will be considered together here. Their serious and important complications (esophageal varices, ascited, hepatorenal syndrome, jaundice, hepatic encephalopathy) will be dealt with in separate chapters.

Cirrhosis may be the end pathological process of most chronic liver disease. The combination of fibrosis, nodules and distortion of the hepatic architecture makes the diagnosis of cirrhosis (Figure). Infection, inflammation, ischemic, and drug/chemical damage begin the process of necrosis of the liver cells, collapse the lobules, and then the development of cirrhosis through fibrosis, nodules and distortion. Once cirrhosis develops, the liver may still have the ability to repair itself (particularly if the inciting cause of the liver damage is removed), and the cirrhosis may regress.

Cirrhosis is the 5th most common cause of death in the UK and 12th in the USA. Because the prevalence of cirrhosis peaks in the mid- to late-50s, it becomes the 4th most common cause of death in that age group. If the diagnosis of chronic liver disease is made early, there may be effective treatment to prevent the development of cirrhosis, or to at least slow or reverse its progression (Table 1).

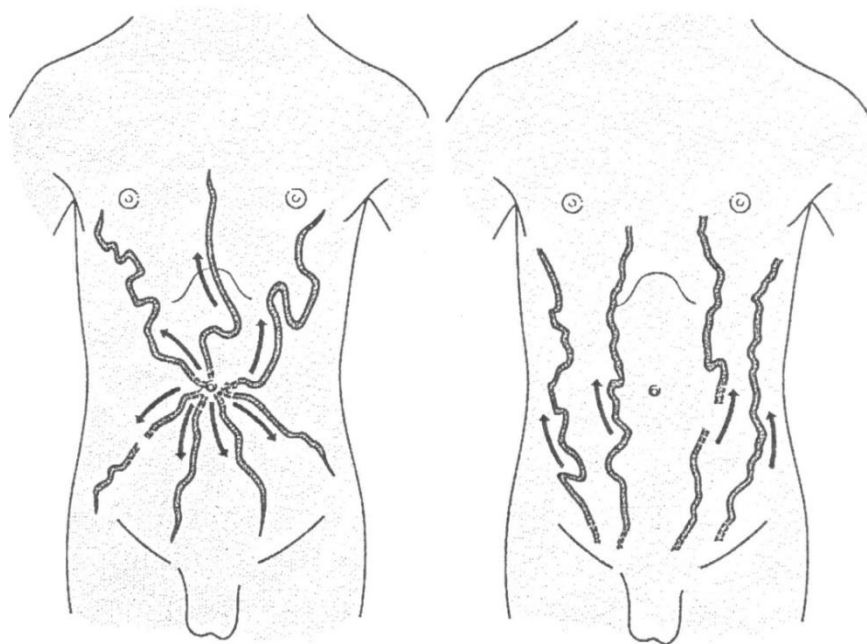


Figure 8. Distribution and direction of blood flow in anterior abdominal wall veins in portal venous obstruction (left; direction of flow is normal) and in inferior vena caval obstruction (right).

Adapted from: *Sleisenger & Fordtran's Gastrointestinal and Liver Disease: Pathophysiology/ Diagnosis/Management* 2006 Fig. 10.11, pg 153.



Table 1. Prognosis of Different Stages of Cirrhosis

Stage	Clinical Perspective	MR
Stage I	compensated, no esophageal varices	1%
II	compensated, with varices	3.4%
III	Ascites	20%
IV	GI bleeding	57%

Abbreviation: MR, mortality rate

The portal vein (PV) is formed from the confluence of the splenic vein and the superior mesenteric vein, behind the neck of the pancreas (Figure). The left gastric vein (aka left coronary vein) drains into the confluence of the splenic vein and the superior mesenteric vein. About 75% of blood flow to the liver is from the PV, and 30% from the hepatic artery (systemic circulation). This venous and arterial blood mix in the hepatic sinusoids. The wall of the sinusoids is highly permeable. Blood constituents pass from here into the space of Disse, and from there are taken up by the sinusoidal membrane side of the hepatocyte.

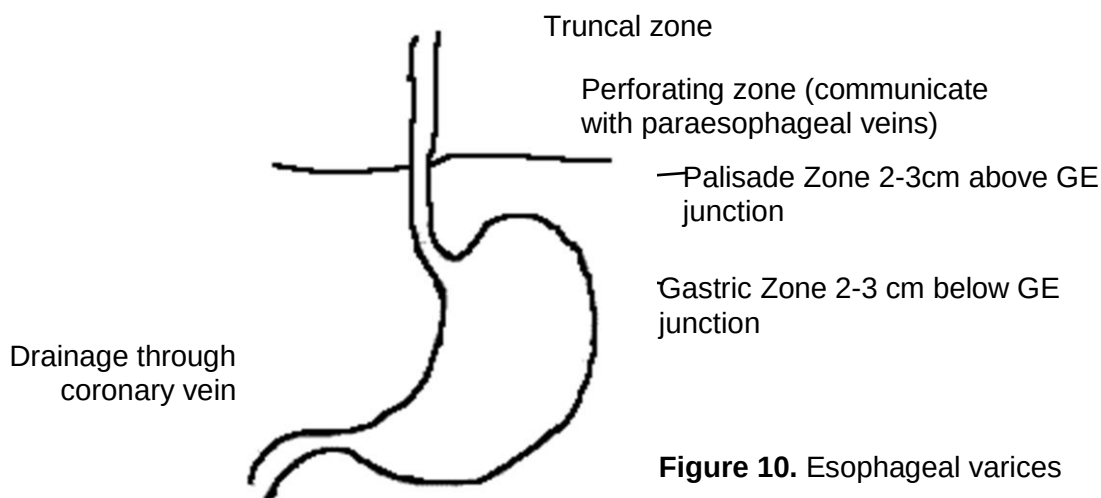
Stellate cells, when activated (for example in cirrhosis and PHT), may contract and worsen the PHT. As PV pressure rises, collateral vessels to the low pressure systemic venous system develop. Also, new vessels develop (angiogenesis) in the body's attempt to lower the PHT. As PHT continues to rise, the PV-systemic collateral circulation develops, such as the left gastric vein and esophageal varices. PHT is caused by both mechanical and vascular factors, with increased intrahepatic resistance (from enhanced intrahepatic vasoconstriction) and increased flow and a hyperdynamic circulatory state (from vasodilation of the splanchnic and systemic systems). The vascular factors are potential therapeutic targets (Table 2).



Table 2. Vascular Factors as Potential Therapeutic Targets

-
- Reduce the intrahepatic vasoconstriction
 - Angiotensin receptor blockers
 - Mononitrates (nitric oxide [NO])
 - Anti-endothelin-1, anti-leukotriene, anti-TGF-B (transforming growth factor-B)
 - Norepinephrine
 - Serotonin
 - Thromboxane drugs
 - Reduce the splanchnic and systemic vasodilation
 - Nonselective B-adrenergic blockers
 - Octreotide / vasopressin
 - The two most important future therapeutic targets will likely be to increase the vasodilator nitric oxide (NO), and to decrease the vasoconstrictor endothelin-1 and possibly also the fibrogenic growth factor TGF-B.
-

These vascular vasoactive factors cause one quarter (25%) of the enhanced portal resistance leading to the PHT in cirrhosis. With the development of cirrhosis, there is the formation of an anastomosis between the portal vein and the hepatic vein (an internal Eck fistulae). The regenerating nodules in cirrhosis are supplied by the hepatic artery.



The palisade zone is the major area of splanchnic-systemic union, and the location which is most likely for bleeding to occur. Esophageal varices will develop when there is a PV gradient of 10 mm Hg, and will bleed when PV gradient is ≥ 12 mm Hg. MRE (magnetic resonance elastography) will measure liver stiffness due to fibrosis, but does not reflect PV pressure. The hepatic venous pressure gradient (HVPG) is the difference between the wedged hepatic venous pressure (WHVP) and free hepatic vein pressure (FHVP): $WHVP - FHVP = HVPG$. HVPG is a useful measure of PHT, used



mostly in research or other very specialized settings. HVPG is not valid to assess PV pressure in presinusoidal causes of PHT.

Numerous factors such as chronic alcohol abuse, viral hepatitis (B and C), autoimmune abnormalities, iron overload will stimulate a host of pathophysiological factors to produce necrosis, regenerative nodules and fibrosis (Table 3 and 4). In turn, there will be alterations in the circulation (Table 5), leading to portal hypertension.

Table 3. Causes of cirrhosis

-
- Viral hepatitis
 - HBV, HCV, HDV
 - Metabolic

○ NASH ○ Hemochromatosis ○ Wilson's disease ○ 1-antitrypsin deficiency ○ Autoimmune	○ Sclerosing cholangitis ○ Primary biliary cirrhosis ○ Autoimmune Hepatitis ○ Galactosemia ○ Tyrosinemia
 - Drugs/toxins
 - Alcohol
 - Conjunctive

○ Cardiac failure	○ Budd-Chiari
 - Cystic fibrosis
-

Adapted from: Heathcote J. *First Principles of Gastroenterology* 2005. page 598.

Table 4. Pathophysiological factors responsible for the development of hepatic fibrosis

-
- Extracellular matrix proteins (EMP)
 - Hepatic stellate cells (HSC)
 - Activation of HSC to form myofibroblasts
 - Other mesenchymal cell populations and bone marrow-derived cells
 - Hepatocyte growth factor
 - TGF- β
 - Renin-angiotensin system (RAS)
 - Angiotensin-converting enzyme (ACE)
 - Angiotensin I and II receptors
 - Endotoxin, lipopolysaccharide (LPS)
 - Toll-like receptor (TLR4)
 - Angiogenesis
 - vascular endothelial growth factor (VEGF)
 - angiopoietin 1, 2
-

Adapted from: Jiao J, et al. *Curr Opin Gastroenterol* 2009; 25: 223-9.



Table 5. The pathophysiological components producing the hyperdynamic circulation and cardiovascular dysfunction in persons with cirrhosis

-
- Peripheral and splanchnic arterial vasodilatation
 - Baroreceptor-induced increase in heart rate
 - Autonomic dysfunction
 - Increased sympathetic nervous activity
 - Vagal impairment
 - Alterations in cardiac preload
 - Increased portosystemic shunting
 - Increased blood volume
 - Effects of posture
 - Decreased blood viscosity
 - Alterations in oxygen exchange
 - Anemia
 - Hypoxemia
 - Hepatopulmonary syndrome
 - Portopulmonary hypertension
-

Printed with permission: Møller, S. and Henriksen, J. H. *GUT* 2008; 58: page 271.

There are many causes of cirrhosis, and in the Canadian setting the most common are alcohol, chronic viral hepatitis B and C, and non-alcoholic steatohepatitis (NASA). In perhaps 5-10% of persons with cirrhosis the cause is unknown (idiopathic; aka cryptogenic), perhaps because the initial pathological signs suggesting the etiology (such as NASA) have disappeared, leaving the unhelpful descriptive term cryptogenic cirrhosis

The cirrhotic nodules may be small (micronodular), large (macronodular), or there may be a mixture of the two in micronodular cirrhosis, the septa are thick and there are regular uniformly small regenerating nodules in every hepatic lobule. In macronodular cirrhosis the nodules are of varying size (Figure 30). This pathological distinction is descriptive, and does not imply any diagnosis or prognosis.

Persons with liver disease may present the non-specific generalized symptoms such as weakness or fatigue, specific symptoms suggesting the underlying cause (eg. Alcoholism) of the presence of cirrhosis and symptoms arising from associated PHT (eg. Bleeding, jaundice, confusion, abdominal distention). The patient may have signs of cirrhosis, its complications (decompensate disease) and causes. Once the suspicion of liver disease has been raised, laboratory tests and diagnostic imaging will prove to be useful to confirm the clinical hypothesis that there is liver disease, but the extent of the abdominal liver enzymes such as transglutaminase and alkaline phosphatase, do not



reflect the severity of the liver damage. In contrast, the extent of the abdominal blood tests reflect deranged hepatic synthetic or excretory function (albumin, bilirubin, INR) is useful to clarify the severity of the liver disease. For example, the Child-Pugh classification (Table 6) or the MELD score are useful to predict prognosis and help to establish when a liver transplantation may be necessary. For example, the mortality rate from bleeding esophageal varices increase with the Child-Pugh class: A, 15%;B, 25%;C, 50%.

Table 6. The Child's classification of hepatocellular function in persons with cirrhosis

Group designation	A	B	C
○ Serum bilirubin (mg/dl)	< 2.0	2.0-3.0	> 3.0
○ Serum albumin (g/dl)	> 3.5	3.0-3.5	< 3.0
○ Ascites	None	Easily controlled	Poorly controlled
○ Encephalopathy	None	Minimal	Advanced (coma)
○ Nutrition	Excellent	Good	Poor ('wasting')

Adapted from: Durand F, Valla D. J Hepatol 2005; 42 and Kim, WR et al, *Hepatology* 1999; 29: 1643-8.

When the patient presents with non-specific symptoms such as fatigue and malaise, or symptoms from the course of the liver disease or its complications, when the physical examination shows signs of chronic liver disease, and the liver enzymes (ALT, AST, AP, GGT) and liver function tests (albumin, bilirubin, INR) are abnormal, then further blood tests are performed to establish the cause of the liver disease (e.g. HBV, HCU, ferritin, caeruloplasmin, AMA, quantitative immunoglobulins), as well as diagnostic imaging (e.g. abdominal ultrasound with/without Doppler ultrasound), and when tolerated, liver biopsy (Table 7). The clinical examination must be detailed to look for manifestations of disease beyond the liver itself (Table 8). Depending upon the initial clinical findings, the search for the cause of the liver disease may need to be considered (Table 3). Indirect indications of the presence of cirrhosis may be found on diagnostic imagery (Table 9). The stage of cirrhosis must be established (Table 6). In later chapters, individual conditions are considered, including the management, but all patients with cirrhosis must be considered for preventive care (Table 10), including special precautions if a cirrhotic patient requires an operative procedure (Table 11).



Table 7. The detailed laboratory and diagnostic imaging investigation of the patient with suspected chronic liver disease

- History and physical examination
 - Fatigue, malaise, anorexia, fever, weight loss/gain, ankle swelling
 - Following blood donation-positive hepatitis B or C test
 - Blood transfusions
 - Drug abuse
 - MSM
 - Extrahepatic manifestations (see question 2)
 - Following acute hepatitis-failure of recovery, whether clinical or biochemical or both
 - Abnormal liver enzyme or function tests, or positive hepatitis B or C markers at routine check-up
 - Abnormal physical findings
 - Hepatomegaly,
 - Signs of portal hypertension, splenomegaly, jaundice, peripheral edema, ascites, hepatic encephalopathy, renal dysfunction, bleeding (varices, coagulopathy)
 - Liver – big/normal/small
 - Cutaneous and endocrine changes
 - Spider nevi, palmar erythema, Dupuytren's contractures
 - Gynecomastia, testicular atrophy, impotence
 - Amenorrhea
 - Parotid enlargement
 - Coagulopathy
 - Hypoprothrombinemia
 - Thrombocytopenia
 - Dysfibrinogenemia
 - Slit lamp Kayser-Fleisher rings
 - Circulatory changes
 - Hyperdynamic circulation
 - *Arterial desaturation, clubbing
- Laboratory tests
 - Liver function tests
 - Bilirubin
 - Aspartate transaminase (AST; SGOT)
 - Alanine transaminase (ALT; SGPT)
 - Gamma-globulin
 - Albumin
 - Alkaline phosphatase (ALP)
 - Gamma glutamyl transferase (GGT)



-
- Hematology
 - Hemoglobin
 - White cell count
 - Platelet count
 - Prothrombin time
 - PPT
 - Special tests
 - Serum antibodies
 - Nuclear
 - Smooth muscle
 - Mitochondrial
 - Liver/kidney microsomal
 - HBsAg
 - HBeAg
 - HBeAb
 - Anti-HCV and HCV RNA
 - Serum iron, transferin, % saturation, genetic testing
 - Serum ferritin
 - Serum ceruloplasmin as well as blood and urinary copper
 - Alpha-fetoprotein
 - Creatine kinase (if smooth muscle disease suspected as cause of ↑ALT/AST fasting total, LDL, HDL cholesterol, triglycerides)
 - Protein electrophoresis (polyclonal ↑ gamma globulins in AIH)
- Abdominal ultrasound, CT, fibroscan
- Core liver biopsy
 - Hematoxylin and eosin, connective tissue stains, “special stains”
-

Source: ABR Thomson. *GI Practice Review*: CAPstone Publishing. 2010.



Table 8. Clinically significant extrahepatic manifestations of acute and chronic liver disease

-
- CNS: depression, anxiety, HE
 - Lung: portopulmonary hypertension, hepatopulmonary syndrome, pleural effusion, congestive heart failure
 - Heart: prolonged QT (from low Mg^{2+}), endocarditis, ↓ systemic vascular resistance, arterial BP ↑, HR, CO, peripheral intravascular vasodilation
 - Blood: Coagulopathy (VK, DIC, fibrinolysis), thrombocytopenia, Hypersplenism, ↓ thrombopoietin, immune mediated destruction, ITP (esp interferon for HCV), direct effect of alcohol, cryoglobulinemia
 - GI
 - esophageal ulcers from sclerotherapy, GERD, varices
 - stomach: delayed gastric emptying, PHG, GAVE
 - small bowel: slow transit, bacterial overgrowth
 - colon: rectal varices
 - Bone: osteoporosis, osteomalacia: cholestasis, liver Tx, malnutrition, alcohol, tobacco, ↓ motility, hypogonadism, malabsorption
 - Renal: hypanatremia; ascites, hepatorenal syndrome, glomerulosclerosis (HCV), nephritic syndrome, amyloid
 - Muscle: spastic paraparesis from demyelination of corticospinal tracts and posterior columns, wasting; arthritis (hemochromatosis)
 - Gonads; hypergonadism, amenorrhea
-

Source: ABR Thomson. GI Practice Review. *CAPstone Publishing* 2010.

Abbreviations: BP, blood pressure; CNS, central nervous system; CO, cardiac output; DIC, disseminated intravascular coagulopathy; GAVE, gastric antral vascular ectasia; GERD, gastroesophageal reflux disease; HCV, hepatitis C virus; HE, hepatic encephalopathy; HR, heart rate; ITP, idiopathic thrombocytopenic purpura; PHG, portal hypertensive gastropathy; VK, vitamin K



Table 9. Hepatic/extrahepatic signs of cirrhosis on hepatic imaging (CT, MR)

-
- Hepatic
 - Nodularity
 - ↑ periportal space
 - Posterior notch
 - ↑ caudate and lateral segment
 - ↑ caudate-to-right lobe size
 - Enlarged gallbladder
 - Extrahepatic
 - Splenomegaly
 - Varices
 - Ascites
 - Gamma-gandy bodies
-

Adapted from: Ito, K, et al. *Magn Reson Imaging Clin N Am* 2002; 10(1): 75-92, vi.

Table 10. Management considerations in the pre- and post-operative care of the patient with advanced liver disease

-
- Prevention of hepatic encephalopathy (HE)
 - Avoidance of nephrotoxic insult
 - Correction of reversible metabolic factors
 - Oral lactulose administration, titrated to ~3-4 bowel movements per day
 - Administration of nonabsorbable antibiotics
 - Supportive care
 - Avoidance of nephrotoxic insult
 - Correction of reversible metabolic factors
 - Treat complications of portal hypertension (PHT)
 - Ascites
 - Antibiotics
 - Steroids
 - Coagulopathy
 - Vitamin K supplementation (oral or parenteral)
 - Fresh, frozen plasma transfusions
 - Intravenous administration of cryoprecipitate
 - Intravenous administration of recombinant factor VIIa
 - Platelet transfusions
 - Paracentesis with analysis of ascitic fluid for evidence of infection
 - Oral diuretic therapy with spironolactone and/or furosemide
 - Fluid restriction (if sodium concentration is <120 mmol/l)
 - Avoidance of excessive saline administration
 - Albumin infusion (with paracentesis volumes >5l)
-



-
- Diet
 - Maintenance of an adequate protein intake (1-1.5g/kg per day)
 - Promotion of a balanced diet
 - Dietary sodium restriction (<2 g daily)
 - Pain control
 - Dilandid
 - Avoid benzodiazepans, NSAIDs, narcotics
 - Assess pulmonary function
Supplemental oxygen

Adapted from: Hanje, A.J., and Pate, T. *Nature Clinical Practice Gastroenterology & Hepatology* 2007; 4: page 272.

Table 11. The preventive care of the patient with cirrhosis.

- Prevention of first variceal hemorrhage EGD q3 years, with banding or beta blockers (primary prophylaxis)
 - Prevention of recurrent variceal hemorrhage (secondary prophylaxis)
 - Beta-blockers
 - Banding
 - Sclerotherapy
 - Shunts (TIPS)
 - Prevention of bacterial infections after GI bleeding (antibiotic prophylaxis)
 - Prevention of SBP (antibiotics for previous SBP)
 - Statins, anticoagulation
 - Assess for minimal (subclinical) HE (grade 0), and treat appropriately; testing for driving competence
 - Vaccination – Influenza, Pneumococcus, HAV, HBV
 - Nutrition assessment and treatment
 - Avoid alcohol, Viagra, vasodilators, NSAIDs, hepatotoxic herbs, benzodiazepines
 - Education, family counseling
 - Screening for CEA, DM, HBP, HCC, osteoporosis, diabetes, hypertension, HCC; usual screening for breast, prostate, cervix, colon
 - Medialert bracelet
 - Ongoing evaluation for possible liver transplantation
-



While the investigation of the patient with possible liver disease may at first appear to be difficult, in fact the clinician needs to ask her/himself only four questions:

Table 12. Does the person have liver disease?

1. Does the clinical presentation suggest that the person has liver disease?

- Symptoms
 - General
 - Weakness
 - Fatigue
 - Specific
 - Underlying disease
 - Cirrhosis/PHT
- Signs
 - Examining the patient
 - Abdomen
- Diagnostic Imaging

2. Do laboratory tests suggest the presence of liver disease?

- Liver Enzymes (LEs)
 - Hepatocellular: ALT, AST
 - Cholestatic: AP, 5'NT, GGT
- Liver Function Test (LFTs)
 - Albumin
 - INR
 - Bilirubin

3. What laboratory tests are done to determine the etiology of liver disease?

- Infection
 - Viral: A,B,C,D,E...EBV, HSV
 - Bacterial
- Infiltration
 - Fe, Cu, FAT (cholesterol, TG, blood sugar)
 - RBC, WBC
 - HCC
- Immune
 - AMA (anti-mitochondrial antibody)
 - Quant, immunoglobulins
 - ATG (anti-transglutaminase)
- Inherited
 - Cystic fibrosis
 - α 1-antitrypsin deficiency



4. What is done to determine the cause of liver disease?

- Ultrasound ($\pm$ Doppler)
- HIDA scan
- MRCP
- CT

Biopsy: US'/CT-guided percutaneous biopsy



With this simple approach: 90% of diagnoses of Liver Disease

4. Management of Cirrhosis, and Portal Hypertension

The response to treatment and the possibility of removing the etiological agent of the chronic liver disease will determine the prognosis.

Even with mild cirrhosis (Stage I), progression to a more severe stage occurs at the rate of about 11 % per year. This progression leads to the complications of portal hypertension (PHT) developing and causing death from bleeding esophageal varices, ascites and renal failure, encephalopathy, infection and hepatocellular cancer (HCC). Since the high mortality rate in cirrhosis is from the complications of PHT, we need to consider the role of preventive therapy of cirrhosis with NSBBs (non-selective beta blockers), antibiotics, statins and anticoagulants.

4.1. Non-selective beta blockers

NSBBs such as propranolol (80 mg bid) or nadolol reduce PHT and splanchnic as well as systemic arterial vasodilation which result from the progressing fibrosis associated with hepatic necrosis, and nodular regeneration. While the portal venous pressure progresses, the risk of complications also increases. The HVPg (hepatic venous pressure gradient) is a useful clinical tool as a surrogate marker for portal venous pressure and the prognosis from PHT (Table 13). Note that HVPg is not valid to assess PV presence in presinusoidal causes of PHT.

Table 13. Prognostic Use of HVPg in Cirrhosis

HVPg, mm Hg

< 10	○ 90% 4-year survival without hepatic decompensation
>10	○ 40% 4-year survival without hepatic decompensation
<12, or ≥ 20% of baseline	○ Reduced risk of first and further episodes of variceal bleeding
	○ Reduced risk of ascites, SBP (spontaneous bacterial peritonitis) and HRS (hepatorenal syndrome)
	○ Reduced mortality rate



It is important to note that while these improvements are, certainly partially due to the beneficial effect of NSBBs reducing PHT (HVPG), there appears to be an additional benefit of NSBBs independent of improved liver functions. For example, NSBBs reduce the risk of SBP in cirrhosis. Antibiotics (see below) also prevent recurrence of SBP, but curiously also reduce HVPG and reduce the likelihood of rebleeding after an acute variceal hemorrhage.

4.2. Antibiotics

Of course antibiotics are useful to treat infections in persons with cirrhosis and PHT. Antibiotics also can be used to reduce the risk of recurrence of SBP, the risk of recurrent acute variceal bleeding, the risk of HRS (especially in cirrhotics with ascites which has a low albumin concentration), and the treatment and risk of recurrence of hepatic encephalopathy (Table 14). It is not certain what is the mechanism by which antibiotics reduce HVPG.

Table 14. Beneficial Role of Antibiotics in Cirrhosis

Treatment and prevention	SBP, HE
Prevention	HRS, rebleeding EV

Abbreviations: EV, esophageal varices; HRS, hepatorenal syndrome; HE, hepatic encephalopathy; SBP, spontaneous bacterial peritonitis

The combination of NSBB plus antibiotic (e.g. propranolol 80 mg bid plus norfloxacin 400 mg/d) reduce hospitalizations, morbidity and mortality in cirrhotics, and are highly cost-effective.

4.3. Statins

Statins, like antibiotics and NSBBs, have benefits beyond their primary therapeutic use of blocking HMG-CoA reductase, thereby reducing cholesterol synthesis and LDL cholesterol levels. Statins also reduce HVPG and improve liver function as well as reduce the risk of the development of HCC. The mechanism of this beneficial effect is unknown.

4.4. Anticoagulation

It might appear to be counterintuitive to use an anticoagulant in a cirrhotic patient with a prolonged INR and with esophageal varices. However, the coagulopathy in cirrhosis involves both pro- and anticoagulant factors by similar amounts, resulting in normal thrombin generation. Anticoagulants act on hepatic stellate cells to reduce hepatic necrosis and fibrosis, and warfarin is currently being studied in a randomized controlled trial in persons with a liver transplantation for HCV. Enoxaparin reduces the risk of the cirrhotic developing portal vein thrombosis, and oral anticoagulation may be used in a cirrhotic to reduce the risk of extension of an established portal vein thrombosis (treatment of associated esophageal varices must preclude anticoagulation).





Chapter 14: Ascites and Spontaneous Bacterial Peritonitis

F. Wong



1. Ascites

1.1. Introduction

Ascites is the detectable collection of free fluid in the peritoneal cavity. The risk of developing ascites after the diagnosis of cirrhosis is approximately 60% over 10 years. The five-year survival after the onset of ascites is only 50%. This is reduced to two years survival with the development of refractory, or diuretic-resistant ascites. This contrasts with a survival rate of 80% in two years following liver transplantation. Ascites also predisposes patients to life-threatening complications such as spontaneous bacterial peritonitis (SBP) and hepatorenal syndrome. Therefore, the development of ascites is an indication for referral for assessment for liver transplantation.

1.2. Pathophysiology

Sodium retention is central to the development of ascites. What leads to the development of sodium retention in cirrhosis is controversial. There is now ample evidence to support that sodium retention in cirrhosis, although subtle, actually begins before the development of ascites. At the pre-ascitic stage of cirrhosis, erect posture induces sodium and hence water retention via the activation of the intrarenal renin-angiotensin. Other mechanisms that contribute to sodium and hence water retention in pre-ascitic cirrhosis include the loss of glomerulotubular balance and possibly increased cell mass of the thick ascending limb of Loop of Henle, which contains the $\text{Na}^+\text{-K}^+\text{-2Cl}^-$ co-transporters. When the patient assumes the supine posture, there is redistribution of the excess volume to the upper part of the body. This leads to atrial natriuretic peptide (ANP) levels increasing to help improve renal sodium excretion in the supine position. The circulation also vasodilates and becomes hyperdynamic in the supine position. Cardiac output increases and renal perfusion improve, as well as secretion of some of the excess sodium.. However, the increased ANP levels and the supine posture are insufficient to eliminate all the sodium retained in the upright posture. Eventually, the pre-ascitic cirrhotic patient will come into a new state of sodium balance at the expense of an expanded intravascular volume.

As the cirrhotic process progresses, further changes in the circulation occur. The hyperdynamic circulation, which is only present in the supine posture in the pre-ascitic stage, becomes more obvious and eventually appears also in the erect posture. The hyperdynamic circulation is the result of increasing vasodilatation occurring both in the splanchnic and the systemic circulations, due to the presence of excess vasodilators. In the “Peripheral Arterial Vasodilatation Hypothesis,” it is proposed that, in cirrhosis, arterial vasodilatation leads to a decrease in splanchnic and systemic vascular resistance. The vasodilation and decreased resistance cause pooling of blood in the splanchnic circulation, resulting in a reduction of the effective arterial blood volume. This in turn further activates various neurohumoral pressor systems to increase renal sodium and water retention in an attempt to restore the effective arterial blood volume and to maintain blood pressure. However, the renal circulation is exquisitely sensitive to the vasoconstrictive effects of these neurohumoral pressor systems, and the glomerular filtration rate (GFR) decreases. This further enhances renal sodium retention. When the increased renal sodium and water retention cannot keep pace with the arterial



vasodilatation, there follows a cascade of further activation of neurohumoral pressor systems follows, leading to further sodium and water retention.

Hepatic dysfunction also stimulates renal sodium retention, through some yet undefined mechanism, as sodium excretion has been shown to be related to a threshold of hepatic function. The presence of sinusoidal portal hypertension stimulates renal sympathetic activity, enhancing renal sodium retention. Sinusoidal portal hypertension also preferentially localizes the excess fluid to the peritoneal cavity as ascites (Figure 1).

Pathophysiology of Ascites Formation

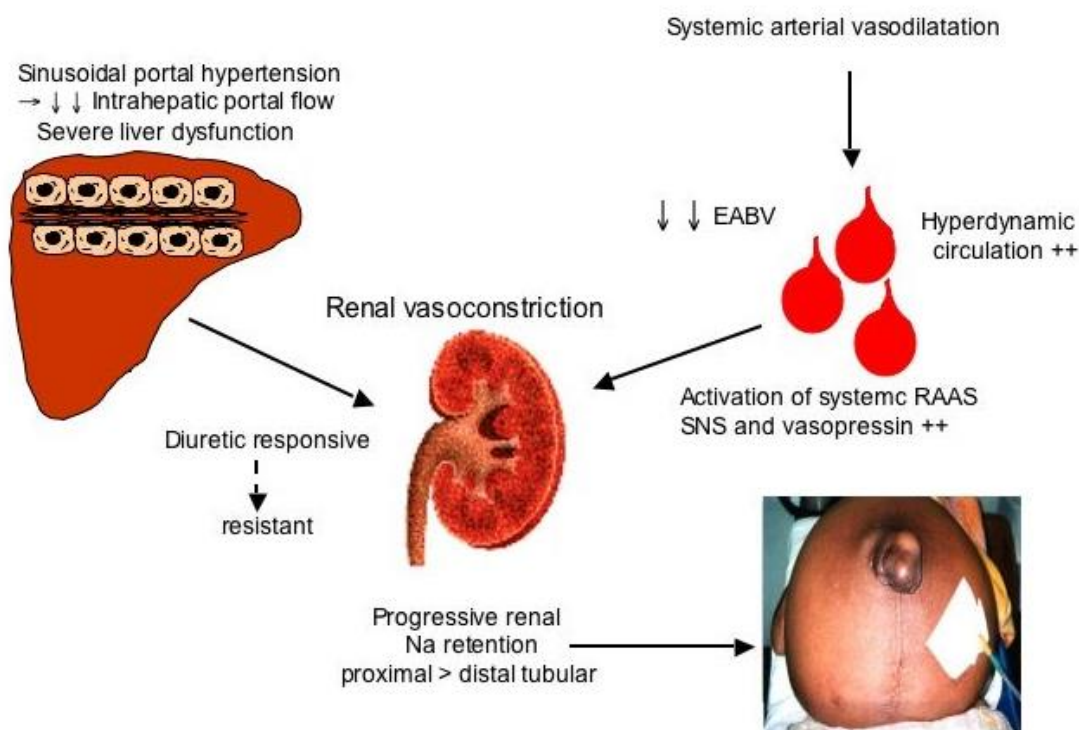


Figure 1. Pathophysiology of ascites formation.

Abbreviations: EABV = effective arterial blood volume, RAAS = renin-angiotensin-aldosterone system, SNS = sympathetic nervous system.

1.3. Clinical Presentation

The first clinical evidence of ascites is body weight gain. Peritoneal fluid of less than 2 litres is difficult to detect clinically, but abdominal ultrasound is useful in defining small amounts of ascites of $\leq 500\text{mL}$. As the volume of ascites increases, the abdomen becomes distended, often with fullness (bulging) in the flanks. Bulging flanks and the presence of flank dullness are the most sensitive physical signs for ascites, whereas eliciting a fluid wave or confirming shifting dullness are the most specific. Complications related to ascites and increased intra-abdominal pressure, such as umbilical hernia may be present. Scrotal and leg edema are found with severe fluid retention. A pleural



effusion can accompany ascites, and it is usually on the right side. This is due to the presence of a normal diaphragmatic defect, which allows ascitic fluid to pass into the pleural cavity. Occasionally, only a pleural effusion is present without any ascites.

Patients will also demonstrate signs and symptoms of a hyperdynamic circulation, such as systemic hypotension, resting tachycardia and warm periphery, as well as evidence of portal hypertension such as distended abdominal wall veins radiating from the umbilicus. Other complications of cirrhosis such as jaundice and muscle wasting, which can be quite profound, may also be present.

Examination of ascitic fluid by diagnostic paracentesis should be performed at the patient's first presentation, or when there is alteration of the patient's clinical state, such as a sudden increase in the amount of ascitic fluid, worsening of hepatic encephalopathy, abdominal pain, or the presence of fever (Table 1). Diagnostic paracentesis is performed to rule out other complications of the cirrhosis such as spontaneous bacterial peritonitis (SBP), hepatocellular carcinoma (HCC), or other non-cirrhotic causes of ascites (Table 2). Ascitic fluid analysis should include a total polymorphonuclear (PMN) count; protein, albumin, glucose, and lipase concentrations, and bacterial cultures. Exactly 10 mL of ascitic fluid should be directly inoculated into blood culture bottles at the bedside. This increases the diagnostic yield from 50% to >80% when the PMN count is >250 cells/ μ L, which is diagnostic of SBP. Variants of SBP are shown in Table 3.

Table 1. Indications for diagnostic paracentesis

-
- New Onset Ascites
 - Hospital Admission of the Cirrhotic Patient
 - Development of:
 - peritoneal signs/symptoms eg. fever, abdominal pain
 - alterations in GI motility
 - encephalopathy
 - renal insufficiency
 - Ascitic Patient with GI Hemorrhage
-



Table 2. Causes of Ascites

-
- Cirrhosis from any etiology (75%)
 - Malignancies (15%)
 - Carcinoma of stomach
 - Carcinoma of colon
 - Pancreatic carcinoma
 - Hepatoma with or without cirrhosis
 - Metastatic intra-abdominal malignancies
 - Hodgkin's and non-Hodgkin's lymphoma
 - Ovarian carcinoma and Meigs' Syndrome
 - Heart failure (3%)
 - Tuberculosis (2%)
 - Pancreatitis (1%)
 - Others (5%)
 - Acute Budd-Chiari syndrome
 - Nephrotic syndrome
 - Myxoedema
 - Ovarian hyperstimulation (result of in vitro fertilization)
-

The appropriate frequency of a given cause of ascites is given in brackets.

Table 3. Variants of Spontaneous Bacterial Peritonitis (SBP)

	Ascitic Fluid Analysis	
	PMN count	Organisms
➤ Spontaneous Infection		
○ Spontaneous Bacterial Peritonitis	>250 cell/μL	single
○ Monomicrobial nonneutrocytic bacterascites (MNNB)	<250 cell/μL	single
○ Culture-negative neutrocytic ascites (CNNA)	>250 cell/μL	negative culture
➤ Secondary Infections	>250 cell/μL	multiple

A serum-ascitic fluid albumin gradient (SAAG) of >11 g/L has a >97% accuracy in predicting cirrhotic ascites. Likewise, a SAAG of <11 g/L confers a >97% accuracy in excluding portal hypertension as a cause of the ascites. A high protein content may be associated with congestive heart failure, or Budd-Chiari syndrome (occlusion of the hepatic vein), and may also be seen in pancreatic ascites. Of note, a low ascitic protein concentration (<10 g/L) puts the cirrhotic patient at increased risk for developing SBP. Either abdominal ultrasound or CT scan of the abdomen may be used for the detection of ascites. In particular, abdominal ultrasound can detect even a few mLs of ascitic fluid and is highly sensitive (>95%) and specific (>90%). Abdominal ultrasound may also be used to establish the optimal site in which to perform the paracentesis, and will show the size of the liver and spleen.



1.4. Management

An algorithm for the management of ascites is given in Figure 3. Treating the underlying etiology of cirrhosis has the potential to reverse the associated hepatic decompensation, thus the management of cirrhotic ascites begins with the treatment of the etiologic factors, if possible, such as abstinence from alcohol. Patients with decompensated cirrhosis from hepatitis B should be treated with antiviral therapy. Although bed rest will result in redistribution of body fluid, salt and fluid restriction is required to mobilise the ascites. The patient is usually prescribed a low salt diet containing 44-66 mmol sodium per day, which is even lower than that contained in a no-added salt diet. Professional dietary advice is necessary, and patients require specific instructions regarding where to purchase low salt food. Salt substitutes are contraindicated, as they often contain potassium chloride, and therefore predispose the patients who are taking potassium-sparing diuretics to the development of hyperkalemia. Patients should be carefully monitored with daily weights and with frequent 24-hour urinary sodium excretion measurements. The rate at which ascitic patients gain or lose weight can be used to assess compliance with the low salt diet, and the efficacy of diuretic treatment (Table 4). The urinary creatinine is measured simultaneously with as the urinary sodium to assess completeness of the urine collection. Random urine sodium assessments are unreliable, as urine sodium excretion varies over the course of the day. However, a urine Na^+/K^+ ratio of >1 predicts with 95% accuracy a urinary Na^+ excretion of >78 mmol/day. Measurement of abdominal girth is unreliable as gaseous distension is common.



Table 4. Predicting weight change in patients compliant with low salt (44 mmol Na/day) Diet

➤ Scenario I	○ Urinary sodium excretion is 100 mmol/day ○ Na intake = 44 mmol/day ○ Na output = 100 mmol/day ○ Na balance = $(44-100)\text{mmol/day}$ = -56 mmol ○ Ascitic [Na] = 130 mmol/L ○ Therefore fluid loss = $-56 \text{ mmol} / 130 \text{ mmol/L}$ = -0.41 L ○ weight loss/day = 0.41 kg
➤ Scenario II	○ Urinary Sodium Excretion 0 mmol/day ○ Na intake = 44 mmol/day ○ Na output = 0 mmol/day ○ Na balance = $(44-0) \text{ mmol/day}$ = +44 mmol ○ Ascitic [Na] = 130 mmol/L ○ Therefore fluid loss = $+44 \text{ mmol} / 130 \text{ mmol/L}$ = 0.34 L ○ weight gain/day = 0.34 kg

Diuretic therapy, in addition to salt and fluid restriction, will be required in 90% of cirrhotic patients to manage their ascites. Spironolactone, a distal diuretic with anti-aldosterone activity, is the preferred first line diuretic. This is because ascitic patients usually have hyperaldosteronism. Furthermore, any sodium reabsorption that is blocked by loop diuretics at the Loop of Henle will be reabsorbed when the sodium is delivered to the distal tubule. Combination diuretic therapy, with both a distal potassium sparing and a loop diuretic, acting on two different sites of the nephron, is now the standard of care. The combination approach has been proven to be more effective than sequential use of different classes of diuretics in the elimination of ascites. Spironolactone is usually started at a dose of 100 mg/day. Spironolactone has a slow onset and offset of action because its half-life in cirrhotic patients can be as long as 35 hours. Therefore, frequent dose adjustments are unnecessary, and patients should still be monitored even after spironolactone is discontinued. One of the unacceptable side effects of spironolactone is painful gynecomastia in men.

Amiloride, another potassium-sparing diuretic, is a less potent but certainly acceptable alternative to spironolactone. The starting dose is 5 mg/day. Either potassium-sparing diuretic is usually combined with furosemide, starting at 40 mg/day. The combination can be increased in a stepwise fashion (Table 5).



Table 5. Step-wise approach to the use of diuretic therapy for the management of ascites *

	I	II	III	IV
➤ Spironolactone/	100 mg	200 mg	300 mg	400 mg
➤ Amiloride	5 mg	10 mg	15 mg	20 mg
➤ Furosemide	40 mg	80 mg	120 mg	160 mg

* Monitor: daily weights
 weekly postural symptoms/signs
 twice weekly electrolytes, renal function
 symptoms/signs of encephalopathy

Increase diuretics if: weight loss < 1.5 kg in 1 week, and if patient is compliant with low Na diet, and if renal function is normal, and no electrolyte abnormalities or hepatic encephalopathy.

Electrolyte abnormalities and renal dysfunction are common in cirrhotic patients on diuretics, and should be monitored regularly. Initial outpatient management may be attempted if the volume of ascites is small, and when the ascites occurs in the absence of complications such as concomitant gastrointestinal hemorrhage, encephalopathy, infection or renal failure. Hypokalemia and hypochloremic alkalosis can precipitate hepatic encephalopathy, and should be avoided by the use of judicious changes in the dose of diuretics. Too rapid mobilization of fluid will result in worsening of renal function.

Patients with peripheral edema can have their fluid mobilized more rapidly, as the edema fluid can easily be absorbed to replenish the intravascular volume. The dose of diuretic should be reduced if there are symptoms of encephalopathy, a serum sodium ≤ 125 mmol/L, or a serum creatinine of ≥ 130 mmol/L. Initially, daily weights and at least twice weekly electrolytes and renal function should be monitored. Urine sodium excretion must be greater than the oral sodium intake in order for the patient to lose weight. Weight loss of greater than 0.5 kg/day should be discouraged. This is because the amount of ascitic fluid that can be mobilized each day is ≤ 700 mL. Therefore, weight loss of >0.5 kg per day usually means loss of fluid from the circulatory volume, thus predisposing the patient to the very unwanted development of renal failure.

Refractory ascites is defined as ascites unresponsive to 400 mg of spironolactone or 30 mg of amiloride plus up to 160 mg of furosemide daily for two weeks, in a patient who has been compliant with sodium restriction. Non-compliance with sodium restriction is a major and often overlooked cause of so-called “refractory” ascites. Other causes of refractory ascites include the development of SBP, hepatocellular carcinoma (HCC), and intrinsic renal pathology. Refractory ascites without any underlying cause usually indicates a grave prognosis, with only 50% survival at 6 months.

Large volume paracentesis is now recognized as a safe and effective therapy for the treatment of refractory ascites. In one large randomized controlled trial, large volume paracentesis was safer and more effective than was diuretic therapy for the



management of ascites, with reduced length of hospitalization. There was, however, no survival advantage of paracentesis over diuretic therapy for the ascites.

Removal of ascitic fluid volume of up to 5 litres without the simultaneous infusion of plasma expanders is safe, even in non-edematous patients. Larger volumes can be removed at one sitting in edematous patients. Albumin infusion of 6-8 g per litre of ascitic fluid removed has been recommended for repeated large volume paracenteses of >5litres. This is because patients may develop a post-paracentesis syndrome known as “circulatory dysfunction”. This is characterized by a further rise in renin-angiotensin activity, and potentially the development of renal impairment. The risk factors for the development of post-paracentesis circulatory dysfunction are unknown.

There is still some controversy regarding the use of albumin post-paracentesis, as patients who do not receive albumin have not been shown definitively to have greater mortality. Other plasma expanders, such as Hemaccel, Dextran 70 and Pentaspan, have also been used and have been shown to be equally effective. However, a group in Barcelona has suggested that albumin is superior to all the other volume expanders in the prevention of post-paracentesis circulatory dysfunction and the development of renal failure. A recent study from Toronto has shown that as long as the ascitic volume removed is less than 8 litres and the standard dose of albumin of 6-8 gm per litre of ascitic fluid removed is given, the development of post-paracentesis circulatory dysfunction is not associated with any renal dysfunction. This represents the standard of CARE in Canada.

Vasopressin receptor antagonists, which are pure aquaretic agents, have been tried in combination with diuretics and large volume paracentesis in the management of ascites, whether the patient is still diuretic-responsive or diuretic-resistant. Vasopressin receptor antagonists are able to reduce the volume of ascites accumulated, and hence the frequency of large volume paracentesis in these patients.

A transjugular intrahepatic portosystemic stent shunt (TIPS) is an effective means of managing refractory ascites. A communication is created between a branch of the portal vein and a branch of the hepatic vein, and this communication is held open by a metal stent. This stenting reduces the sinusoidal portal pressure, and allows a slow but effective elimination of ascites. There are five published randomized controlled trials showing that TIPS is better than large volume paracentesis in the control of ascites. Without the use of diuretics, sodium excretion begins after the first month, and slowly increases thereafter. Within 6 months, complete resolution of ascites eventually occurs in approximately two-thirds of patients, and a partial response in the other third.

Unfortunately, patients with advanced liver disease have higher morbidity and mortality after TIPS, so that placement of a TIPS is not recommended for patients with a Child-Pugh score of >12 or a Model for End-Stage Liver Disease (MELD) score of >14. Elderly patients with cirrhotic ascites also fare less well with a TIPS. Predictors of early mortality from a TIPS include active bleeding at the time of TIPS insertion for ascites, a prior history of hepatic encephalopathy, significant jaundice (bilirubin >51 $\mu\text{mol/L}$), and elevated transaminases (ALT >1000 IU/L). Absolute contra-indications to TIPS insertion include ongoing high-grade encephalopathy, cardiac or intrinsic renal disease, non-compliance with sodium and water restriction, and the very elderly (> 70yrs).



The major complications of TIPS are shunt stenosis and hepatic encephalopathy. Therefore, regular assessments of shunt patency with doppler ultrasound and/or angiography are required. In recent years, the use of covered stents has significantly reduced the rate of shunt stenosis. Also, prophylactic use of lactulose can reduce the incidence of post-TIPS encephalopathy. If the serum bilirubin increases post-TIPS insertion, shunt hemolysis should be considered, in addition to worsening liver function.

In the patient who is suitably selected for a TIPS, the result can be very gratifying, with improved nutritional status once the ascites is eliminated. TIPS provides a survival advantage over large volume paracentesis in patients with refractory ascites, especially in patients who are young and who have relatively normal liver function (Figure 2).

Liver transplantation should always remain a treatment option in patients with refractory ascites (Figure 3).

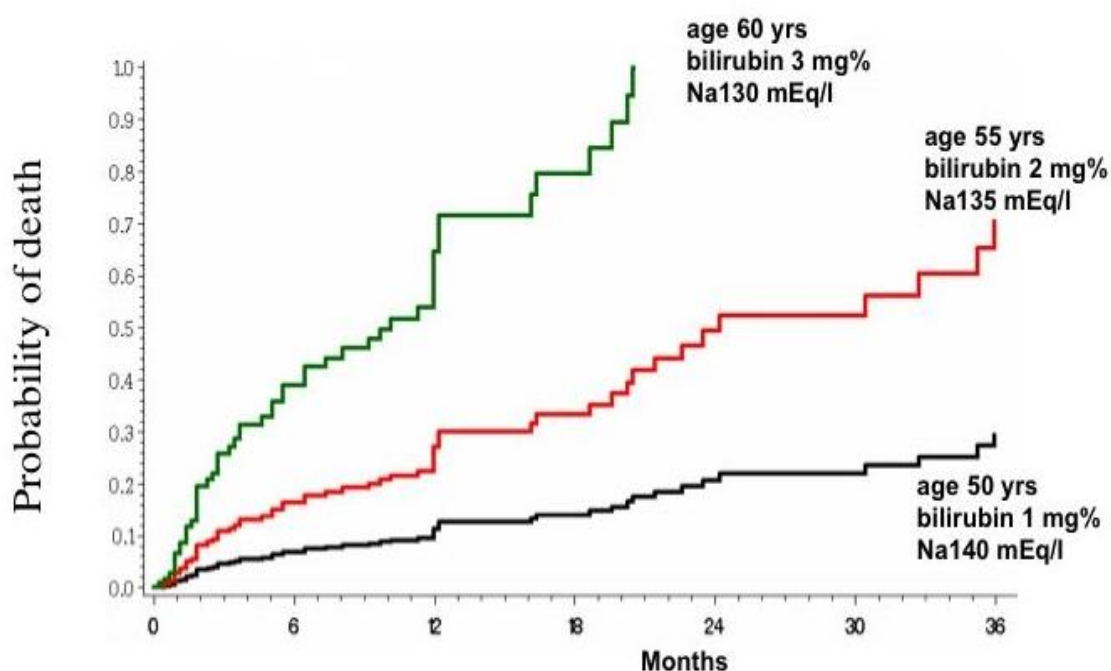


Figure 3. Survival of patients according to patient characteristics following the insertion of a transjugular intrahepatic portosystemic stent shunt for treatment of refractory ascites.



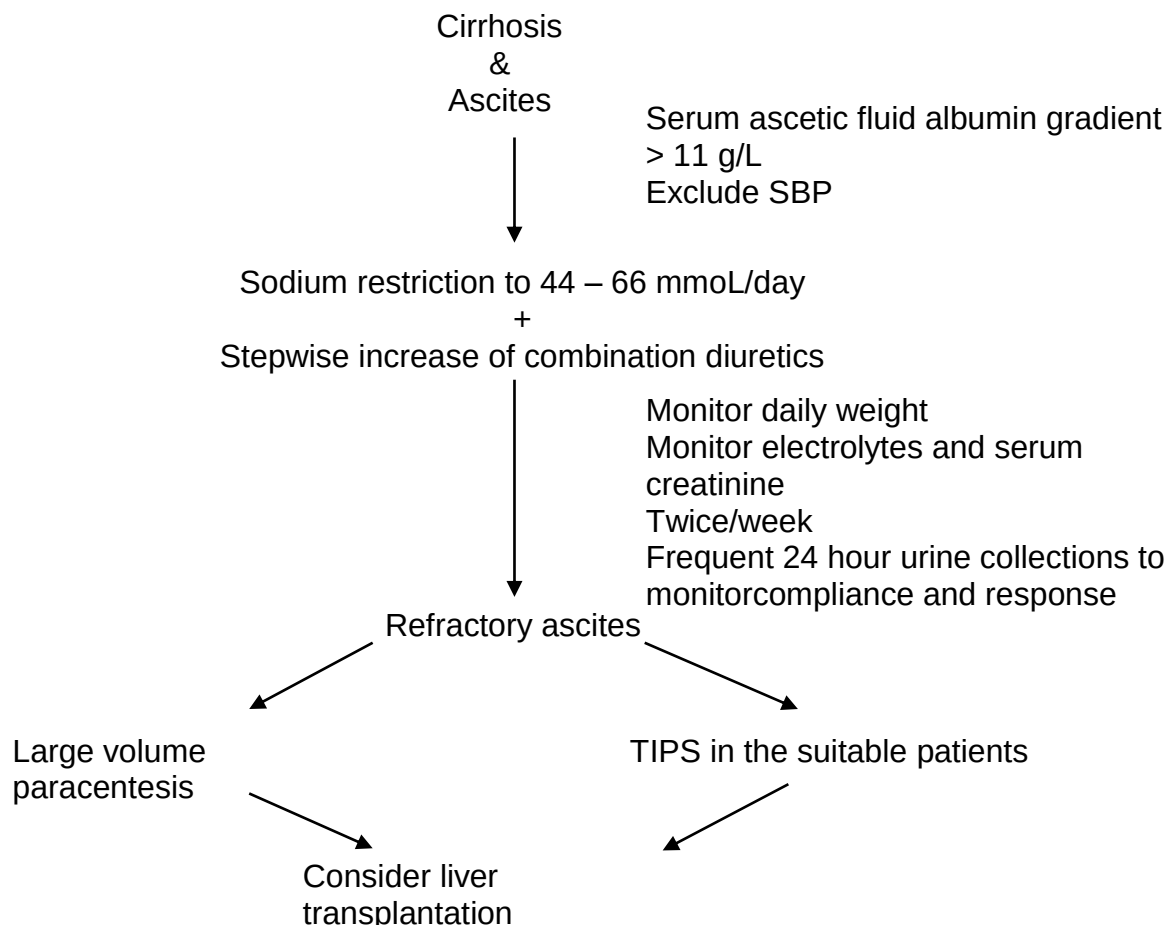


Figure 3. Management of ascites

2. Spontaneous Bacterial Peritonitis

Spontaneous bacterial peritonitis (SBP) is a common and often fatal complication of cirrhosis. It is a condition in which the ascites becomes infected in the absence of a recognisable cause of peritonitis (other than cirrhosis itself). The yearly risk of developing SBP after the onset of ascites is approximately 20-30%. Risk factors include a prior episode of SBP, recent esophageal variceal hemorrhage, an ascitic fluid protein of less than 10g/L and jaundice (bilirubin >43 μ mol/L). Curiously, in most cases, the infection occurs after the patient's admission into hospital. About one third of cases of SBP are asymptomatic, and the attending clinician should not hesitate in performing a diagnostic paracentesis in all persons admitted with ascites. The indications for diagnostic paracentesis to rule out a diagnosis of SBP are shown in Table 1.

Some patients with SBP may present with fever and/or abdominal pain. More often, the presentation is atypical, with worsening of hepatic encephalopathy or renal function. The "gold standard" for diagnosing SBP is an ascitic fluid PMN count of >250 cells/ μ L. A variant of SBP, known as culture-negative neutrocytic ascites are culture



negative cases of suspected SBP with an ascitic fluid PMN count of >250 cells/ μL . The patients with culture-negative neutrocytic ascites have the same clinical presentation, and carry the same unfavorable prognosis as those with SBP (Table 2). Positive culture results may take 48 hours, and Gram stains of ascitic fluid are only positive in 10-50% of infected patients. Therefore, treatment for suspected SBP should start immediately after the diagnostic PMN count, rather than waiting for positive culture results.

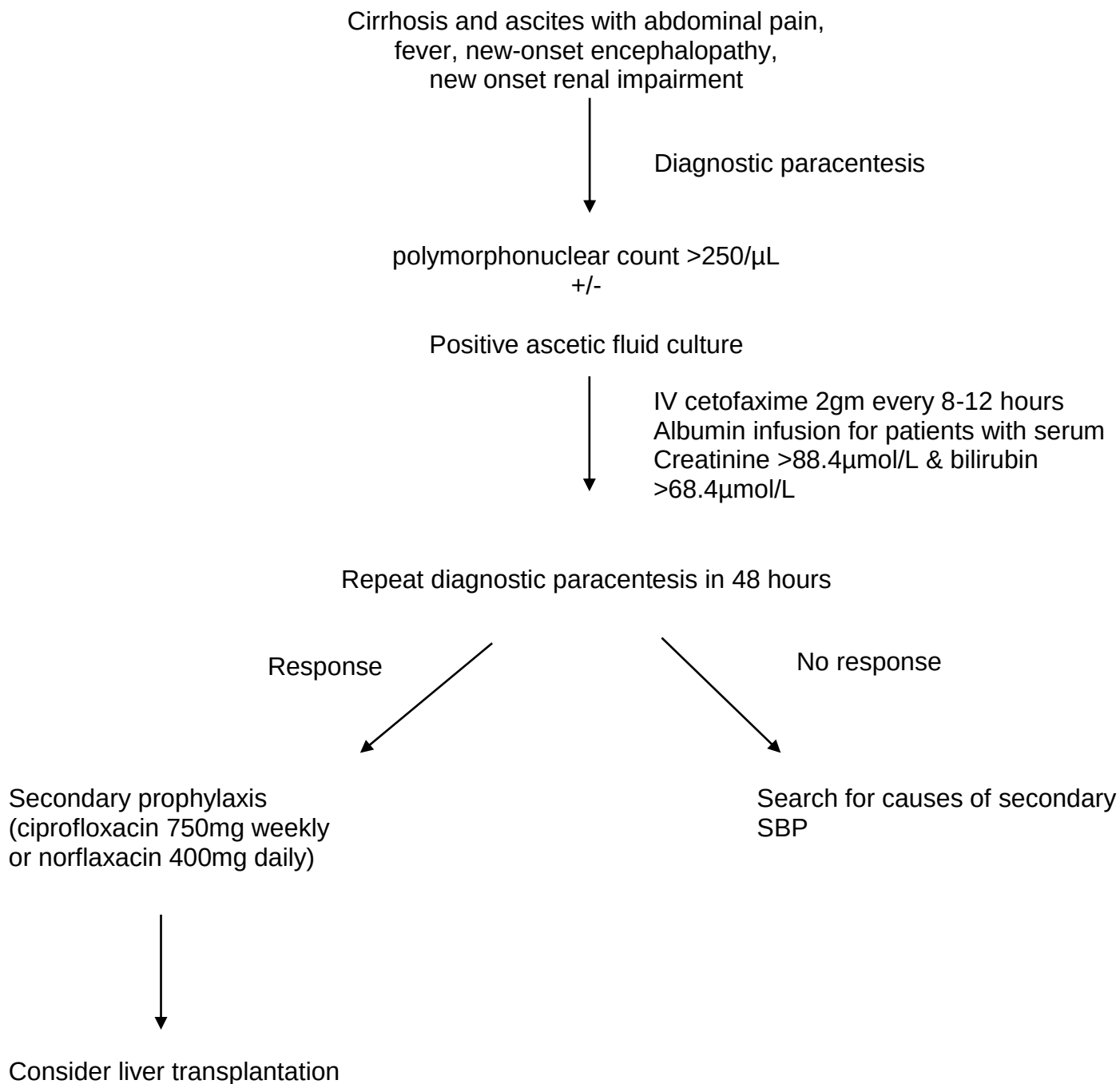
Another variant of SBP is monomicrobial non-neutrocytic bacterascites. In this scenario, the ascitic PMN count is <250 cell/ μL , but the subsequent ascitic culture is positive. It is not known if this represents an early stage of SBP. It is recommended that the patient undergoes repeat paracentesis. If either the ascitic culture is again positive or the PMN count is >250 cells/ μL , then the patient should be treated as having presumed SBP.

Gram negative bacilli account for 70% of cases of SBP. *E. coli* is the commonest pathogen isolated (Table 6). Anaerobic organisms are uncommon causes of SBP, as the oxygen tension in the ascitic fluid is too high for their survival. Among these, *Bacteroides* species appear to be more common than other anaerobes. A management algorithm for SBP is shown in Figure 4 Cefotaxime, a broad-spectrum third generation cephalosporin, is the treatment of choice for SBP. Its spectrum includes most organisms responsible for SBP, and it is not nephrotoxic when dosed in the usual therapeutic range. A five-day course of Cefotaxime 2 g intravenously every 8-12 hours is effective as a ten-day course.

Table 6. Micro-organisms that can cause spontaneous bacterial peritonitis

Gram negative bacilli	Gram positive organisms	Anaerobes
<i>E. coli</i>	Streptococcus	<i>Bacteroides</i>
Klebsiella	Group D Streptococcus	Clostridia
<i>C. freundii</i>	<i>S. pneumoniae</i>	Lactobacillus
Proteus	<i>S. aureus</i>	
Enterobacter		



Figure 5. Management of spontaneous bacterial peritonitis

Other treatment options for SBP include intravenous followed by oral amoxicillin/clavulanic acid, or intravenous ciprofloxacin followed by oral treatment, or oral ciprofloxacin in patients without septic shock, encephalopathy, azotemia, gastrointestinal bleed or ileus. These options explore the possibility of giving part of the treatment course as outpatients, thereby shortening the duration of hospital stay. However, monitoring patient compliance becomes mandatory if this course of action is to be followed.

Aminoglycosides should not be used for the treatment of SBP, since cirrhotic patients are particularly sensitive to their nephrotoxic effects and monitoring serum aminoglycosides levels is no guarantee against aminoglycoside induced nephrotoxicity. One study has shown that the concomitant use of albumin can reduce the risk of renal impairment in these patients. However, further studies have shown that only patients with a baseline serum creatinine of $>88.4 \mu\text{mol/L}$ and serum bilirubin $>68.4 \mu\text{mol/L}$ will require albumin infusion for protection from renal failure, as the risk for the development of renal failure is very low in patients with serum creatinine and bilirubin levels below these cut-off values.

The response to treatment should be assessed by both evaluating the symptoms and signs of infection, and performing at least one follow-up paracentesis after 48 hours of antibiotic therapy. Clinical improvement should parallel a fall in the ascitic PMN count. A reduction of less than 25% in relation to the pre-treatment value is often considered to represent failure of antibiotic treatment.

Secondary bacterial peritonitis should be considered if the following features are present: (i) poor clinical response to antibiotic therapy; (ii) multiple organisms grown from the ascitic fluid; (iii) ascitic fluid protein concentration $>10 \text{ g/L}$ or ascitic glucose $<3 \text{ mmol/L}$; (iv) PMN count remains high despite antibiotic therapy. If secondary bacterial peritonitis is suspected, antibiotic coverage should be broadened with the addition of metronidazole and ampicillin. Radiographic examinations are required to exclude perforation of the gastrointestinal tract, with emergency surgery only where gut perforation is confirmed.

Despite successful treatment of SBP, the prognosis of these patients remains poor. The one-year mortality probability of SBP recurrence is 40-70% in patients who have had previous episodes of SBP. Routine selective intestinal decontamination with oral non-absorbable antibiotics has proved to be effective in reducing recurrence. Norfloxacin 400 mg daily, Trimethoprim/sulfamethoxazole 160/800mg daily, or Ciprofloxacin 750 mg weekly are the drugs of choice, as they rarely cause bacterial resistance and have a low incidence of side effects when administered chronically. Trimethoprim/sulfamethoxazole 160/800mg daily may confer greater gram-positive coverage. Cirrhotic patients with upper gastrointestinal bleeding are at a high risk for developing severe bacterial infections, including SBP, within the first days of the hemorrhagic episode. Antibiotic prophylaxis is effective in improving survival in cirrhotic patients with gastrointestinal hemorrhage. Thus, antibiotic prophylaxis is recommended in all cirrhotic patients who have a GI bleeding. The optimal dose and the duration of treatment in this setting have not yet been established. There is no evidence to support routine primary prophylaxis of all ascitic patients against SBP, and indiscriminant use of antibiotics in cirrhosis may lead to the development of antibiotic resistance. However, in



certain settings such as patients with significant jaundice or low protein ascites, it may be prudent to consider primary SBP prophylaxis.

A recent meta-analysis has demonstrated that the use of non-selective beta-blockers can retard bacterial translocation across the bowel wall, and therefore can reduce the risk for SBP in patients with ascites. Although not widely available, the detection of bacterial DNA in ascitic fluid without the occurrence of SBP has been shown to be associated with decreased survival. There are no studies to date to determine whether these patients require antibiotic prophylaxis. Despite decreased SBP recurrence rates with prophylactic antibiotics, no change in mortality has yet been demonstrated.

All patients who have experienced one episode of SBP should be considered for liver transplantation.





Chapter 15: Hepatorenal Syndrome

S. E. Congly and A. I. Aspinall



1. Definition

Hepatorenal syndrome (HRS) was first described in 1994 by the International Ascites Club as a specific form of renal insufficiency (RI) associated with end stage liver disease (ESLD), occurring in the absence of another cause of acute kidney injury (AKI) (Ginès 2009, Ginès 2010, Runyon 2009, Salerno Gut, 2007). HRS is not an uncommon complication in patients with cirrhosis with a one-year incidence of 18% and 39% by five years (Ginès 1993).

The 2007 revised criteria of the International Ascites Club for diagnosing HRS are presented in Table 1. There are two forms of HRS, distinguished by the rapidity of renal decompensation. In a cirrhotic patient with ascites and HRS, a doubling of creatinine within two weeks to over 220 $\mu\text{mol/L}$ (2.5 mg/dL) is the definition of Type 1 HRS. Type 1 HRS, which is rapidly progressive, often develops after an inciting event (such as spontaneous bacterial peritonitis (SBP) or an esophageal variceal hemorrhage) although it still can develop in the absence of a clear precipitant. Although usually ascites is present, the presence of current ascites is not necessarily a requirement for HRS Type 1; infection or a systemic inflammatory response can precipitate HRS. Prognosis is poor in patients with Type 1 HRS with historically, median survival being two weeks (Ginès 1993). With current therapy, the overall median survival is approximately three months; the median survival drops to approximately one month in those with a high Model for End-stage Liver Disease (MELD) score and Type 1 HRS.

Type 2 HRS also develops in the presence of ascites and is characterized by a slow but progressive deterioration in renal function. Patients with Type 2 HRS will typically have refractory ascites and usually the renal impairment is less [creatinine between 133-220 $\mu\text{mol/L}$ (1.5-2.5 mg/dL)]. In such patients, a precipitating event such as SBP may result in the development of Type 1 HRS. The median survival of patients with Type 2 HRS is approximately 6 months. (Ginès 2003)

Table 1. International Ascites Club 2007 Diagnostic Criteria for HRS (Salerno 2007)

-
- Cirrhosis with ascites.
 - Serum creatinine >133 $\mu\text{mol/L}$ (1.5 mg/dl).
 - No improvement of serum creatinine (decrease to a level of $\leq 133 \mu\text{mol/L}$) after at least 2 days with diuretic withdrawal and volume expansion with albumin. The recommended dose of albumin is 1 g/kg of body weight per day up to a maximum of 100 g/day.
 - Absence of shock.
 - No current or recent treatment with nephrotoxic drugs.
 - Absence of parenchymal kidney disease as indicated by proteinuria >500 mg/day, microhaematuria (>50 red blood cells per high power field) and/or abnormal renal ultrasonography.
-



2. Pathogenesis

There is derangement of cardiovascular and neuroendocrine function in HRS and several factors have been proposed to be important in the development of HRS; this is summarized in Figure 1. The splanchnic arterial vasodilation that results from severe portal hypertension is a key initiating event. This results in a decrease in peripheral effective arterial volume and a decrease in mean arterial pressure (MAP). In turn there is activation of the systemic renin-angiotensin-aldosterone system (RAAS), subsequent renal arterial vasoconstriction, and greater sensitivity of renal perfusion to small changes in MAP. Overtime, cirrhotic cardiomyopathy develops leading to an inappropriately low compensatory increase in cardiac output, further compromising renal perfusion. A number of soluble circulating vasoactive mediators have also been implicated in decreasing renal perfusion and the glomerular microcirculation.

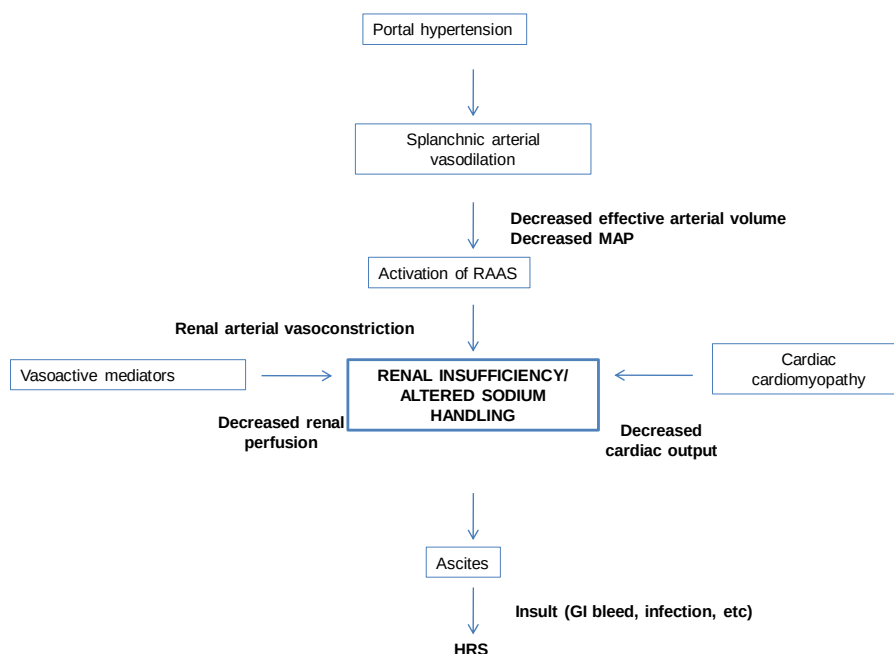


Figure 1. Pathogenesis of HRS

3. Differential Diagnosis and Evaluation of Acute Kidney Injury

Apart from HRS, cirrhotics are at increased risk of AKI for a variety of reasons. Hypovolemia due to excessive diuresis, gastrointestinal (GI) hemorrhage, or other GI losses (such as excessive lactulose administration or diarrheal illness) can produce a clinical picture similar to HRS. Parenchymal kidney disease can result from many different causes, including diabetic or hypertensive nephropathy, glomerulonephropathies associated with chronic viral hepatitis, and nephrotoxic medications (such as NSAIDs or aminoglycosides). An active urine sediment characteristic of parenchymal kidney disease can help discriminate these etiologies



from HRS. Occasionally, a renal biopsy is required to discriminate between causes of parenchymal kidney disease. Contrast dyes, such as those used in abdominal CT imaging and angiography, can also precipitate AKI. Acute tubular necrosis (ATN) can result from both long-standing HRS and pre-renal AKI and ATN is suggested by the presence of granular casts (epithelial cells) on urinalysis. A fractional excretion of sodium $<1\%$ suggests intact tubular function (and thus the absence of ATN).

In cirrhotic patients with AKI, thorough investigations are warranted to determine the cause of AKI and the etiology of any precipitant of HRS. An assessment of liver function and investigations to rule in or out the presence of sepsis are indicated. Urine microscopy and studies for electrolytes and protein can help rule in or out parenchymal renal disease. A renal ultrasound helps rule out obstructive etiologies of renal failure. A trial of volume repletion with 1g/kg of albumin daily to volume replete the patient may help differentiate between hypovolemia and HRS. Daily serum electrolytes and creatinine help follow responses to therapy and to screen for the development of serious electrolyte disturbances (such as severe hyponatremia and hyperkalemia).

4. Treatment

The initial strategy to manage pre-renal acute renal insufficiency in a cirrhotic patient, which also includes HRS, is to stop all diuretics as well as any nephrotoxins such as NSAIDs. In addition, discontinuing of beta-blockers should be considered as these also negatively impact renal perfusion. Initial aggressive fluid hydration with albumin [1g/kg daily] is an important adjunct for all pharmacologic therapies for HRS.

Given that the mechanism of HRS is peripheral vasodilation resulting in renal arterial vasoconstriction (see “Pathogenesis” above), current pharmacologic therapies for HRS include administration of agents that cause alpha-adrenergic receptor-mediated vasoconstriction, and those that increase the effective arterial volume, thereby promoting renal perfusion. Collectively, such therapy is associated with improved short-term survival and reversal of HRS in 52% of patients (Gluud 2010). Treatment with agents thought to be directly vasodilatory for the renal arterial supply (such as non vasoactive doses of dopamine) is ineffective (Angeli 1999).

4.1 Terlipressin

Terlipressin, which is not currently available in North America, is the most comprehensively studied vasoactive agent (Table 2). In randomized controlled trials (RCT), terlipressin usually has been co-administered with albumin. A meta-analysis of the literature for terlipressin suggest that there is both mortality reduction (RR 0.76, CI 0.61-0.95) and improved renal function with terlipressin but the data strength is equivocal (Gluud 2012); further studies are ongoing. Contraindications to terlipressin include ischemic cardiovascular disease, and patients should be observed for the development of ischemic heart disease, arrhythmias, mesenteric and digital ischemia and volume overload. Patients usually are treated for up to 14 days.



4.2 Midodrine

Two small studies have shown a role for midodrine in treating HRS when used in combination with octreotide and albumin (Angeli 1999, Wong 2004), and a single small uncontrolled trial with norepinephrine also showed efficacy (Duvoux 2002). Collectively, a meta-analysis of randomized studies using vasoactive agents in HRS (Gluud 2010) has shown a significant decrease in all cause mortality (RR 0.82, CI 0.70-0.95), improvement in renal function (RR 2.00, CI 1.11-3.62) and resolution of HRS (RR 3.76, CI 2.21-6.39).

4.3 Transjugular intrahepatic portosystemic shunts (TIPSS)

Non-pharmacologic therapy using transjugular intrahepatic portosystemic shunts (TIPSS) has been studied in HRS in small uncontrolled trials. TIPSS insertion has been successful in normalizing renal function in some HRS Type 1 patients first treated with midodrine (Wong, Hepatology, 2004). Renal function has also been shown to improve in a small uncontrolled trial of seven patients treated with TIPSS as primary therapy for HRS (Guevara 1998). Intermittent hemodialysis (IHD) is not associated with any significant survival improvement in patients with HRS and is often inadequate and limited by hypotension during the dialysis run. However, IHD is sometimes viewed as a bridge to liver transplantation (LT) and should be reserved only for those patients who are LT candidates.

Table 2. Pharmacological Treatment of HRS

Treatment	Level of evidence	Dose	Outcomes
○ Terlipressin (with Albumin)	○ Randomized and non-randomized controlled trials	○ 0.5-1.0 mg i.v. bolus q4-6h, increased to 2.0 mg i.v. q4-6h after 3 days of therapy if Cr has not decreased by at least 25%	○ Renal function improved in 40-50% of patients and improved 30 day survival
○ Octreotide/ Midodrine (with Albumin)	○ Non-randomized controlled trial/Case series	○ Octreotide 100-200 ug s.c. t.i.d. Midodrine 7.5-12.5 mg po t.i.d.	○ Renal function improved and improved 30 day survival
○ Norepinephrine (with Albumin)	○ Case Series	○ 0.5-3.0 mg/hr i.v.	○ HRS Type 1 reversed in 10/12 patients
○ Albumin	○ Randomized and non-randomized controlled trials	○ Various doses (i.e. 1 g/kg i.v. day 1 followed by 20-40 g i.v. daily)	

Abbreviation: Cr, serum creatinine



4.4 Liver Transplantation

LT is well recognized to reverse HRS; as such, all patients with HRS should be considered for LT assessment. When ATN complicates longstanding HRS in LT candidates, resulting in irreversible RI, combined LT and kidney transplantation can be considered, and criteria have been proposed to identify those who may benefit from combined transplantation (Ginès 2009).

4.5 Prevention of HRS

Measures can be taken to minimize the evolution of HRS in cirrhotics with ascites. The administration of albumin in patients with SBP reduces the evolution of HRS (Salerno 2007) and has been shown to have a mortality benefit (Sort 1999). The recommended dose is 1.5 g/kg of albumin on day 1 of admission and 1 g/kg on day 3 of admission. Pentoxifylline, at a dose of 400 mg PO t.i.d., in severe alcoholic hepatitis may also reduce the development of HRS (Ginès 2010).

5. Summary

AKI is a common and severe complication in decompensated cirrhotic patients. There are multiple possible causes of AKI in these patients, and HRS in particular is associated with poor survival in the absence of LT. Pharmacologic and non-pharmacologic therapy is effective in treating HRS in some patients. First line therapy for HRS Type 1 is the administration of vasoconstrictors with albumin.



Chapter 16: Hepatatic Encephalopathy

J. Leonard



1. Definition

Hepatic encephalopathy (HE), also known as portosystemic encephalopathy, is a complex, potentially reversible neuropsychiatric syndrome that occurs as a consequence of acute or chronic liver failure, and is associated with excessive neuro-inhibitory neurotransmission.

2. Clinical Presentation

Patients with this condition will present in a variety of ways (Table 1). Usually there will be a history of chronic liver disease. Occasionally this will be the first sign of an acute liver problem. Patients with chronic disease often have other manifestations of their liver disease including jaundice, ascites and gastrointestinal bleeding. Occasionally HE is the only apparent manifestation of decompensated liver disease. The usual physical signs and laboratory abnormalities associated with advanced liver disease may be present. These physical findings include muscle wasting, jaundice, peripheral edema, and ascites. Occasionally fetor hepaticus, a sickly-sweet smell from the mercaptanes in the breath, will be present. In some cases HE accompanies acute, fulminant hepatic failure. In those cases the physical signs of chronic liver disease will be absent. Typical laboratory abnormalities of both acute and chronic disease include an elevated INR, elevated bilirubin and possibly low albumin concentration. Hypoglycemia may be seen, but this is typically a late finding.

Table 1. Clinical Presentation of HE

-
- Acute Liver Failure
 - Chronic Liver Disease
 - With decompensation (Jaundice, ascites, esophageal varices)
 - No symptoms (mHE)
 - Symptoms (West Haven Criteria: Table 2)
 - Refractory HE
 - Dementia, spastic paresis, cerebellar degeneration, extrapyramidal movement disorders
-

The clinical picture of HE can be quite variable, representing a continuous spectrum of disease, from subtle disturbances in the sleep-wake cycle to overt coma. Hepatic encephalopathy is characterized by changes in personality, consciousness, behavior and neuromuscular function. The most commonly used grading system is the West Haven Criteria (Table 2).



Table 2. West Haven Criteria for Hepatic Encephalopathy

Stage	Consciousness	Intellect and Behaviour	Neurological findings
0	- Normal	- Normal	- Normal exam
1	- Mild lack of awareness	- Shortened attention span Impaired attention or subtraction	- Mild asterixis or tremor
2	- Lethargic	- Disoriented - Inappropriate behavior	- Obvious asterixis - Slurred speech
3	- Somnolent but arousable	- Gross disorientation - Bizarre behaviour	- Muscular rigidity and clonus - Hyperreflexia
4	- Coma	- Coma	- Decerebrate posturing

HE may be present in up to 80% of patients with cirrhosis and accounts for a significant proportion of admissions to hospital. The earliest feature is often reversal of the diurnal sleep pattern or subtle personality changes and irritability. This can progress to include apathy, hypersomnia, and personal neglect. Later stages include delirium and even coma. Neurologic signs may include hyperreflexia, rigidity, and myoclonus. Asterixis (asymmetric flapping motions of the outstretched, dorsiflexed hands) can be easily checked in a routine clinical exam. It may be present in HE, but is not diagnostic as it may occur in other causes of metabolic encephalopathy.

Hepatic encephalopathy associated with acute liver failure has a rapid onset and progression. It is usually complicated with cerebral edema, which can lead to seizures and lateralizing neurologic signs. HE associated with chronic liver disease may present acutely, but may also present gradually with slow progression of symptoms. Occasionally, a refractory pattern emerges leading to debilitating syndromes such as dementia, spastic paresis, cerebellar degeneration and extrapyramidal movement disorders.

When approaching a patient with severe liver disease who has an altered level of consciousness or other neurological features, it is important to rule out other causes of changes in mental status and neurologic disease. This includes exclusion of central nervous system disease such as subdural hematoma, tumor, or CVA, as well as CNS infection and drug ingestion. One may need to distinguish the neurologic changes commonly seen in patients with alcoholic liver disease and Wilson disease.

3. Theories of Pathogenesis

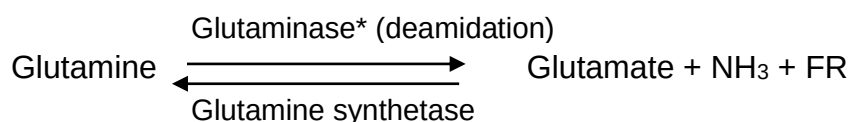
The syndrome of HE is not a single clinical entity. It may reflect either a reversible metabolic encephalopathy, brain atrophy, brain edema or any combination of these conditions. The mechanisms of brain dysfunction in liver failure are not clearly known (Table 3). In advanced HE, the effects of brain swelling, impaired cerebral perfusion and abnormalities in neurotransmitter systems cannot be distinguished. Factors of importance in the pathogenesis of HE are the shunting of portal venous blood around the liver into the systemic circulation and the presence of hepatocellular dysfunction. Encephalopathy probably results from a number of mechanisms that include, in part, one or more toxic



products that originate in the gut that are usually metabolized by the liver entering the systemic circulation and reaching the brain.

Table 3. Theories of Pathogenesis of HE

-
- ↑ NH₃
 - GUT: urease bacteria, ↑ glutaminase activity* (Increased glutamate, NH₃ and free radicals)
 - Liver: ↓ urea cycle metabolism by hepatocytes, ↑ shunting to systemic circulation
 - Muscle: atrophy leads to less NH₃ metabolism by urea cycle
 - Kidney: ↑ renal production in presence of hypokalemia and metabolic alkalosis
 - Brain: ↑ BBB permeability to NH₃ and glutamate; astrocyte edema, neuro-inhibition
 - ↑ Endogenous benzodiazepine-like substances, ↑ GABA-ergic transmission
 - ↑ Neurotoxic SCFAs, phenols, mercaptanes
 - ↑ NH₃ toxicity
 - ↑ SCFAs and AAA + ↓ BCAA
 - ↑ False neurotransmitters, ↓ neuro-excitatory neurotransmission (glutamine, catecholamines)
 - ↑ Neuro-inhibitory neurotransmitters (GABA, gamma-aminobutyric acid; AAA, aromatic amino acids; BCAA, branched chain amino acid)
-



Abbreviation: AAA, aromatic amino acid; BCAA, branched chain amino acid; FR, free radicals; NH₃, ammonia

Abnormalities of ammonia metabolism are most frequently implicated in the pathophysiology of HE. The normal gut flora produce a urease enzyme that enzymatically cleaves NH₃ from protein in the lumen. Ammonia derived from colonic bacteria and from deamination of dietary glutamine in the small bowel is absorbed into the portal circulation. The intact liver clears almost all of portal vein ammonia, converting it to glutamine and preventing its entry into the systemic circulation. In severe liver disease, ammonia reaches the systemic circulation because of spontaneously created vascular shunts within and around the hepatocytes and the inability of the liver to metabolize the ammonia. Increased blood-brain barrier permeability likely facilitates the entrance of ammonia and other toxic metabolites into the brain. This contributes to astrocyte swelling and edema.

Alternative proposals of gut-derived toxins include endogenously produced benzodiazepine-like substances which activate GABA-ergic transmission, as well as neurotoxic short-chain fatty acids, phenols and mercaptanes which may potentiate ammonia toxicity. Another hypothesis proposes that increased levels of short-chain



fatty acids and aromatic amino acids associated with decreased levels of branched-chain amino acids cause production of false neurotransmitters. As well, the principle neuro-inhibitory neurotransmitter γ -aminobutyric acid (GABA) is increased in encephalopathy. False neurotransmitters, including an endogenous modulator of GABA receptors, suggest involvement of the GABA-diazepam receptor complex in the pathogenesis of HE. Thus, the synergistic action of ammonia with other toxins likely accounts for many of the abnormalities occurring in liver failure, such as the changes in blood-to-brain transport of neurotransmitter precursors, the metabolism of amino acid neurotransmitters and cerebral glucose oxidation. These changes may lead to activation of inhibitory (GABA, serotonin) and impairment of excitatory (glutamine, catecholamines) neurotransmitter systems, resulting in enhanced neural inhibition and HE.

4. Diagnosis

There is no specific diagnostic test for HE. It is usually based on the clinical impression, but this sometimes makes a definite diagnosis difficult. The history and the clinical examination, including a complete mental status and neurologic examination, are the most important tools for diagnosing HE. HE also needs to be accurately distinguished from other causes of neurologic disease and encephalopathy.

The presence of asterix is helpful but not pathognomonic for HE. It can also be seen in carbon dioxide intoxication and uremia. It is usually tested when the patient is sitting erect with outstretched hands. A flapping tremor can then be seen. If the patient is unable to sit forward, then gripping the examiner's hand could elicit the same oscillatory movement. Upon examination of the motor system, focal deficits are typically not seen, and should prompt further investigations to search for an alternate diagnosis such as intracranial bleeding or an ischemic event.

Imaging with either CT or MRI is usually necessary in these cases. Blood tests help verify the presence and severity of liver disease, and rule out other causes of encephalopathy such as renal failure, hypoxia, CO₂ retention and drug overdose. Blood tests are also helpful in identifying precipitating factors of HE such as hypoglycemia, azotemia, electrolyte imbalance (hypokalemia and hyponatremia) and infection. An elevated serum ammonia (NH₃) concentration is often observed, but correlates poorly with the degree of encephalopathy and may be normal in up to 10% of cases with HE. It is not useful to follow the serum NH₃ concentration once a diagnosis of HE has been made. Trends of the NH₃ level over time do not correlate with response to therapy, and degree of elevation of NH₃ does not correlate with the severity of HE.

Lumbar puncture is usually not necessary but in certain situations may be required to rule out other CNS pathology. In HE the cerebrospinal fluid is usually normal, or may show increased protein and increased GABA levels. The EEG shows slow, triphasic wave activity mainly over the frontal areas. Although this pattern is highly sensitive and characteristic of HE, it is not specific for this condition.

In patients with clinical symptoms of HE, neuropsychiatric testing is not necessary. It may be helpful in establishing the diagnosis of mild HE where the diagnosis is not clear. A Psychometric Hepatic Encephalopathy Score (PHES) includes a battery of five paper-pencil tests including the line tracing test, digit symbol test, serial



dot test and two number connection tests. The psychometric tests are particularly useful to diagnose minimal hepatic encephalopathy (mHE). It is important to make the diagnosis of mHE since these persons with chronic liver disease have an increased risk of having motor vehicle accidents, and then driving privileges may need to be restricted.

5. Management

HE occurring in acute liver failure is usually accompanied by cerebral edema, and carries with it a poor prognosis. Unless the liver shows signs of spontaneous recovery, these patients should be considered for urgent orthotopic liver transplantation. Patients with grade 3 or 4 HE should be managed in intensive care, as there is often associated multi-organ failure. Management may include elective ventilation, mannitol infusion and intracranial pressure monitoring.

Provision of meticulous medical and nursing care to these confused and often comatose patients is very important for their recovery, and to avoid potential complications.

Most HE occurs in patients with chronic liver disease and is due to a clinically apparent precipitating event or the development of a portosystemic shunt, either spontaneously or surgically created (Table 4). The most important aspect of management is the prompt recognition and treatment of these precipitating factors (Figure 1). Exogenous factors include markedly increased dietary protein, constipation, administration of certain drugs (especially sedatives or narcotics), gastrointestinal bleeding, azotemia, hypoxia and infection (urinary, respiratory, spontaneous bacterial peritonitis). Development of underlying hepatocellular carcinoma may present as worsening HE. Dehydration, hyponatremia, hypokalemia and alkalosis (often the result of diuretic therapy) should be corrected. Correction of it is essential as hypokalemia increases renal ammonia production.



Table 4. Common precipitants of hepatic encephalopathy in chronic liver disease

- Increased ammonia production or absorption
 - Excessive dietary protein
 - Gastrointestinal bleeding
 - Electrolyte disturbance (hypokalemia)
 - Zinc deficiency
 - Metabolic alkalosis
 - Constipation
 - Azotemia
 - Infection
 - Spontaneous bacterial peritonitis (SBP)
 - Urinary tract infection
 - Pulmonary
 - Dehydration
 - Vomiting
 - Diarrhea (spontaneous, or due to laxative use)
 - Diuretics
 - Large volume paracentesis
 - Drugs
 - Narcotics, sedatives
 - Alcohol
 - Portosystemic shunting
 - Transjugular intrahepatic portosystemic shunt (TIPS)
 - Surgical shunts
 - Spontaneous shunts
 - Vascular Occlusion
 - Portal vein thrombosis
 - Hepatic vein thrombosis
 - Additional Liver Disease
 - Hepatocellular Carcinoma
 - Superimposed liver injury (acute hepatitis, drug-induced liver injury)
 - Noncompliance with medical treatment
 - Surgery
-



In conjunction with treating the potential triggering events, the next goal of therapy is to lower the level of neurotoxic substances by emptying nitrogenous wastes from the gut. Restricting dietary protein has never been shown to be effective in treating HE. Often these patients have already lost significant muscle mass, and restricting dietary protein only worsens this problem.

Constipation can be avoided by the use of laxatives. A commonly used laxative is lactulose, a synthetic disaccharide that is degraded by intestinal bacteria into lactate and acetate to produce stool acidification and an osmotic diarrhea. The acidification of colonic contents reduces ammonia absorption in part by trapping nitrogenous compounds in the lumen ($\text{NH}_3 + \text{H}^+ \rightarrow \text{NH}_4$). The daily dose of lactulose should be titrated to produce two to four soft, acidic ($\text{pH} < 6.0$) stools per day. For most patients, this will be between 15-30 cc orally once to four times per day. Patients in coma or with small bowel ileus can receive lactulose by enema. Patients will often complain of an excessively sweet taste, flatulence, diarrhea and cramping as the most common side effects. Lactitol can be used instead of lactulose. Overdosing can lead to excessive diarrhea, which can result in fluid and electrolyte depletion. The resultant renal failure can worsen HE. Lactulose can be used chronically to reduce the frequency of episodes of HE. Patients should be instructed to adjust their dose based on their stool output. Although lactulose is considered by most to be the mainstay of therapy, randomized controlled studies proving the efficacy are lacking.

Alternatively, antibiotics such as neomycin and metronidazole may be used. These inhibit urea-splitting and deaminating bacteria, thereby reducing the production of ammonia and other potential toxins. Neomycin use is now limited due to its potential nephrotoxic and ototoxic side-effects. Because of the potential toxicity, long-term use of these antibiotics is not recommended. Limited data support a short course of the combined use of lactulose and antibiotics in selected resistant cases.

Rifaximin is a nonsystemic antibiotic, and is better tolerated with fewer side effects and complications than lactulose. It has been approved for use in the United States but not in Canada. It appears to be effective for the treatment of both acute episodes and maintenance therapy.

When HE becomes refractory, nutritional support with formulas rich in branched chain amino acids (BCAA) but low in aromatic amino acids has been suggested (on the basis of increased aromatic amino acids and decreased BCAA found in HE and their effect on neurotransmitter synthesis). Most studies with oral BCAA have shown clinical improvement of mild HE, with increased protein tolerance. In contrast, studies with IV BCAA have been inconclusive. Intravenous ornithine aspartate has been proven helpful, and the efficacy of the oral form is being tested in controlled trials.

Two of the five enzymes involved in the metabolism of ammonia to urea are zinc dependent. There is a significant incidence of zinc deficiency in cirrhosis, and some studies have shown improvement of HE with zinc replacement. Therefore, zinc deficiency should be sought and corrected if present.

Decreased dopaminergic neurotransmission activity has also been suggested to play a role in HE. However, controlled trials failed to demonstrate a beneficial effect of levodopa or bromocriptine treatment. Also, increased benzodiazepine receptors have been suggested to play a role in HE, but in controlled trials, benzodiazepine receptor



antagonists such as flumazenil showed only modest success. Unfortunately, both bromocriptine and flumazenil can potentially decrease the seizure threshold, and because of this and their questionable efficacy, they are typically no longer used.

Other therapies being explored include the use of probiotics to modify enteric bacteria population, and the use of sodium benzoate to help eliminate ammonia from the body.

HE as a complication of spontaneous or surgically created portosystemic anastomoses or transjugular intrahepatic shunts (TIPS) is usually managed successfully with conventional therapy. Refractory HE complicating TIPS can be helped by implanting a reducing stent to reduce blood flow through the TIPS. Orthotopic liver transplantation has the potential to entirely reverse HE. Thus, this procedure should be considered in all patients with HE whose liver disease makes them suitable for liver transplantation.

Possible HE – perform complete history and physical exam

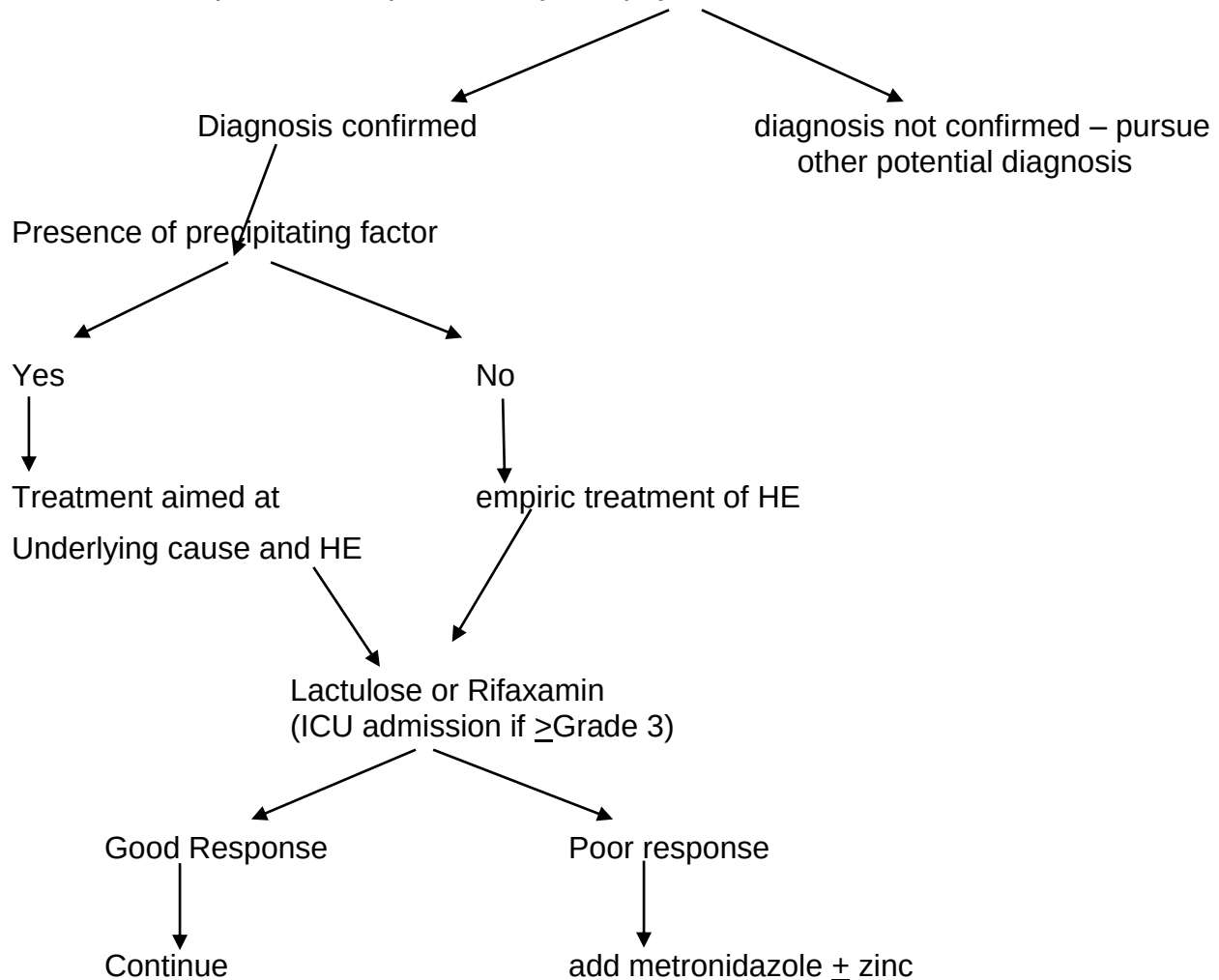


Figure 1. Suggested management of Hepatic Encephalopathy (HE)





Chapter 17: Liver Transplantation

E. L. Renner, L. B. Lilly and G. A. Levy



1. Introduction

Starzl performed the first human liver transplant in 1963 in a 3-year-old boy with biliary atresia. The first successful liver transplant was not performed until 1967, when a one and a half year old girl with hepatocellular carcinoma was transplanted. Unfortunately, she died of recurrent tumour at 17 months. One-year-survival in the early years was 25 to 35%, using methylprednisilone and azathioprine as immunosuppression. However, with the introduction of cyclosporine in the early 1980s, liver transplantation became a clinical reality, and now offers one and five year survival rates of 80-90% and 70-80%, respectively. With the dramatic improvement in results, liver transplantation became recognized as the definitive management for end stages of acute and chronic liver diseases.

The number of liver transplant centres in North America has proliferated to more than 100, and more than 6,000 liver transplants are performed yearly in the United States alone. In Canada, there are active centres in Halifax, NS; Montreal, PQ; Toronto and London, ON; Edmonton, AB and Vancouver, BC. Around 400 liver transplants are performed yearly in Canada. The rate-limiting step in the application of transplantation to persons with liver disease has become donor availability.

2. Assessment for Transplantation

A person should be considered for liver transplantation when three conditions are met: 1) the diagnosis of irreversible acute or chronic liver failure is made, from which the anticipated survival is clearly inferior to that of transplantation; 2) no alternative medical or surgical therapy exists (such as TIPS for recurrent portal hypertensive bleeding or refractory ascites); and 3) no absolute contraindications or significant comorbidities are present that might significantly raise the risk of transplantation and compromise long-term outcome. In most patients with chronic liver disease, it is decompensation, i.e. the development of complications of portal hypertension (ascites, encephalopathy or variceal hemorrhage) and/or of liver dysfunction (jaundice) that prompts referral for transplantation.

The most common indications for liver transplantation in adults and children are shown in Table 1. End-stage liver disease due to hepatitis C remains the most common indication in adults, comprising around 40% of patients on the waiting list. In most programs, patients with alcoholic liver disease make up a further 15-20%, with non-alcoholic steatohepatitis (NASH) and hepatitis B contributing each approximately 5-10%. Cholestatic liver diseases (Primary Biliary cirrhosis, Primary sclerosing cholangitis; 10-15%) and cirrhosis attributable to hemochromatosis, alpha-1-antitrypsin deficiency or autoimmune hepatitis, in addition to occasional patients with polycystic liver disease and other unusual indications, make up the remainder. Most programs perform fewer than 5% of their transplants for persons with fulminant liver failure.



Table 1. Liver transplantation: indications

- End-stage chronic liver disease
 - Cirrhosis related to viral hepatitis
 - HBV ± HDV (HBV-DNA below detection limit)
 - HCV
 - Alcoholic cirrhosis
 - Cirrhosis related to non-alcoholic steatohepatitis (NASH)
 - Cholestatic liver disease
 - Primary biliary cirrhosis (PBC)
 - Primary sclerosing cholangitis (PSC)
 - Biliary atresia
 - Cholestatic sarcoidosis
 - Graft-vs-host disease
 - Chronic ductopenic rejection
 - Secondary sclerosing cholangitis
 - Drug-induced cholestasis and secondary biliary cirrhosis
 - Neoplasms
 - Hepatocellular carcinoma (HCC) within Milan criteria (see text)
 - Only exceptionally other liver tumors

(These include hepatoblastoma, fibrolamellar cancer, hemangiendiothelioma, and neuroendocrine tumors. Hilar cholangiocarcinoma is generally regarded as a contraindication for liver transplantation outside, of clinical trials)
 - Fulminant hepatic failure

(drugs, viral hepatitis A–E, herpes, adenovirus, Wilson’s disease, Reye’s syndrome)
 - Metabolic liver disease

(alpha-1-antitrypsin deficiency, Wilson’s disease, hemochromatosis, glycogenosis type 4, tyrosinemia, Gaucher’s disease, cystic fibrosis)
 - Vascular disease
 - Budd-Chiari syndrome
 - veno-occlusive disease)
 - Congenital
 - Caroli’s disease, choledochal cyst, polycystic disease, hemangioma
-



The hepatitis C virus (HCV) universally (ie. 100%) infects the graft upon reperfusion of the liver at the time of transplantation. In 10-30% of patients, recurrent hepatitis C after liver transplantation runs an aggressive course, leading to graft cirrhosis, with associated morbidity and mortality in ≤ 5 years. Treatment-induced HCV clearance (sustained virological response) prior to liver transplantation prevents HCV recurrence post transplant. Unfortunately, the current standard therapy (pegylated interferon alpha and ribavirin) is suboptimally tolerated and effective in most decompensated HCV patients who are on the waiting list for transplantation. Nevertheless, antiviral therapy for HCV should be considered in selected cases.

Liver transplantation is not a therapy for alcohol dependence. Only selected patients with end-stage alcohol related liver disease, i.e. those who have proven to be compliant and able to stay away from alcohol, should be considered for transplantation. In most liver transplantation programs, a ≥ 6 months supervised abstinence period in the community, (i.e. with potential access to alcohol), is required prior to listing for liver transplantation. The liver function of a sizable proportion of patients with end-stage alcoholic liver disease will recover during this minimum 6-month time period, thereby eliminating the need for transplantation. In addition, most centers will require some form of addiction counseling, including documentation that the patient understands and accepts that alcohol was the problem leading to his/her liver disease, and a stable psychosocial situation with an intact support network.

In parallel with the obesity epidemic, patients with NASH cirrhosis (or those classified as cryptogenic cirrhosis with a history or the presence of risk factors for NASH, such as diabetes or obesity) are increasingly referred for transplant assessment. Many of these patients have an increased perioperative and long-term cardiovascular risk that needs to be thoroughly addressed prior to listing.

Transplantation for hepatitis B (HBV) has become standard. While initial efforts were plagued by high recurrence rates of HBV and suboptimal patient survival due to the lack of effective antiviral therapy, current preventive strategies using perioperative anti-HBs immunoglobulin (HBIG) in combination with long-term nucleoside or nucleotide analogues such as lamivudine have almost eliminated HBV disease recurrence. Thus, patient and graft survival rates are today similar to those for other transplant indications. Most programs still require that patients have low levels of viral replication (either occurring spontaneously, or induced by antiviral therapy) prior to transplantation, in order to reduce the risk of recurrence, and thereby to improve outcome.

Hepatocellular carcinoma (HCC), particularly in patients with viral hepatitis, is an increasingly common indication for liver transplantation. In Toronto for example, 30-40% of patients transplanted in recent years had hepatomas. The best results (around 80% disease-free 5-year survival) have been described in patients fulfilling the so-called Milan criteria, i.e. a single HCC nodule ≤ 5 cm in diameter, or maximally 3 HCC nodules each ≤ 3 cm in diameter, in the absence of evidence of vascular invasion and extrahepatic spread. Recently, several programs have proposed to expand these Milan criteria by demonstrating reasonable outcomes with so called “extended Milan criteria,” allowing for the transplantation of larger and/or more multifocal HCCs. Note that none of these extended criteria are generally accepted.



Physicians should be aware of their transplant centre's policy when considering patients for referral. The exclusion of patients with contraindications to liver transplantation (Table 2) allows the best use of scarce donor resources, while maximizing patient benefit. Given the scarcity of donor organs, selection of the patient and the timing of the transplantation require individual assessment. The patient with decompensated cirrhosis should not be moribund, since this increases the risk of transplantation to an unacceptable degree. On the other hand of course, the liver patient should not be in such a stable condition that she/he might be able to live an independent life in the absence of liver transplantation.

In general, liver transplantation carries a survival benefit only if the MELD score (Table 3) is ≥ 15 points. To allow for the time required for evaluation and decision making, the treating physician should consider patient referral for liver transplantation when a patient with cirrhosis (and without obvious contraindications, Table 2) decompensates. Decompensation is considered to have applied when the patient develops ascites, portal hypertensive bleed, encephalopathy or jaundice and has a MELD score above 11 points.

Table 2. Liver transplantation: contraindications

- Absolute
 - Sepsis outside the biliary tree
 - Extrahepatic malignancy
 - Advanced cardiopulmonary disease
 - Severe pulmonary hypertension (Pulmonary Artery pressure >40 -60 mm of Hg)
 - HIV/AIDS
 - Active alcohol and/or substance abuse
 - Inability to accept the procedure, understand its nature, or cooperate in the
 - Medical care required following liver transplantation (including noncompliance and lack of psychosocial support)
 - Relative
 - Chronic renal insufficiency (may require liver/kidney transplant)
 - Advanced Age
 - Vascular access problems (portal and superior mesenteric vein thrombosis, or prior hepatic shunt surgery)
 - Other significant extrahepatic disease(s)
 - Inadequate psychosocial support
-



Table 3. Three month mortality for potential liver transplant recipients based on Model for End-Stage Liver Disease (MELD) and Child-Turcotte-Pugh (CTP) score

	MELD					CTP		
	<9	10-19	20-29	30-39	>40	<7-9	10-12	13-15
No.	124	1800	1098	295	120	318	2357	588
%Mortality	1.9	6.0	19.6	52.6	71.3	4.3	11.2	40.1

MELD Score = $9.57 \times \log_e \text{ creatinine mg/dL} + 3.78 \times \log_e \text{ bilirubin mg/dL} + 11.20 \times \log \text{ INR} + 6.53$

Table adapted from Wiesner et al. Gastroenterology 2003; 124:91-96

3. Preoperative Workup

The principles behind the liver transplant workup are 1) to definitively establish the etiology of the liver disease; 2) to ensure that the patient's liver disease is a sufficient indication for the procedure; and 3) to identify contraindications, i.e. to ensure that liver transplantation will translate into a survival benefit and an acceptable long-term outcome for the patient. Given the scarcity of donor organs, a 50% 5-year survival is generally accepted as the threshold below which liver transplantation is regarded as futile. Assessment by a multidisciplinary team (which includes medical, surgical, anaesthetic, radiology, social and psychiatric specialists) is performed in all patients being considered for a liver transplantation, in order to ensure the success of the transplantation process.

4. Timing of Transplantation

Liver transplantation for end-stage chronic liver disease carries a survival benefit only if the recipient's MELD score (Table 3) is ≥ 15 points. In some liver transplantation centres, the MELD score may be adjusted upwards with MELD exception points (a modified MELD score), given for complications of end-stage liver disease that carry either a mortality or a drop out rate from the waiting list that is not adequately reflected by the non-modified MELD score. These MELD exception points might include presence of HCC or hepatopulmonary syndrome. Also, exceptional individual patients with MELD scores below 15 may warrant liver transplantation, for example the patient with Primary Sclerosing Cholangitis (PSC) and frequently recurring severe cholangitis episodes. Due to the scarcity of donor organs in most centers, poor quality of life *per se*, even if clearly related to the patient's liver disease, is not a sufficient indication for transplantation.

While the survival benefit of liver transplantation increases with increasing severity of liver disease (i.e. the MELD score), transplant recipients with very high MELD scores (30-40) utilize significantly higher health care resources to achieve similar outcomes than less sick patients. Thus, ideally liver transplantation would be performed in patients with a MELD score above 15 who are still in a reasonably good general condition (e.g. muscle mass, mobility).

Catastrophic complications and the need for life support may impair post-transplant outcomes to such an extent that liver transplantation has to be regarded as



futile and should no longer be performed. Note that there are no uniformly accepted objective criteria to indicate this is the case; the decision to take a potential liver transplant recipient temporarily or permanently off the waiting list for “being too sick” therefore requires a team decision after thorough multidisciplinary assessment.

5. Deceased Donor Liver Allocation and Model for End-Stage Liver Disease (MELD)

The primary criterion for organ allocation in liver transplantation is urgency. In most programs, ABO blood group identity (or at least compatibility) between the donor and recipient is a prerequisite, because of otherwise inferior outcomes. Urgency means that the potential recipient with the highest mortality on the waiting list should first receive a liver for transplantation. In many programs/jurisdictions in Canada, livers are currently still allocated to potential liver recipients based on medical status (and within a given status, waiting time). Medical status is defined as follows: status 1, patient at home waiting for liver transplantation; status 2, patient hospitalized; status 3, patient in a step-down unit with renal failure and/or encephalopathy; status 4, patient in the intensive care unit (ICU), intubated and ventilated. Patients with fulminant liver failure receive a status 3F or 4F, and have a higher priority than other status 3 and 4 patients, respectively. Patients with an HCC are listed as a status 1T, and have a higher priority than other status 1 patients. This system is similar to the UNOS “status system” that was used in the United States up until 2002. However, the “status system,” i.e. the location of a listed patient, does not necessarily correlate with medical urgency, i.e. with the patient’s mortality on the waiting list. Thus, about 2/3 of all patients are listed as status 1, (i.e. at home), but their disease severity, (i.e. their mortality on the waiting list varies widely). In addition, waiting time used to break status ties, does not correlate with medical urgency. To overcome this shortcoming and to base liver allocation on objective parameters that better reflect waiting list mortality, the Model for End-stage Liver Disease (MELD) was developed.

The MELD score incorporates the patient’s INR, bilirubin and serum creatinine. Scores are rounded to the nearest integer, and yield values from 6 to 40. MELD was originally developed as a predictor of survival in patients with end-stage liver disease undergoing insertion of a transjugular intrahepatic portosystemic stent shunt (TIPS). MELD is the most accurate predictor of short-term (3 months) survival in patients with end-stage liver disease. Its predictive accuracy exceeds that of the older Child-Pugh score. The main features that distinguish MELD from the Child-Turcotte-Pugh (CTP) score (another system originally devised to predict survival in cirrhotic patients undergoing surgical shunts and subsequently used to predict survival in patients with advanced liver disease), is the absence of the two subjective clinical parameters, ascites and encephalopathy, and the incorporation and acknowledgement of renal dysfunction as a powerful predictor of survival in these patients.

MELD is based on three biochemical variables that are readily available, reproducible and objective. Table 3 demonstrates the MELD formula, and shows three-month mortality figures for potential transplant recipients based on MELD and Child-Turcotte-Pugh scores. MELD has repeatedly and independently been validated in large



patient populations. Thus, the MELD score is the most accurate and best validated predictor of transplant urgency in potential liver transplant recipients available today.

In the USA, the MELD score has been used for liver allocation since 2002. More recently, some Canadian centers/jurisdictions have incorporated MELD, at least in some form, in their liver allocation algorithm.

6. Live Donor Liver Transplantation

Adult live donor liver transplantation (LDLT) evolved in the late 1990s to address the issue of relatively fixed liver supply (i.e. static organ donation rates), and the ever-increasing demand with growing liver transplant waiting lists and waiting list mortality. At the Toronto General Hospital, around 200 patients are currently wait-listed for a liver transplant, and waiting times for medical status 1 patients may easily reach several years. This waiting time leads to a waiting list mortality of around 20%.

In adults, LDLT consists of a right hepatectomy in a healthy person who has volunteered to donate part of their liver, and the subsequent transplantation of the donated right liver lobe into the recipient. The procedure can be safely performed only if certain anatomical and size requirements are met. To assure this, the liver donor undergoes an in-depth evaluation. This includes a thorough psychological evaluation to assure that the decision to donate is uncoerced, and that benevolence is its sole motivation.

The remnant left liver lobe in the donor and the transplanted right liver lobe in the recipient both regenerate within a couple of months, to a close-to-normal liver volume providing a normal liver function. LDLT is planned surgery, and allows for shortening of recipient waiting times. This is of particular benefit in situations where waiting time is critical for prognosis, i.e. the risk of drop out from the waiting list due to progression of disease, such as in HCC.

There are risks to the live donor, including a risk of death of up to 0.5%, as well as substantial morbidity. A highly publicized death of a donor in January 2002 subsequently tempered enthusiasm for live liver donation, and led to a decrease in LDLT activity in the USA. Presently, LDLT comprises less than 5% of total adult liver transplant activity in that country. The ethics, as well as the appropriate application of LDLT, continue to evolve in the USA and Canada. At the Toronto General Hospital, over 300 adult living donor liver transplants have been performed since April 2000, with no donor death and with both recipient and graft survivals being similar to deceased donor liver transplantation. Given the lengthy waiting times and substantial waiting list mortality, most recipients are being offered LDLT in situations where a suitable living donor comes forward. Presently, only recipients who are candidates for deceased donor liver transplantation are being considered for LDLT. However, this practice may change as the ethics in this field evolve.

It is highly debated whether recipients with indications and/or a perioperative risks (co-morbidities) that would not normally be accepted for deceased donor liver transplantation should be accepted for LDLT when a suitable donor volunteers. This applies in particular to recipients with HCC and other tumors that fall outside current practice guidelines for liver transplantation, but also includes healthy elderly potential recipients. It is the policy in most liver transplantation programs that it is not justified to



put a healthy donor at risk of morbidity and mortality when the recipient outcome is likely below the usually accepted futility threshold of a 50% 5-year survival.

7. Donation after Cardiac Death

The use of organs from donors who have died from a cardiac death, (i.e. had an irreversible cessation of circulatory function due to cardiac arrest), was the norm in the beginning of solid organ transplantation until the brain-death criteria were accepted some 40 years ago. In recent years, organ donation after cardiac death has been rediscovered, and is increasingly used in an attempt to address organ shortages. Donation after cardiac death occurs after the decision has been made to withdraw life support for medical reasons, in a hopelessly sick patient who does not fulfill brain-death criteria.

Donation after cardiac death can proceed in either a so-called controlled or uncontrolled fashion. In the controlled situation, life support is withdrawn in the operating room (OR) or intensive care unit (ICU), and organs are obtained after the patient has been pronounced dead, i.e. after a documented cardiac arrest of at least 5 min duration. In the uncontrolled situation, resuscitation measures in an urgent event are deemed futile and stopped. Many programs will accept donation after a controlled cardiac death, but, for ethical and logistic reasons, not in the uncontrolled situation. Donation after cardiac death invariably implies an agonal period of warm hypoxia/ischemia before the organs can be cooled by perfusion with preservation solution. While the hepatic parenchyma tolerates hypoxia/ischemia relatively well, the biliary tree is exclusively arterially perfused and is exquisitely sensitive to hypoxia/ischemia. Liver grafts obtained after cardiac death are therefore prone to develop ischemic type biliary strictures, with their associated morbidity and mortality. Nevertheless, transplantation of livers obtained after cardiac death can be life-saving, and several centers are currently working on improving its outcome.

8. Operative Procedure

Technical details of the procedure are beyond the scope of this discussion. However, the following salient points are worth mentioning: during the procedure the liver is mobilized and both the inflow to the liver and the inferior vena caval return to the heart are interrupted. This may cause hemodynamic instability, which can usually be managed without the use of a veno-veno bypass (in which the inferior vena cava [IVC] and portal blood are diverted through an extracorporeal bypass circuit to the axillary vein, and which was regularly used in the beginning of liver transplantation). The patient's original liver is subsequently removed, and the new liver graft is sewn in place. This involves anastomosing the IVC, the hepatic artery, the portal vein, and a duct-to-duct or biliary-enteric Roux-en-Y bile duct reconstruction. Although the liver is flushed of the high potassium preservation solution prior to reperfusion, significant cardiac abnormalities can occur upon removing the clamps and reperfusion of the liver. These intraoperative events demand a thorough preoperative assessment of cardiac status.



9. Postoperative Management

Issues that must be addressed in the postoperative period include: management of fluid, electrolytes and renal function; respiratory function; monitoring of neurologic status; immunosuppression; and graft function. While most patients are extubated within 24 hours of surgery, some can be extubated immediately after surgery and go directly to an intermediate care unit. In some recipients, ventilatory support may be needed for an extended period, particularly when the recipient is severely deconditioned, there is delayed graft function, presence of large pleural effusions, pulmonary infiltrates and/or diaphragmatic dysfunction or paralysis. Patients who were deeply encephalopathic prior to transplantation, in particular those with fulminant hepatic failure, may require an extended period of ventilatory support and ICU care.

Bleeding and bile leaks can occur early after surgery, and may require surgical re-intervention. Close clinical monitoring of the abdomen, of hemodynamics, and of blood hemoglobin concentration are mandatory in the early postoperative period.

Most patients are in a state of fluid overload after transplantation. These patients usually have a low serum albumin concentration, and respond well to colloid supplementation and diuretics. Renal insufficiency, occasionally requiring dialysis, is not uncommon postoperatively, particularly as patients deteriorate with lengthening waiting lists before they can undergo surgery. Renal failure may be due to a combination of factors, including preexisting intrinsic renal disease, hepatorenal syndrome, intraoperative blood loss and hypotension leading to tubular necrosis, drug induced nephrotoxicity (especially cyclosporine or tacrolimus), poor liver function, and sepsis.

Graft function resumes in the vast majority of cases immediately following transplantation. Abnormalities of coagulation are sensitive markers of hepatic dysfunction, and in most patients coagulation parameters should return to close to normal levels within 48 hours. Delayed graft function and primary non-function are rare events, and may present with coagulopathy, hepatic encephalopathy, hypoglycaemia, hyperkalemia or renal failure. The failure of coagulation parameters to normalize, especially if accompanied by encephalopathy and a hepatorenal pattern of renal dysfunction, is therefore an ominous sign of graft failure, and suggests the unfortunate need for retransplantation.

The causes of significant hepatic dysfunction within the first 48 hours include hepatic artery thrombosis, primary nonfunction, and very rarely accelerated cellular rejection. These can be difficult to differentiate on clinical grounds, and radiological investigations such as abdominal ultrasound with Doppler or angiography are required for diagnosis. Immediately following transplantation, narcotics and sedatives are kept to a minimum. Confusion and seizures may occur, and are usually related to metabolic disturbances (e.g., low serum magnesium levels), but are a recognized complication of both cyclosporine and tacrolimus.

10. Immunosuppression

There are many immunosuppressive agents available to the transplant physician. It is no longer a question of how to achieve adequate immunosuppression in order to avoid rejection. Rather, the issue is how to tailor immunosuppression with the different agents available (and their differing side effect profiles) to the specific needs of the



individual patient. In liver transplantation where acute rejection can almost always be managed with intravenous (IV) glucocorticoids (“steroids”), avoiding overimmunosuppression is clearly more important for good long-term outcome than avoiding rejection at any cost. While there is a wealth of data on the efficacy and safety of individual agents, the best combination of agents for certain populations, such as HCV-infected or insulin-resistant/diabetic recipients, remains to be defined.

- *Corticosteroids.* In the vast majority of programs, all patients receive methylprednisolone perioperatively, typically starting at doses of 200-1000 mg preoperatively or in the operating room (anhepatic phase). Subsequently, i.v methylprednisolone is tapered, typically within 1-2 weeks, to an oral prednisone dose of 20 mg/day. In most programs, oral steroids are subsequently tapered and discontinued within three to six months. Major side effects include impaired wound healing, psychosis with the high perioperative doses, an increased incidence of infections (bacterial and fungal), insulin resistance/diabetes mellitus, weight gain, dyslipidemia, and osteoporosis. Steroid-free protocols typically replace steroids with induction using an IL-2 receptor antagonist (please see below) are feasible and safe. However, particularly in HCV patients, it remains to be shown if the steroid-free protocols improve outcome and are beneficial.
- *Cyclosporine A.* The introduction of cyclosporine A (currently available in the microemulsified form as Neoral®) is one of the most important factors in improving results of liver transplantation. With its introduction, the one year graft survival increased abruptly from 30% to > 70%. Cyclosporine A binds to a specific cell protein, cyclophilin, and through a series of intracellular events prevents activation of T-cells and production of interleukin-2 (IL-2). The drug is given preferentially by the oral route; intravenous infusion is rarely required. In the early postoperative period, the dosage of cyclosporine A is adjusted to maintain a trough cyclosporine A level of 200-250 ng/mL, or a two-hour post ingestion level (C₂) of 800-1,200 ng/mL. Daily monitoring of cyclosporine A levels in the immediate postoperative period is mandatory, as the drug has a narrow therapeutic index (efficacy vs. toxicity).

Cyclosporine A is metabolized in the liver by the P450 system (CYP3A4). Drugs that are metabolized or interfere with this hepatic drug metabolizing enzyme system will therefore affect cyclosporine A levels. For example, rifampicine and anticonvulsants such as carbamazepine induce CYP3A4 and thereby decrease cyclosporin A blood levels. Inhibitors of the P450 system, such as macrolide antibiotics (e.g. clarithromycine) and antifungals such as fluconazole, inhibit cyclosporine A metabolism, and lead to increased blood levels. These and many other drug interactions have to be kept in mind when starting transplant recipients on cyclosporine A on additional drugs.

Common side effects of cyclosporine A include renal dysfunction, tremor, headaches, arterial hypertension, dyslipidemia, weight gain and insulin resistance/diabetes mellitus. Hirsutism and gingival hyperplasia are less frequent.



- *Tacrolimus (FK506; Prograf®)*. Tacrolimus is a newer calcineurin inhibitor, and binds to FK binding protein before subsequently inhibiting T-cell activation by blocking IL-2 production, in a similar fashion to cyclosporine A. Monitoring is through trough levels, with a target of approximately 8-10 ng/mL early following transplantation. In the doses clinically used, tacrolimus seems to be at least equally, and maybe slightly more immunosuppressive than cyclosporine A. While most of the adverse effects of qualitatively similar with the use of immunosuppressants, insulin resistance/diabetes mellitus is more frequent with tacrolimus, and hirsutism as well as gingival hyperplasia is more frequent with cyclosporine A. Tacrolimus may play a role in the management of chronic rejection. Tacrolimus is metabolized in the liver similarly to cyclosporin A, and similar considerations regarding drug interactions apply.
- *Azathioprine (Imuran®)*. Azathioprine is a purine synthesis inhibitor, and as such inhibits the proliferation of cells, especially those rapidly dividing cells such as leucocytes (including T and B cells). Azathioprine is an old immunosuppressive agent that was routinely used in the early days of liver transplantation. Its side effects include bone marrow suppression. It has largely been replaced by the more potent mycophenolate preparations (please see below), and is only rarely used in transplantation today.
- *Mycophenolate Mofetil (MMF / Cellcept®)*. Mycophenolate, the active compound in MMF, is a potent reversible non-competitive inhibitor of inosine monophosphate dehydrogenase. It acts as a selective inhibitor of T- and B-cell proliferation by blocking the production of guanosine nucleotides and interfering with the glycosylation of adhesion molecules. The main side effect of MMF is bone marrow suppression. Importantly, it has no nephrotoxicity, and is an important agent in triple drug regimens, allowing a decrease in the dosage and therefore the toxicity of calcineurin inhibitors. Many patients experience significant gastrointestinal side effects from MMF, and dose modification is commonly required. Drug levels of MMF are not currently monitored in most transplant centres.
- *Mycophenolate sodium (MPA / Myfortic®)*. MPA is slow delayed release enteric coated galenic form of mycophenolate. Its immunosuppressive mechanisms of action, and its efficacy and side effect profile are identical to MMF. Whether gastrointestinal tolerability is improved due to the enteric coating remains debated.
- *Anti-Lymphocyte Products*. Anti-lymphocyte products can be monoclonal (OKT3) or polyclonal (ALG, ATG, thymoglobulin). In either case, the aim of therapy is to prevent or to treat rejection through lymphocyte, especially T-cell depletion. The use of these products has been associated with higher rates of viral infections, in particular cytomegalovirus (CMV), as well as an increased risk of (typically EBV-associated) lymphoproliferative disorders. OKT3 has been associated with side



effects secondary to the release of cytokines (such as tumor necrosis factor and IL-1) that can range from mild flu-like symptoms, to life-threatening pulmonary edema and circulatory collapse. With other T-cell depleting agents having become available, OKT3 is therefore no longer used in most centers. In liver transplantation the use of these drugs is generally limited to induction immunosuppression in the presence of renal failure or significant neurologic dysfunction (to spare the use of calcineurin inhibitors), and in the treatment of the very rare steroid-resistant rejection.

- *Rapamycin (Rapamune®)*. This secondary macrolide metabolite has a distinctly different mechanism of action than the calcineurin inhibitors. It binds to the FK binding protein, and inhibits the growth factor-dependent proliferation of hematopoietic and non-hematopoietic cells at the G1 to S phase, through the calcium-independent signals, called the mTOR pathway. Rapamycin effectively prevents allograft rejection (as well as reversing ongoing rejection), and is widely used in human renal transplantation. Rapamycin has antiproliferative effects *in vitro* and has therefore been proposed to be useful in liver transplantation for HCC, potentially reducing tumor recurrence rates. Clinical trials in this regard are ongoing. Rapamycin is not currently licensed for liver transplantation. In fact in the initial clinical trials, there was an increased hepatic artery thrombosis rate observed early post liver transplant. Side effects include bone marrow depression (anemia), impaired wound healing, and rarely there may be interstitial pneumonitis or proteinuria/nephrotic syndrome.
- *RAD (Everolimus®)*. Similar to rapamycin, this compound is currently undergoing clinical trials in human liver transplantation. Recent studies have established its benefit in heart transplantation, where it has been shown to reduce chronic allograft vasculopathy.
- *IL-2 Receptor antagonists*. Basiliximab (Simulect®) and Daclizumab (Zenapax®) are IL-2 receptor specific monoclonal antibodies which inhibit proliferation of T-cells by binding to the alpha chain of the IL-2 receptor complex on activated T-cells. The IL-2 receptor antagonists have been shown to reduce the incidence of acute allograft rejection in kidney transplantation patients, and improve the one-year graft and patient survival. While the role of these agents in liver transplantation remains less well defined, they are used particularly in calcineurin- or steroid-sparing protocols.
- *Campath-1H*. Campath-1H is a humanized monoclonal antibody directed at CD52, a protein which is on lymphocytes and other cells of the immune system. It has been tested extensively in lymphoid malignancies, autoimmune diseases including rheumatoid arthritis, and multiple sclerosis. Its role in solid organ transplantation, in particular in liver transplantation, is not well defined. Immune cell depletion using Campath-1H allows the use of lower doses of maintenance



immunosuppressive drugs, such as calcineurin inhibitors. This feature may be important in tolerance induction.

- *Other immunosuppressive agents.* There are several other immunosuppressive agents currently in early clinical development. These include belatacept, a chimeric antibody designed to inhibit the co-stimulatory signal during T cell activation, and sotrastaurin (AEB071), a protein kinase C inhibitor that prevents T lymphocyte activation.

11. Postoperative Complications

- Primary Non-function complications common to any surgical procedure can occur with liver transplantation. Several complications are peculiar to liver transplantation. The most concerning post-operative complication is *primary non-function (PNF)* of the new graft. Incidence rates of PNF range from less than 1% to over 5%. PNF becomes evident by persisting post-transplant symptoms and signs of liver failure, i.e. coagulation parameters that worsen and cannot be corrected, increasing acidosis, deterioration in the patient's mental status (hepatic encephalopathy), and hepatorenal type renal failure. The etiology of PNF is unclear, and the treatment is urgent retransplantation.
- *Primary graft dysfunction* is a postoperative liver dysfunction of a lesser degree that may recover with time. The value of medical measures such as prostaglandin E-1 and/or N-acetyl cysteine in this situation is controversial, and none has been unequivocally proven to change outcome.
- *Vascular thromboses* that occur in the early postoperative period are generally technical in nature. Although thrombectomy of both portal vein and hepatic artery has been reported with some success, urgent retransplantation is usually required should these vessels thrombose early postoperatively.
- The *bile duct* has been termed the Achilles heel of liver transplantation. Bile duct problems occur in 10-20% liver transplantation cases. Early biliary leaks are secondary to ischemia, sepsis, or rarely to severe rejection. The bile duct can be irreversibly damaged in hepatic artery thrombosis immediately post transplant (ischemic type biliary injury).
- *Acute allograft rejection* (also termed acute cellular rejection [ACR]) occurs in about 20% of liver transplant recipients, usually in the first three months after transplantation. ACR is suspected in patients with rising liver enzymes. The pattern of enzyme elevation is non-specific and can be either hepatocellular (high serum concentrations of AST and ALT) or cholestatic (high bilirubin and alkaline phosphatase). Low grade fever, malaise and right upper quadrant discomfort can be present, but these are late findings and should not be required for the diagnosis of ACR.
- ACR is diagnosed by liver biopsy. Histologic findings of ACR include a mixed cellular periportal inflammation with mononuclear cells and eosinophils, bile



duct injury, and endothelialitis, i.e. (sub)endothelial inflammatory changes in small portal and/or central veins. ACR usually responds to high dose steroid therapy (500 mg methylprednisolone i.v. daily for 3 consecutive days), followed by a gradual oral prednisone taper.

- The rare patient whose rejection fails to respond to IV steroid bolus therapy is usually rescued with a seven to 14 day course of an antithymocyte globulin preparation. Another approach is an intensification of the maintenance immunosuppression by switching to or increasing the dose of tacrolimus and/or adding a mycophenolate preparation.
- Late ACR episodes, i.e rejection episodes occurring after 3 months post transplant, are most frequently due to under-immunosuppression, be it secondary to malcompliance, therapeutic misadventures (drug interactions), or drug malabsorption (nausea/vomiting, diarrhea).
- Chronic Ductopenic Rejection: Failure of ACR to respond to immunosuppressive therapy, as well as other ill defined mechanisms, may result in *chronic ductopenic rejection* (CDR). CDR leads to the disappearance of small interlobular bile ducts, and eventually to biliary cirrhosis. CDR results in graft loss, i.e. the need for re-transplantation or death, in 2-5% of all liver transplanted recipients.
- *Infectious complications* are the major cause of death early following liver transplantation. The three main determinants of the risk of infection in transplant recipients are: those related to surgical problems e.g. bile leaks, the net state of immunosuppression and environmental exposure. Immunosuppressed patients are at risk for bacterial, viral and fungal infections. Bacterial infections with non-opportunistic organisms are usually seen in the early postoperative period, while opportunistic bacterial infections are seen one to two months or more after transplantation. Viral infections are seen frequently in immunosuppressed patients and usually occur at six weeks or later. The most important pathogen affecting transplant recipients is Cytomegalovirus (CMV). CMV causes both direct effects including tissue injury and clinical disease as well as a variety of indirect effects. In the absence of CMV prophylaxis, seronegative recipients of organs from seropositive donors have a greater than 50% risk of developing symptomatic disease. The diagnosis of CMV disease is accomplished by demonstrating viremia or tissue invasion. Patients who are mismatched, or those who receive anti-lymphocyte products, are therefore generally treated pre-emptively with ganciclovir or valganciclovir, often for three months following engraftment.

Other viral infections seen in the transplanted recipient include herpes simplex, Epstein-Barr virus, varicella zoster and adenovirus. Fungal infections are diagnosed in up to 20% of liver transplant patients and carry a significant mortality rate. Infections in general are usually proportionate to the degree of immunosuppression.



- *Malignant tumors* of all kinds, in particular EBV-associated post-transplant lymphoproliferative disorder (PTLD) and non-melanoma skin cancers, are well known consequences of immunosuppression, and their risk of development is proportionate to the level and duration of immunosuppression. Malignant tumors are a major cause of mortality late after liver transplantation.
- *Cardiovascular events*: Steroids and calcineurin inhibitors increase the prevalence of cardiovascular risk factors such as obesity, insulin resistance/diabetes mellitus, arterial hypertension and dyslipidemia. One or a combination of these cardiovascular risks are present in a majority of liver transplant recipients who survive for more than one year post transplant. Not too surprisingly, therefore, the incidence of non-fatal and fatal *cardiovascular events* is increased around 3-fold in liver transplant recipients, as compared to a comparable normal population. In fact, cardiovascular conditions and malignancy are the most frequent causes of death occurring late after liver transplantation.

12. Results of Liver Transplantation

A one-year survival of >85% after liver transplantation is now typical. Most mortality occurs within the first 90 days, and is often related to the degree of pre-operative deconditioning and malnutrition of the recipient. After one year, few patients or grafts are lost and the 5 year survival rate for many indications exceeds 80% (see Table 4). Furthermore, a majority of patient rates their quality of life as normal or close to normal ≥ 6 months after surgery, and 60% of patients return to gainful employment. This demonstrates that liver transplantation is not only of benefit to the individual patient, but to society as a whole.

Although there are few reports of cost effectiveness, investigators from Pittsburgh and elsewhere have demonstrated that liver transplantation is less expensive than the costs of caring for similar patients treated for complications of cirrhosis. Indeed, the cost of a life year gained from liver transplantation is well below the US\$ 50,000 generally accepted as the cost-effectiveness threshold. Patients with diseases that do not or only rarely recur after liver transplantation such as cholestatic liver diseases, have an excellent long-term prognosis (see Table 4).

In contrast, patients transplanted for hepatitis C have a poorer long-term outlook due to the almost universal recurrence of HCV infection in their graft. At least 10-30% of these patients progress within five years to cirrhosis, with its associated morbidity and mortality. Donor age, pre-transplant HCV RNA titers, and high dose steroid therapy for acute cellular rejection are among the most important determinants of the course of post transplant HCV recurrence and of patient survival. Having said that, recent data from Toronto and other centers show that overall up to 50% of these patients (40% genotype 1, 70-80% genotype 2/3) can be successfully treated with a pegylated interferon/ribavirin combination; HCV clearance halts disease progression and normalizes survival. Retransplantation of patients losing their graft due to HCV recurrence within 2-5 years is associated with poor patient and graft survival, and is not offered in most centers.



Table 4. Results of liver transplantation

Result	Cause of liver failure	Comments
➤ Excellent	○ Cholestatic liver disease ○ Autoimmune hepatitis ○ Alcoholic cirrhosis (with appropriate patient selection) ○ Metabolic disease ○ Congenital disease ○ HBV (with HBIg and antiviral prophylaxis)	- Low recurrence rates
➤ Good	○ HCV ○ HCC (small tumors)	- Moderate recurrence rates
➤ Fair	○ Fulminant hepatic failure Retransplantation ○ Biliary atresia	- Results depend strongly on pretransplant status of patient
➤ Poor	○ Large tumors ○ Cholangiocarcinoma	- High recurrence rates

13. Recent Advances and Future Directions

The availability of new immunosuppressive agents targeting different sites in the immunologic cascade offers the potential to individualize therapy for transplant patients. For example, starting patients with renal dysfunction or insulin resistance/the metabolic syndrome on a CNI-free immunosuppressive regimen may preserve their Glomerular Filtration Rate (GFR) or prevent the development of diabetes, respectively. Similarly, use of sirolimus and avoidance of CNIs in patients transplanted for hepatocellular carcinoma may improve long-term outcomes. Isolated hepatocyte or stem cell transplantation may offer treatment of metabolic and maybe other liver diseases. The former has already been successful in the laboratory setting.

While clinical trials have so far demonstrated little efficacy of available artificial liver support systems, they may eventually become successful in bridging patients to transplantation, or even allow for spontaneous recovery through normal hepatic regeneration, thereby reducing the need for transplantation. The elusive goal of tolerance has been produced in animal models, and if tolerance were induced in humans, this would obviate the need for immunosuppression and its associated complications.

As a step further forward, transcription profiling has been reported to allow identification of liver transplant recipients who have spontaneously developed operational tolerance. Xenotransplantation has moved to the farther horizon, but the use of transgenic animals may eventually offer a solution to the shortage of donor organs and permit a wider application of liver transplantation to liver disease.





Chapter 18: The Biliary System

E. A. Shaffer and J. Romagnuolo



1. Cholelithiasis

Gallstones (cholelithiasis; calculous disease) are the most common cause of biliary tract disease in adults, afflicting 20-30 million persons in North America. Approximately one-fifth of men and one-third of women will eventually develop cholelithiasis. In Canada, calculous disease of the biliary tract is also a major health hazard, accounting for about 130,000 admissions to hospital and 80,000 cholecystectomies annually. Cholecystectomy is the second most common operation in Canada and the United States, where it is performed six to seven times as often as in the United Kingdom or France. Although the frequency of gallstone disease does vary between countries and regions, it is high in both Western Europe and North America (Table 1). Laparoscopic cholecystectomy has further increased the use of surgery. Such variance suggests overuse of our health-care system, particularly as few (20%) individuals with cholelithiasis ever become symptomatic.

1.1. Classification of Gallbladder and Bile Duct Stones

Two major types of gallstones exist (Table 2).

1. *Cholesterol stones* are hard, crystalline stones whose composition is more than 50% cholesterol, plus varying amounts of protein and calcium salts. They predominate (> 85%) in developed countries.

2. *Pigment stones* are characterized by and acquire their colour from the insoluble pigment, calcium bilirubinate.

Table 1. Frequency of gallstone disease in different countries

Very Common (30-70%)	Common (10-30%)	Intermediate (<10%)	Rare (<0%)
○ American Indians	○ United States (whites)	○ United States (blacks)	○ East Africa
○ Sweden	○ Canada (whites)	○ Japan	○ Canada (Inuit)
○ Chile	○ Russia	○ Southeast Asia	○ Indonesia
○ Czechoslovakia	○ United Kingdom	○ Northern India	○ West Africa
○ United States (Hispanics)	○ Australia	○ Greece	○ Southern Africa
	○ Italy	○ Portugal	
	○ Germany		



Table 2. Classification of Gallstones

Characteristic	Cholesterol	Pigment	
		Black	Brown
○ Composition		- Pigment polymer - Calcium salts (phosphates, carbonates)	- Calcium bilirubinate - Calcium soaps (palmitate, stearate)
○ Consistency	- Crystalline	- Hard	- Soft, greasy
○ Location	- Gallbladder (+/- common duct)	- Gallbladder - Bile Ducts	- Common Duct
○ Radiodensity	- Lucent (85%)	- Opaque (50%)	- Lucent (100%)

1.2. Basis for Gallstone Formation

1.2.1. Cholesterol Stones

Cholesterol gallstones form in three stages (Figure 1).

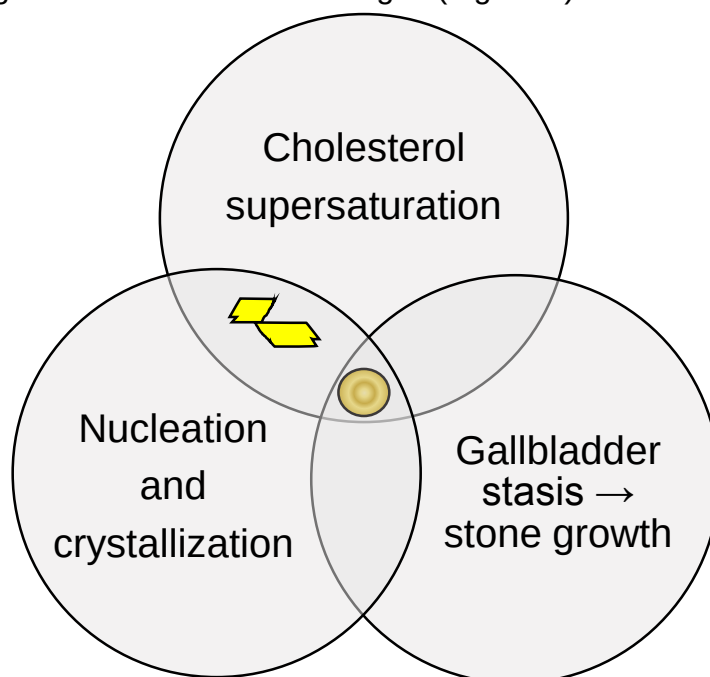


Figure 1. Three key stages in cholesterol gallstone formation, expressed as a Venn diagram: 1. Excess cholesterol secretion causes bile to become supersaturated; 2. Pronucleating proteins (especially mucins) then precipitate cholesterol microcrystals (shown as two notched rhomboids); and finally 3. Impaired gallbladder emptying in the final stage results in stasis that allows the time for these microcrystals to be entrapped in a mucin gel, which aggregates and attracts other insoluble components of bile (such



as bile pigment and calcium), and so becomes biliary sludge and evolves into overt gallstones.

Cholesterol gallstones result primarily from an imbalance of the constituents of bile, aided by bile stasis. Bile is composed of three major organic molecules that are lipids: bile acids, phospholipids (phosphatidylcholine or lecithin) and cholesterol, in addition to its chief constituents: water and electrolytes. ATP-dependent transport proteins (ABC transporters), located on the canalicular membranes of the liver, actively secrete these lipids. In the first stage of cholesterol gallstone formation, the liver secretes excess cholesterol, forming supersaturated bile that cannot be solubilized by bile salts and lecithin. Certain genetic factors affecting the canalicular transporters are likely responsible, eliciting their phenotypic effect through exposure to environmental factors like female sex hormones and obesity. With time and in the presence of pronucleating agents particularly mucin gel, cholesterol microcrystals precipitate out of solution – the second stage. Mucin, a glycoprotein secreted by the gallbladder, then acts as a matrix scaffold for stone growth. The excessive cholesterol in bile also becomes incorporated into gallbladder smooth muscle, stiffens its sarcoplasmic membranes, and so impairs signal transduction and contraction. In the third stage, gallbladder hypomotility and stasis facilitates retention, allowing the microcrystals to agglomerate and grow into overt gallstones.

“Biliary sludge” consists of calcium bilirubinate (formed from bilirubin), cholesterol microcrystals and mucin. On abdominal ultrasound, biliary sludge is echogenic material that layers but unlike gallstones, sludge does not cast an acoustic shadow. Sludge develops in association with conditions causing gallbladder stasis, such as during pregnancy or total parenteral nutrition. Though frequently asymptomatic and prone to disappear, sludge in the gallbladder can evolve into overt stones, or may escape into the biliary tract producing biliary-type pain, cholecystitis or even pancreatitis.

Risk factors for cholesterol gallstone formation are a family history (genetic), obesity/metabolic syndrome, female gender and aging. Certain ethnic groups such as First Nations persons are especially prone to cholelithiasis (Table 3).



Table 3. Mechanisms and clinical presentation for gallstone formation

	Cholesterol gallstones	Black pigment stones	Brown pigment stones
➤ Mechanisms	○ Excessive cholesterol secretion	○ Chronic hemolysis ○ Altered bilirubin metabolism ○ Excessive bilirubin excretion	○ Stasis ○ Strictures
➤ Associations	Metabolic: ○ Family history ○ Obesity/Metabolic syndrome ○ First Nations person ○ Female sex hormones ○ Aging	○ Cirrhosis ○ Cystic fibrosis ○ Crohn disease ○ Advanced age	○ Infection ○ Inflammation

1.2.2. Pigment Stones

Black pigment stones constitute about 15% of gallstones found at surgery (cholecystectomy) in North America. These small, hard gallstones are composed of calcium bilirubinate as a polymer plus inorganic calcium salts (e.g., CaCO_3 , CaPO_4). The basis for their formation is excessive (or abnormal) bilirubin excretion in bile. They tend to form in alcoholic patients, chronic hemolytic states and with old age. (Table 3) Curiously, pigment stones also are associated with bile salt malabsorption. When ileal disease or loss causes bile salts to escape into the colon (especially the cecum) in large quantities, this biological detergent can then solubilize the bile pigment and return it via the portal vein to the liver. This creates an enterohepatic circulation for pigment material whose subsequent secretion into bile becomes excessive, creating black pigment stones.

Brown pigment stones, soft and greasy, are composed of bilirubinate and fatty acids that respectively account for their color and slippery texture. These brown stones form in bile ducts associated with inflammation, infection (often from a stricture or tumor) or parasitic infestation (e.g., liver flukes) of the biliary tract. Bacteria and inflamed tissues release β -glucuronidase, an enzyme that deconjugates bilirubin. The resultant free bilirubin then polymerizes and complexes with calcium to form calcium bilirubinate that precipitates in the bile duct system. Hydrolytic enzymes, acting on phospholipids, meanwhile produce fatty acids like calcium palmitate and stearate. Biofilm, a glycoprotein produced by bacteria as their glycocalyx, then agglomerates this pigment material, leading to brown stones. Stagnation and recurrent infection predispose to chronic cholangitis and eventually in some, cholangiocarcinoma.



1.3. Natural History of Gallstone Disease

Gallstones grow at the rate of about 1-2 mm per year, over a five- to 20-year period, before symptoms develop (often symptoms never develop). Gallstone disease is a common problem, affecting 10 to 15% of adults in developing countries, yet most (80%) never develop symptoms or complications. Gallstones frequently are clinically “silent,” being incidentally detected on routine abdominal ultrasound performed for another purpose. If problems do occur, the symptoms usually arise in the form of biliary pain (at a frequency of about 2% per year during the first five years, and then decreasing over time). Thus, biliary pain rather than a biliary complication represents the initial manifestation in most (90%) people with previously asymptomatic gallstones. As the rate of a biliary complication is very low (3% at 10 years), prophylactic cholecystectomy is not warranted in those with stones who lack symptoms.

Complications arise when stones in the gallbladder:

1. Obstruct the cystic duct, leading to cholecystitis: this begins as a chemical inflammation that later may become complicated by bacterial invasion; or
2. Pass out of the gallbladder into the common duct and either obstruct the bile ducts (producing biliary pain and cholestasis), often accompanied by bacterial infection in the bile ducts (cholangitis), or lodge in the common pancreaticobiliary channel, temporarily blocking the pancreatic duct (or causing bile reflux into the pancreatic duct) and resulting in pancreatitis (Figure 2).

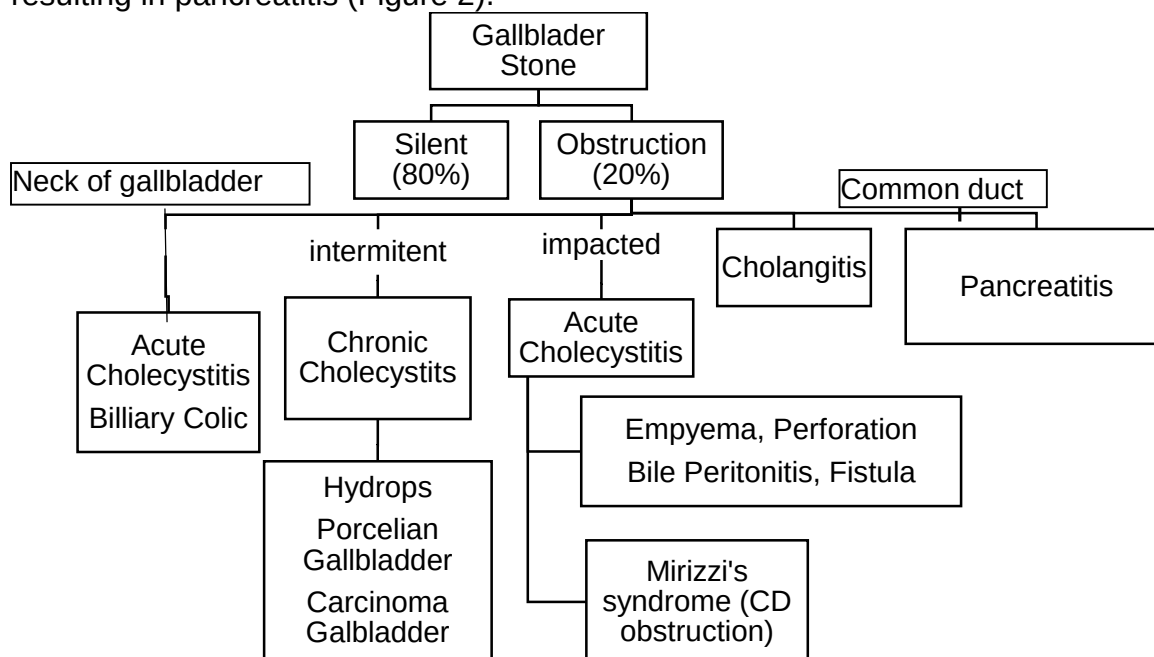


Figure 2. Potential complications of cholelithiasis.

Migration of the stone in the gallbladder to impact in the neck of the gallbladder or the bile duct can cause obstruction and result in complications. Cystic duct obstruction results in cholecystitis. It is often suggested that chronic calculous cholecystitis may be associated with carcinoma of the gallbladder, but causality is



unproven. Common duct obstruction leads to cholangitis, cholestatic jaundice and/or pancreatitis. Chronic cholestasis results in malabsorption of lipids. Stricture formation and recurrent cholangitis on occasion can lead to secondary biliary cirrhosis. Chronic duct obstruction and injury may lead to cholangiocarcinoma.

1.4. Clinical Features

Biliary colic ensues when a stone obstructs the cystic duct, causing sudden distension of the gallbladder. “Colic” is a poor term, as biliary pain typically does not increase and decrease spasmodically. Rather, the right upper quadrant or epigastric pain begins rather suddenly, quickly becomes intense, remains steady for 15 minutes to some six hours and then gradually disappears over 30 to 90 minutes, resolving spontaneously (though occasionally there remains a transient, vague ache for up to a few days). Its duration is seldom shorter than 15 minutes and is often sufficiently severe for many sufferers to seek medical attention and to require narcotics for relief.

Although biliary-type pain can follow a large meal, the old adage “fatty food intolerance” is not specific for biliary tract disease. Such dyspepsia is more a feature of a functional gut problem. A more regular (even daily) pattern of crampy abdominal pain, particularly when relieved by defecation, accompanied by a history of bloating and altered bowel motions suggests the irritable bowel syndrome (IBS) rather than a clinically “innocent” gallstone.

Biliary colic is a visceral pain that is steady and deep-seated. The pain is poorly localized in the right upper quadrant (RUQ) or central epigastric area. Lower abdominal pain from biliary disease is rare. Movement does not aggravate it. Mediated by splanchnic nerves, biliary colic may radiate like angina to the back, right scapula or shoulder tip, down the arm or into the neck, or even rarely biliary colic pain may be confined to the back. The patient is usually restless, and may exhibit vasomotor features such as sweating and pallor. Nausea with some vomiting may accompany a severe attack. Fever and rigors are absent when the cystic duct is obstructed and there is no inflammation. Such presence of fever and rigors suggest that a stone has migrated and become lodged in the cystic duct, causing cholangitis, or that the gallbladder is acutely inflamed (acute cholelithiasis).

Findings consist of mild-to-moderate right upper quadrant or epigastric tenderness. There are no peritoneal signs. Indeed, the examination is often quite normal, especially between attacks. Laboratory tests are characteristically normal.

Once gallstones are complicated by an attack of biliary pain, a recurrent pattern is likely to ensue, days or weeks apart. Symptomatic gallstones have a more aggressive course than those that are asymptomatic. Episodes of even uncomplicated biliary pain tend to recur at nearly 50% per year. Although 30% of patients with one episode of biliary pain do not have further episodes, most experience a recurrent pattern that remains fairly constant. These episodes may be sporadic separated by pain-free periods lasting from days to years, during which the patient feels well and the liver biochemistry is normal. However, complications requiring surgery may arise at any time, with a frequency of 1 to 2% per year. Pain lasting more than six to 12 hours, especially if accompanied by persistent vomiting or fever, suggests another process such as cholecystitis or pancreatitis (Table 4).



Table 4. Comparison of biliary colic to acute cholecystitis

	Biliary colic	Acute cholecystitis
○ Pain	- Constant visceral	- - Constant - parietal
○ Duration	- < 6 hours	- Hours to days
○ Nausea /Vomiting	- Some nausea	- More prominent - after pain onsets
○ Onset	- Rapid	- Variable
○ Jaundice	- No	- Later in 20%
○ RUQ Tenderness	- Modest	- Marked, with guarding (Murphy's sign)
○ Fever	- No	- Yes
○ Leukocytosis	- Absent	- Present
○ Resolution	- Spontaneous, in < 6 h	- Spontaneous in ~½, but 10% risk septic complication (abscess, perforation)

1.5. Diagnostic Imaging

Detecting gallstones (as opposed to diagnosing clinically symptomatic gallstone disease) is by diagnostic imaging. Plain abdominal x-rays will only identify the 10-15% with high calcium content as radiopaque densities in the right upper quadrant. Ultrasonography is the most sensitive and specific method for detecting gallstones (appearing as echogenic objects that cast an acoustic shadow) or a thickened gallbladder wall (indicating inflammation). (Figure 3) Small stones (<2-3mm) can be missed on abdominal ultrasound. MRCP (magnetic resonance cholangiopancreatography) is non-invasive test that can also detect gallstones, but is costly. Abdominal CT scan is less sensitive than ultrasound to detect stones, unless the patient is obese. Also, if the gallbladder is fibrotic and shrunken, ultrasound may not visualize the gallbladder.

1.6. Management

Once symptoms develop (e.g., as biliary colic), repeated attacks are likely. Although most episodes of biliary colic resolve spontaneously, pain eventually recurs in 20-40% each year. Furthermore, complications such as cholecystitis, choledocholithiasis, cholangitis or gallstone pancreatitis emerge at a frequency of 1-2% per year, often necessitating emergency cholecystectomy. Because of recurrent attacks of pain and these increased risks, cholecystectomy is indicated once biliary colic develops. The risk of any emergency procedure is greater than elective surgery, so this is why elective cholecystectomy is recommended.



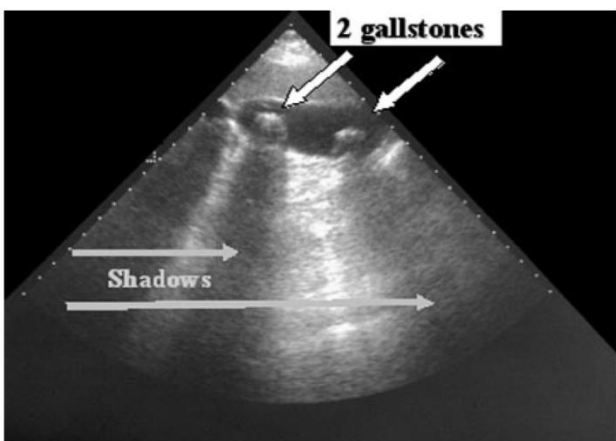


Figure 3. Abdominal ultrasound of two gallstones. In addition to each being

echogenic, they each cast an acoustic shadow.

1.6.1 Medical Therapy

Uncomplicated biliary pain will respond to general medical support, and the judicious use of analgesics such as meperidine and nonsteroidal anti-inflammatory drugs (NSAIDs) like diclofenac.

Bile Acid Dissolution of Cholesterol Gallstones

Administered orally, the bile acid, ursodeoxycholic acid (UDCA), lowers cholesterol saturation in bile and can dissolve gallstones. Such therapy has limited value because of a high recurrence rate of stones (50% at five years), and limited applicability: stones ideally should be small (<5 mm is best) and composed of cholesterol (radiolucent), while the gallbladder must fill/empty (by HIDA scanning, or by oral cholecystography now rarely used). UDCA is reserved to prevent gallstone formation in obese individuals undergoing rapid weight loss via dietary caloric restriction or bariatric surgery.

1.6.2. Cholecystectomy

1.6.2.1. Open cholecystectomy

The term “open” connotes the need for an incision to open the abdominal cavity for direct visualization in the course of removing the gallbladder. Open cholecystectomy is usually necessary in Mirizzi’s syndrome, an infrequent complication in which large gallstones compress and so obstruct the common bile duct. Mortality of open cholecystectomy is low at <0.5%, but reaches 3% for emergency surgery in acute cholecystitis or for common duct procedures, and is high in the elderly with co-morbid conditions. The open technique has largely been replaced by laparoscopic cholecystectomy.

1.6.2.2. Laparoscopic cholecystectomy

This minimally invasive technique employs an endoscope that displays large images on a TV monitor to view the abdominal contents (with the peritoneal cavity insufflated with gas) and uses instruments (like clips, scissors and graspers) inserted through small incisions in the abdominal wall to perform surgical manipulation. In



addition to the obvious cosmetic appeal, these smaller incisions result in less postoperative pain and shortened recovery time, allowing an early discharge from hospital (sometimes the same day as an outpatient) and return to work. The disadvantages include a somewhat higher complication rate, particularly from common duct injury and retained common duct stones, plus the potential for overuse. In 5% of cases the procedure must be converted to an open cholecystectomy because of technical problems. Laparoscopic cholecystectomy is now the standard for elective removal of the gallbladder in those with significant symptoms (e.g., necessitating repeated visits to the emergency room for narcotic relief) or with complications. Prophylactic cholecystectomy is not warranted in those with asymptomatic stones except for rare cases suspected of developing/ harboring carcinoma of the gallbladder (e.g., very large stones > 3 cm or a calcified gallbladder wall termed the “porcelain gallbladder”).

1.6.2.3. Notes

Natural orifice transluminal endoscopic surgery (NOTES) is an experimental endoscopic technique that uses a natural orifice (such as the mouth, anus, or vagina) and then an endoscopically created internal incision (like through the stomach or colon) as the route through which instruments are passed via an endoscope to perform an operation and retrieve the specimen. Transgastric and transvaginal cholecystectomies have been successfully performed in humans, avoiding external abdominal incisions and scars, although to date these have mostly been done as a “hybrid” technique, involving a single laparoscopic port in addition to the NOTES instrument. Pure NOTES human experience for cholecystectomy is scant. It remains unclear if improvements in cosmetic and potential recovery time will be outweighed by the much longer operative time and other potential adverse events of NOTES cholecystectomy.

2. Cholecystitis

2.1. Chronic Calculous Cholecystitis

Chronic inflammation of the gallbladder is the most common histological process, often manifest as mild fibrosis of the gallbladder wall with a round cell infiltration and an intact mucosa. Some degree of chronic inflammation inevitably accompanies gallstones, but the stones will have developed first. Even transient obstruction of the cystic duct can produce biliary colic and an element of inflammation that is chemical in origin. There is little correlation between the severity and frequency of such biliary episodes and the degree of inflammation or fibrosis. Chronic inflammation thus may follow the resolution of acute cholecystitis, evolve with recurrent episodes of biliary colic or develop insidiously. It is the presence of true biliary colic which drives the indication for cholecystectomy, not the possible presence of chronic cholecystitis.

2.1.1. Clinical Features

The clinical features are those of either biliary colic or a previous episode of acute cholecystitis that has resolved leaving the gallbladder chronically inflamed and scarred. The pain characteristically is a constant dull ache in the right upper quadrant or epigastrium, and sometimes also in the right shoulder or back. Nausea is frequent.



Flatulence, fatty food intolerance and dyspepsia occur, but are equally frequent in patients without gallstone disease. Fever or leukocytosis suggests acute cholecystitis or another entity. There may be local tenderness in the right upper quadrant of the abdomen but no peritoneal findings.

2.1.2. Diagnosis

Diagnosis largely depends upon detecting gallstones, either by plain films of the abdomen or CT (10-15% are calcified) or preferably by abdominal ultrasonography (95% accuracy). In addition, ultrasound (or CT) can identify signs of inflammation, such as free fluid around the gallbladder, and/or gallbladder wall thickening. If the gallbladder is fibrotic and shrunken, ultrasound visualization may be difficult. A nuclear medicine cholescintigraphy scan may be positive with the gallbladder failing to fill, but non-visualization is rather insensitive for chronic cholecystitis, because of frequent false positive and false negative tests.

2.1.3. Management

Once symptoms begin, they are most likely to recur, whereas asymptomatic stones, or stones associated with dyspepsia without biliary colic, are generally treated expectantly. Medical management depends upon gallstone size, gallbladder function and any co-morbid conditions (e.g., age, obesity, diabetes). Cholecystectomy provides definitive treatment, removing the stones and the gallbladder, and eliminating recurrences of true biliary pain.

2.2. Acute Cholecystitis

Here the gallbladder becomes acutely inflamed. In most (>90%), a stone has obstructed the cystic duct for a prolonged period, resulting in a vicious cycle of increased secretion of fluid, causing distension, mucosal damage and the release of chemical mediators of the inflammatory process. Inflammatory damage is primarily chemical. Bacterial infection is a late complication. Obstruction of the cystic duct results in the gallbladder becoming distended with bile plus an inflammatory exudate or even pus. The gallbladder wall can become thickened and go on to necrosis and perforation. If resolution occurs, the mucosal surface heals and the wall becomes scarred, but the gallbladder may not function – e.g., may not fill on HIDA or oral cholecystography.

In a minority, acute cholecystitis can occur in the absence of obvious stones (*acalculous cholecystitis*). Although *acalculous cholecystitis* can occur in healthy individuals, it tends to affect elderly men who have co-existent vascular disease, debilitated individuals and even young children. (see section 3.2.1 below)

2.2.1. Clinical Features

Acute cholecystitis begins like biliary colic (Table 4). The abdominal pain rises to a plateau and remains constant. Its location is usually the right upper quadrant or epigastrium, sometimes radiating to the back or the right shoulder. There may be a previous history of biliary pain (in ~75%). Pain in acute cholecystitis, unlike biliary colic, persists for more than six to 12 hours. As the gallbladder becomes inflamed, the visceral pain is replaced by parietal pain, which is better localized and is aggravated by



movement. Once the pain begins, nausea and vomiting often follow. Fever is usually low-grade in the absence of perforation or abscess formation. If rigors occur, one should suspect a bacterial infection and/or bacteremia. Abdominal examination characteristically shows tenderness in the right upper quadrant. During palpation of the right upper quadrant, a deep breath may worsen the pain and inspiration suddenly ceases (Murphy's sign). Severe cases exhibit peritoneal signs of guarding and local rebound tenderness. A reflex paralytic ileus may be present. Patients appear unwell and are reluctant to move with such parietal pain. An enlarged gallbladder is sometimes palpable, particularly with the first attack before fibrosis contracts it.

2.2.2. Diagnosis

Leukocytosis is common. Blood cultures may be positive. Liver biochemistry is often normal. Clinical Jaundice with mild hyperbilirubinemia ($<2\times$ normal) and elevated liver enzymes occur in about 20% of cases, even in the absence of common duct stones. Cholestasis can develop from either a concomitant bile duct stone, or a distended gallbladder that compresses the common duct (Mirizzi's Syndrome). Markedly elevated bilirubin levels suggest that a stone resides in the common duct. High levels of aminotransferase or alkaline phosphatase imply a common bile duct stone. A elevated amylase or lipase indicates gallstone pancreatitis from a bile duct stone that has recently been present; but most times (80%) the stone will have already passed on its own. A hepatitis-like picture (high aminotransferase) often develops from liver bed inflammation due to the cholecystitis, but could be an early indication that a stone has passed into the common duct even before the blood concentration of bilirubin, alkaline phosphatase or GGT rises.

The clinically suspected diagnosis of acute cholecystitis is best confirmed by ultrasound, which detects the stone(s) and a thickened gallbladder wall. In doing the procedure, the radiologist may elicit marked tenderness when pressing over the gallbladder (the ultrasonographic Murphy's sign). In suspected cases of acute cholecystitis, cholescintigraphy (HIDA), a nuclear medicine scan, assists the diagnosis by failing to fill the gallbladder with radionuclide because of a stone obstructing the cystic duct. Non-visualization also can occur in chronic cholecystitis due to failure to concentrate and in cholestasis because of impaired marker secretion.

2.2.3. Management

The definitive treatment is cholecystectomy (surgical removal of the gallbladder). General measures include rehydration, observation, analgesia and antibiotics. In mild cases of acute cholecystitis that resolve, cholecystectomy can be delayed for up to six weeks. Because of the risk of recurrent cholecystitis, surgery (usually as a laparoscopic cholecystectomy) should generally be performed soon after the current admission, once the patient has been stabilized.

2.2.4. Complications

Acute cholecystitis usually resolves spontaneously, usually within 3-7 days. Inflammation may progress to necrosis, empyema or perforation in about 10% of cases if untreated. These complications will be heralded by: (1) a continuation of the pain,



along with tachycardia, a high fever, peritoneal signs and marked leukocytosis; (2) features of a secondary infection, such as empyema or cholangitis; or (3) a suspected perforation. Emergency cholecystectomy then becomes mandatory.

Empyema is a suppurative cholecystitis with an intraluminal abscess (i.e., inflamed gallbladder containing pus). It develops from continued obstruction of the cystic duct leading to secondary infection. The abdominal findings of acute cholecystitis are accompanied by systemic features of bacteremia, with fever and rigors. Treatment includes analgesics, antibiotics, IV fluids and prompt cholecystectomy.

Perforation of the gallbladder occurs when unresolved inflammation leads to necrosis of the wall, often in the fundus (a part of the gallbladder that is relatively avascular). Gallstones also may erode through a gangrenous wall. Free perforation with bile peritonitis is fortunately uncommon, as the mortality reaches 30%. If localized, the perforation spawns an abscess, clinically evident as a palpable, tender mass in the right upper quadrant. The pain and temperature may also transiently resolve, only to be replaced by acute peritonitis. Both localized and free perforations demand surgery, with or without preoperative percutaneous drainage of the abscess. Rupture into adjacent viscera (e.g., the small intestine) is rare; this creates an internal biliary fistula. Large stones that pass through this type of fistula can produce a mechanical small intestine obstruction (*gallstone ileus*). Obstruction usually occurs at the terminal ileum, rarely at the duodenal bulb or the duodenojejunal junction. Radiologic diagnosis comes from finding air in the biliary system, a small bowel obstruction and perhaps a calcified gallstone ectopically located. Urgent surgery with appropriate antibiotic coverage is imperative.

Hydrops of the gallbladder occurs when the inflammation subsides but the cystic duct remains obstructed. The lumen becomes distended with clear mucoid fluid, the bile pigment having been reabsorbed. The hydropic gallbladder is evident as a right upper quadrant mass that is not tender. Treatment is cholecystectomy.

Limy bile occurs when prolonged gallbladder obstruction causes loss of the pigment material from bile and the residual calcium salts precipitate. The hydropic, obstructed gallbladder secretes calcium into the lumen. *Porcelain gallbladder* occurs when calcium accumulates in the wall of the gallbladder, readily identified on abdominal plain films. Although presumably there has been at least one episode of acute cholecystitis in the past, most patients with a porcelain gallbladder are asymptomatic. One-quarter will develop carcinoma of the gallbladder, prompting the need for prophylactic cholecystectomy.

2.3. Choledocholithiasis

Stones in the common bile duct (aka choledocholithiasis) are classified according to their site of origin: *primary stones* form in the bile ducts; *secondary stones* originate in the gallbladder and then migrate into the common duct. In North America, virtually all cholesterol stones and most pigment stones are considered secondary when the gallbladder is intact. Thus, more than 85% of patients with common duct stones also have stones or sludge in the gallbladder. Conversely, about 10% of patients undergoing cholecystectomy for chronic cholecystitis also have common duct stones. *Residual*



stones are those missed at the time of cholecystectomy; *recurrent stones* develop in the ductal system more than three years after surgery.

The composition of stones also varies with their site of origin. Stones are predominantly (approximately 80%) cholesterol when situated in the gallbladder and in the common duct. After cholecystectomy, the proportion of ductal stones that are pigment rises with time: most recurrent ones (more than three years after surgery) are pigment stones. These brown stones result from stasis (e.g., a postoperative stricture or a tumor) and infection.

2.3.1. Clinical Features

Most common duct stones eventually become symptomatic, causing biliary colic, obstructive jaundice, cholangitis or pancreatitis (Figure 2). Biliary colic results from sudden obstruction of the common duct, which increases biliary pressure. The abdominal pain is steady, located in the right upper quadrant or epigastrium, and can bore through to the back.

Acute cholangitis results when duct obstruction leads to infection. Obstruction and ductal damage permit bacteria to regurgitate across the ductal epithelium into the hepatic venous blood, causing a bacteremia with chills and a spiking fever, hence the concept of it being “pus under pressure”. The raised intrabiliary pressure also causes abdominal pain. The classical “Charcot’s triad” consists of jaundice, upper abdominal pain and fever. Jaundice results from the mechanical obstruction of the ducts plus a component of intrahepatic cholestasis due to sepsis (endotoxin, for example, impairs hepatic bile formation). Pain and fever are common, though jaundice may not be clinically apparent on presentation. There is abdominal tenderness; a large, tender liver should raise a suspicion of coexistent liver abscesses. Hypotension, confusion and a septic picture predominate in critical cases.

Pancreatitis can result from gallstones impacting at the ampulla of Vater. Acute pancreatitis consists of “pancreatic”-type pain (epigastric, often radiating to the back), elevated pancreatic enzymes (amylase/lipase >3 times the upper limit of normal) and radiologic evidence of pancreatic inflammation. The basis for gallstone pancreatitis is either from a stone obstructing the pancreatic duct at the ampulla, or from bile refluxing into the pancreas, if the stone is impacted in a common biliopancreatic channel. Acute biliary pancreatitis does not differ clinically from other forms of acute pancreatitis. Gallstone pancreatitis tends to be more commonly associated with jaundice and higher serum levels of bilirubin, alkaline phosphatase and aminotransferase than alcohol-induced pancreatitis, but there is considerable overlap. Ultrasound should detect any stones in the gallbladder in addition to the inflamed pancreas, with or without biliary dilatation, but gallbladder imaging in the acute setting may be limited due to tenderness (inability to perform certain maneuvers) and associated ileus (gas-filled stomach/intestine obscuring areas). In the absence of alcohol as a factor, pancreatitis in the setting of gallbladder stones/sludge is presumed “biliary” in etiology. Most non-alcoholic pancreatitis is due to gallstones, so repeating an ultrasound after an attack is settled may be needed to rule out occult cholelithiasis missed on the first normal (perhaps limited) study.



2.3.2. Diagnosis

Mild leukocytosis and abnormal liver biochemistry are common. Although usually cholestatic in pattern, the liver enzymes may be predominantly hepatitis-like (aminotransferases spiking to 1000IU/l or more, and being more prominent than alkaline phosphatase increase) in the early phases of the attack. Urine may be positive for bilirubin and then appears tea-colored (which some patients interpret incorrectly as hematuria).

Diagnostic imaging is the key to identify duct dilatation as the hallmark of obstruction and to clarify the cause. Ultrasound (the diagnostic imaging technique of choice) will often show dilated ducts >6 mm and, in advanced cases, liver abscesses. Ultrasound is highly specific for duct dilation (80% sensitivity), though insensitive for the biliary stone itself (30-40%). A previous cholecystectomy can result in bile ducts up to 10 mm in size without any obstruction; such dilation develops slowly after removal of the gallbladder rather than being an immediate event. Indeed, the common duct even dilates slightly with age at ~1 mm every decade above the age of 60. Hepatobiliary scintigraphy is insensitive. Helical CT cholangiography can detect biliary dilatation and bile duct stones, but is primarily used to evaluate complications such as liver abscesses.

Magnetic resonance cholangiopancreatography (MRCP) uses a heavily T2-weighted technique to clearly depict the fluid-filled biliary and pancreatic ducts without the need for contrast agents. MRCP is non-invasive, highly sensitive and specific for detecting stones and ductal dilatation, and identifying the site of biliary obstruction (Figure 4A).

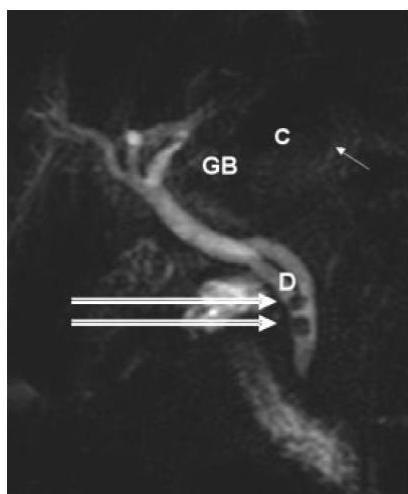


Figure 4A. MRCP showing 2 stones (large arrows) in the common duct. Small arrow indicates the pancreatic duct.

Abbreviations: D, Duodenum; GB, gallbladder; C, cystic duct.

Endoscopic ultrasound (EUS) uses a specialized endoscope with an ultrasound probe at the tip (echoendoscope) to image the bile duct through the apex of the duodenum, under conscious sedation. It is also highly sensitive and specific for ductal stones and is likely more sensitive than MRCP when biliary dilatation is absent and/or when stones are small (< 5 mm) (Figure 4B).

Although both MRCP and EUS are very accurate, they are generally indicated for patients with low/intermediate probability for a stone, they are not used in patients with cholangitis since a negative test will not change the decision to go on to ERCP.





Figure 4B. A radial endoscopic ultrasound image showing part of a “stack sign” imaged through the duodenal bulb (common bile duct (CBD) pancreatic duct (PD) and portal vein (not shown) in long-axis view, seen as dark (hypoechoic) stripes parallel to one another). A wedge shaped dark (hypoechoic) acoustic shadow is seen behind the bright (hyperechoic) 4-5 mm stone (arrow), making even this small stone appear quite obvious. P=probe at tip of scope; W= water filled balloon around probe. Small arrows indicate tangential view of duodenal wall.

ERCP (endoscopic retrograde cholangiopancreatography) was the “gold standard” for biliary imaging. Because of the need for conscious sedation and the injection of dye into the ampulla of Vater, this invasive procedure is associated with a 2-5% risk of pancreatitis. Moreover, in the 1% complicated by severe pancreatitis, mortality reaches 10%. ERCP is thus no longer used as a primary diagnostic tool but does offer important therapy: cutting open the sphincter of Oddi with cautery (sphincterotomy) to remove stones, sometimes assisted by lithotripsy (stone fragmentation) and/or stenting. Bleeding, perforation, and cholangitis are other rare complications.

2.3.3. Management

General medical care should include blood cultures and broad spectrum antibiotics to cover gram-negative microorganisms, anaerobes, and enterococcus: e.g., gentamycin, metronidazole and ampicillin. Noninvasive biliary imaging (MRCP, EUS) is most appropriate for scenarios with a low to intermediate probability of ductal stones, as an ERCP will follow in only a few cases. Intermediate to high probability situations (e.g., cholangitis, jaundice, biliary dilatation) have a higher probability of requiring a therapeutic ERCP (sphincterotomy and stone removal), and generally should go directly to ERCP.

Acute cholangitis represents a medical emergency that necessitates urgent decompression of the biliary system. ERCP with sphincterotomy followed by extraction of the stone is definitive therapy for cholangitis. If ERCP is unavailable or unsuccessful, percutaneous transhepatic cholangiography (PTC) decompresses the biliary tract and provides drainage that should be maintained, awaiting permanent relief of obstruction. Surgical bile duct exploration is rarely needed. Laparoscopic cholecystectomy should then be done electively, preferably within a few weeks of the attack. Although open cholecystectomy with common duct exploration will remove the gallbladder and all



biliary stones, this once standard procedure carries with it a longer recovery period and a higher operative morbidity than the combination of ERCP with laparoscopic cholecystectomy. Laparoscopic exploration of the common bile duct is technically difficult and generally restricted to stones < 7-8 mm.

In *gallstone pancreatitis*, bile duct stones will pass spontaneously into the duodenum in about 70% of patients. Rising liver enzymes over subsequent days, bilirubin more than twice normal and ultrasonographic evidence for biliary dilatation represent independent predictors of a retained stone. In mild-to-moderate gallstone pancreatitis, MRCP or EUS should be performed. ERCP is reserved for patients with increasing liver enzymes, jaundice or biliary dilatation. In severe pancreatitis, cholangitis, or ongoing biliary obstruction (as evidenced by jaundice, ultrasonographic biliary dilatation), early ERCP (within 24-48 hrs) and sphincterotomy becomes warranted.

Once ERCP clears bile duct stones, cholecystectomy should follow, ideally prior to discharge, but preferably in the following few weeks as recurrent biliopancreatic problems are frequent in the next few months. Unlike alcoholic pancreatitis, gallstone-related disease does not progress to chronic pancreatitis, unless the acute attack was associated with necrosis and permanent damage, such as a pancreatic stricture.

3. Acalculous Gallbladder Disease And Postcholecystectomy Syndromes

3.1. Congenital Anomalies

Congenital abnormalities of the gallbladder and biliary system result from embryonic maldevelopment. They are pertinent for the surgeon attempting to identify biliary anatomy at cholecystectomy. Agenesis of the gallbladder is rare. Curiously, it is associated with common duct stones, likely because the duct attempts to take over some of the reservoir role of the gallbladder. This topic is covered in specialized texts.

3.2 Painful Acalculous Gallbladder Disorders

3.2.1. Acute Acalculous Cholecystitis

Inflammation of the gallbladder can occur in the absence of gallstones. In adults, acute acalculous cholecystitis may appear in: elderly men, those with vasculitis others debilitated with sepsis, burns, trauma or following surgery; and with pregnancy. Biliary stagnation accompanied by occult sludge appears to be a factor. Impaired blood flow to the gallbladder, coagulation factors and prostaglandin may also have roles. Opportunistic infections like cytomegalovirus or cryptosporidia can cause gangrenous cholecystitis in patients who harbor HIV or are immunocompromised such as with bone marrow transplantation. In young children, acute cholecystitis may develop following a febrile illness like that with the Ebstein-Barr virus.

Clinical presentation may differ from acute calculous cholecystitis. The abdominal pain and tenderness are often obscured by the patient's underlying critical condition with seemingly obscure sepsis as the primary feature. Diagnosis is then revealed at laparotomy, but sometimes can be determined preoperatively by non-visualization of the gallbladder on HIDA (although non-visualization is less sensitive here because of the prolonged fast in these often debilitated patients – the resultant viscous bile prevents filling). Here too, ultrasonography is the best imaging procedure yielding: evidence of a



thickened gallbladder wall, a pericholecystic cystic fluid collection and/or a positive sonographic Murphy's sign. Perforation, gangrene and empyema are all too frequent complications. The best treatment is prompt cholecystectomy. Prevention is possible in some patients on complete TPN (total parenteral nutrition with no oral intake) following major surgery, trauma or burns. Daily injections of cholecystokinin (CCK) to stimulate gallbladder evacuation can prevent sludge formation and its complication, cholecystitis.

3.2.2. Acalculous Biliary Pain, Chronic Acalculous Cholecystitis and Biliary Dyskinesia

Recurrent biliary-type pain in the absence of gallstones has been attributed to a variety of often overlapping disorders, including chronic acalculous cholecystitis, and gallbladder/biliary dyskinesia, which share symptomatology but differ any pathologic findings in the resected gallbladder. Episodic biliary pain in the absence of demonstrable gallstones accounts for almost 15% of cholecystectomies performed, especially in young women. Ultrasonography-based surveys indicate that this figure may be even higher in the general population. In some, such acalculous biliary pain has been associated with rather modest, albeit nonspecific, gallbladder inflammation: chronic acalculous cholecystitis. The basis has been attributed to a motility disorder, impaired gallbladder evacuation: hence the alternative term "biliary dyskinesia." Relief can follow cholecystectomy but difficulties arise in attempting to make this diagnosis: the symptoms are often not clear-cut (sometimes having coexisting features of the irritable bowel syndrome or non-ulcer dyspepsia). Abnormal gallbladder emptying in response to CCK may be evident on cholescintigraphy but its true value remains unclear.

In others who have undergone a cholecystectomy for recurrent RUQ pain, the origin of the problem has been attributed to sphincter of Oddi dysfunction, either as a motor disorder or hypersensitivity of the sphincter. In many, the pain may represent just one facet of a more diffuse functional gut disorder and/or visceral hypersensitivity or intense spasms of a nearby structure in the right upper quadrant such as the duodenal sweep or hepatic flexure of the colon.

3.3. Cholecystoses

Cholesterosis consists of deposits of cholesterol esters and triglycerides within the gallbladder wall. Some of the cholesterol deposits may protrude like polyps that can be detected on ultrasound (cholesterol polyps). A rather common histopathological finding discovered post mortem or on ultrasound done for other reasons, cholesterosis is not associated with any well-defined symptom complex. It has been associated with vague dyspeptic complaints, the irritable bowel syndrome, or idiopathic recurrent right upper quadrant abdominal pain. As cholesterosis is not thought to cause symptoms, no treatment is warranted.

Adenomyosis is characterized by hyperplasia of the gallbladder mucosa and by deep clefts. Coexisting biliary-type symptoms are generally felt to be incidental, when present.



3.4. Postcholecystectomy Complications

3.4.1. Post-Cholecystectomy Inflammatory Conditions

Bile leaks can occur after laparoscopic cholecystectomy, usually because of either a cystic duct clip that is not secure or from inadvertent transection of a small branch (duct of Luschka) of the right intrahepatic duct that runs through the gallbladder bed on its way to the common duct. The presentation results from bile irritating the peritoneum and causing post-operative pain, sometimes with fever or peritoneal signs. Bile may be evident in the peritoneal drains. Serum bilirubin (reabsorbed after leaking) and liver enzymes are often elevated. Diagnosis comes from a hepatobiliary scan demonstrating the leak and/or by ultrasound showing a biloma (collection of bile). ERCP will confirm the diagnosis and provide therapy by inserting a stent for four to six weeks. The stent decreases resistance across the papilla and so encourages bile to flow into the duodenum, rather than through the leak site. Such leaks often heal in the first few weeks, avoiding re-operation. In 20-30% of patients, another obstructing diagnosis, such as a retained bile duct stone or an ampullary adenoma, coexists.

Strictures can arise after cholecystectomy either from mechanical trauma when attempting to clip the cystic duct or because of focal ischemia. Presentation is post-operative pain and jaundice. Some require re-operation and biliary reconstruction. Endoscopic therapy may be attempted for ligations that are incomplete. Ischemic strictures can present months later, with progressive cholestasis or abrupt jaundice if they are complicated by sludge. ERCP provides the diagnosis and treatment, employing progressive balloon dilatation and stenting. Temporary (removable) covered metal stents can also be used, especially in refractory cases. Strictures may be persistent, necessitating repeated procedures.

3.4.2. Post-Cholecystectomy Syndromes

Cholecystectomy relieves the symptoms of most, but definitely not all patients with biliary calculi. In general, the surgical complications discussed above, such as bile leaks and strictures, are rare and present early.

The *postcholecystectomy syndrome* is a term that primarily refers to pain that returns weeks or years after removal of the gallbladder. A few are experiencing recurrent biliary tract problems such as a retained common duct stone, best investigated with MRCP or EUS. In some patients, a careful history may reveal that the original complaint leading to cholecystectomy may not have been true biliary pain, but rather gastroesophageal reflux, functional dyspepsia or the irritable bowel syndrome. Diagnostic cholangiography using ERCP is generally not recommended in these patients because of the high risk pancreatitis following the procedure.

Sphincter of Oddi dysfunction, though not common, should be suspected when true biliary pain is recurring in the absence of a gallbladder (i.e.; post-cholecystectomy), but no duct pathology can be identified to explain the pain on MRCP or EUS. The basis is increased tone in the sphincter of Oddi that produces recurrent biliary-type pain, often with abnormal liver biochemistries, a dilated bile duct, or even pancreatitis. When



clear cut features are present during an attack (typical pain, enzyme changes and a dilated common bile duct, endoscopic sphincterotomy should be considered, as >90% will experience relief of pain. In those with few features, biliary nuclear medicine scanning can show delayed drainage from the biliary system, but its true value in equivocal cases, especially when the duct is not dilated, remains unproven. Sphincter of Oddi pressure measurements (manometry via ERCP showing basal pressures > 40 mmHg) may be the gold standard for sphincter of Oddi dysfunction, but ERCP when performed in such patients is associated with a higher than average post-ERCP pancreatitis rate (5-15%) and thus should be reserved for expert centers.

Some patients following cholecystectomy experience “diarrhea”, often with postprandial urgency. The basis for such diarrhea following removal of the gallbladder likely results from the unmasking of bile salt malabsorption that leads to a cholerrheic (bile salt-related) diarrhea. A nuclear medicine scan for bile using a radiolabeled, synthetic bile salt can assess its absorption in the terminal ileum (SeCAT scan). Bile salt diarrhea should respond to bile acid binding resins like cholestyramine, and empiric trials of this are reasonable.

3.5. Neoplasms of the Gallbladder

Carcinoma of the gallbladder is fortunately uncommon, as its prognosis is extremely poor. Adenocarcinoma is generally cured only when incidentally discovered at cholecystectomy for cholelithiasis. Gallstones are present in most (75%) cases, probably as innocent bystanders rather than as causal agents. The carcinoma risk however is too low to advocate prophylactic cholecystectomy in the many people with asymptomatic gallstones. Conversely, a porcelain gallbladder with calcifications in the wall predisposes to adenocarcinoma and calls for cholecystectomy. Large gallstones (> 3 cm) are also a risk factor for carcinoma, as is primary sclerosing cholangitis.

The clinical features of gallbladder carcinoma consist of abdominal pain, a hard mass in the right epigastrium, jaundice, pruritus and weight loss. Ultrasound and CT scan help define the mass and metastases. Prognosis is grim, as it is common for the cancer to spread. The five-year survival is less than 5%. Therapy is palliative; most are not resectable at presentation unless found incidentally at the time of a cholecystectomy performed for another indication.

Benign tumors of the gallbladder are uncommon. Adenomas are asymptomatic, being detected on ultrasound or found incidentally at surgery. Small masses in the wall of the gallbladder, however, are relatively common findings on ultrasound; when multiple they usually represent cholesterol polyps or adherent gallstones. If polyps are larger than 1 cm, cholecystectomy is recommended. Routine follow-up (ultrasound) of those <1 cm is controversial.

4. Other (Non-Calculous) Diseases of the Bile Ducts

4.1. Congenital

Fibrocystic disorders: This group of disorders comprises biliary tree maldevelopment. Cystic dilatation and/or fibrosis are due to genetic abnormalities in the



remodeling of the ductal plate. The type of disease depends on the part of the ductal plate involved. All, except Caroli's disease, may be associated with polycystic kidney disease. The prognosis usually depends on the extent of renal involvement. The later the presentation, the less significant is the renal component of the syndrome: 90% in perinatal vs. 25% in three- to six-month-old infants.

Caroli's disease (congenital intrahepatic biliary dilation) is a rare condition in which saccular, dilated segments of the intrahepatic bile ducts can lead to stone formation, recurrent cholangitis and/or liver abscesses. Episodes of abdominal pain, fever and jaundice, most commonly occur in childhood or young adult life. About 75% of patients are male; hepatomegaly is common. Cholangiocarcinoma and amyloid can be rare late complications. Cholangiography reveals the irregularly dilated segments of the intrahepatic bile ducts that connect with the main ducts. The common duct is normal. Management is conservative, using antibiotics for infectious complications of the duct system. Endoscopy (or surgery) can remove some stones but does little for the process that affects small bile ducts in the liver. If involvement is unilateral (usually left-sided), partial hepatectomy can be curative. These recurrent episodes of cholangitis can rarely progress to secondary biliary cirrhosis, portal hypertension and eventually cholangiocarcinoma. In such cases, liver transplantation may become necessary.

Congenital hepatic fibrosis frequently accompanies Caroli's disease; the combination is termed *Caroli's syndrome*. This phenomenon perhaps reflects a developmental defect of the small interlobular ducts. Congenital hepatic fibrosis presents as portal hypertension with esophageal varices in children. Liver biopsy is diagnostic, revealing broad bands of fibrous tissue entrapping bile ducts.

Choledochal cyst is an uncommon congenital dilation of a portion of the common bile duct that develops because of an uneven proliferation of the duct epithelial cells. The cyst wall consists of fibrous tissue, lacking epithelium or smooth muscle. More than 50% of cases are associated with an anomalous pancreaticobiliary junction, due to an arrest of the normal descent of this junction from outside the duodenum to within the duodenal wall in the last eight weeks of gestation. A long common pancreaticobiliary channel (> 15 mm) may allow pancreatic juice reflux in the bile duct, causing distal stricturing and thinning of the bile duct proximally, at least in some cases. Choledochal cysts have been classified into subtypes dependent upon site, most commonly as a fusiform dilatation of the extrahepatic bile duct, but also as a sidewall diverticulum or even bulging as a sac into the duodenum. Presentation may be as cholestasis in infants (if the cyst and/or stricture is complicated by sludge), as an abdominal mass, or rarely, as an acute abdomen if the cyst bursts and causes bile peritonitis. The cysts can be quite large: 2-8 cm in size and having up to 8 L of dark brown fluid. Later in life, they present as intermittent jaundice, biliary pain and cholangitis. Chronic obstruction rarely can lead to biliary cirrhosis and the development of ductal carcinoma (cholangiocarcinoma). Diagnosis is provided by ultrasound or CT scan and verified by endoscopic cholangiography. Because of the risk of malignancy, either related to the cyst itself or to the abnormal pancreaticobiliary junction, a radical excision with



hepaticojejunostomy is preferred. This also helps reduce the postoperative risk of stricturing and stone formation when the bile duct is surgically attached to the intestine.

Alagille's syndrome is a marked reduction in intrahepatic (actually interlobular) bile ducts. Although it is believed to be congenital, being inherited in an autosomal dominant pattern, presentation may be as a neonatal jaundice or as cholestasis in older children. There are associated triangular facies, cardiovascular anomalies (e.g., pulmonary artery stenosis) and vertebral body abnormalities. A mutation in the JAG1 gene is found in 70% of cases. Outcome is variable, depending upon the attendant anomalies and the severity of the liver disease.

Biliary atresia is a common cause of neonatal cholestatic jaundice. Although congenital (appearing at birth), it is not inherited. Complete absence of the extrahepatic bile ducts reflects either an arrest in remodeling of the ductal plate in utero or, more probably, an inflammatory destruction of the formed bile ducts during the postpartum period. An initial viral injury may initiate the epithelial injury that then progresses by an immune-mediated sclerosing process, abetted by bile salt leakage that adds detergent damage. The resultant sclerosing inflammation obliterates both the intra- and extrahepatic bile ducts, resulting in profound cholestasis and then secondary biliary cirrhosis. Severe cholestasis presents in the neonatal period. The stools are pale; the urine is dark and devoid of urobilinogen. Chronic cholestasis then leads to steatorrhea, skin xanthomas, bone disease and failure to thrive. Surgery is usually necessary to confirm the diagnosis and attempt some form of biliary drainage. In some, existence of a patent hepatic duct or dilated hilar ducts allows correction of the obstruction by anastomosis to the small intestine (e.g., a Roux-en-Y choledochojejunostomy). More common is an absence of patent ducts; dense fibrous tissue encases the perihilar area and precludes conventional surgery. Such obliteration of the proximal extrahepatic biliary system requires the Kasai procedure. A conduit for biliary drainage is fashioned by resecting the fibrous remnant of the biliary tree and anastomosing the porta hepatis to a roux-en-Y loop of jejunum. With either surgery, most children eventually develop chronic cholangitis, hepatic fibrosis/cirrhosis and portal hypertension. When the child is larger, hepatic transplantation dramatically improves the prognosis. Liver transplantation becomes necessary in 50% by 2 years of age, 80% by 20 years.

Other causes of neonatal cholestasis can be attributed to hepatocellular transport defects, best exemplified by familial intrahepatic cholestatic syndromes.

Von Meyenberg's complexes are biliary microhamartomas. They are thought to arise from a maldevelopment of the ductal plate. These small, multiple cysts are usually asymptomatic though potentially complicated by cholangiocarcinoma. They are usually only treated if symptomatic.



4.2. Inflammatory

4.2.1. Cholangitis

Cholangitis is any inflammatory process involving the bile ducts, but common usage implies a bacterial infection, usually above an obstructive site (usually a bile duct stone). The presence of bacteria in the biliary tree plus increased pressure within the system results in severe clinical features of cholangitis (*suppurative/bacterial cholangitis*). Any condition producing bile duct obstruction is likely to cause bacterial infection of bile. Most commonly, this takes the form of a common duct stone (Section 2.3), stasis in a congenital biliary cyst (Section 4.1), a parasite residing in the ducts (*Clonorchis sinensis*, *Opisthorchis viverrini* or *Fasciola hepatica*), an occluded biliary stent, or extrinsic compression from a diseased papilla or pancreas. Whenever the duct has been contaminated via an ERCP/stent, there is an intermediate risk of cholangitis.

A less likely cause of infection is a stricture (such as a neoplasm) that has not been contaminated by a stent; only 10-15% of malignant biliary obstructions are associated with infection at presentation. The difference relates to the slowly progressive obstruction of non-contaminated strictures versus the intermittent blockage with a stone or acute blockage of a stent within a duct that has been colonized by bacteria via the stent. Such intermittent blockage allows retrograde ascent of bacteria: the stone or stent acting as a nidus for infection. The bacteria ascend the biliary tree (hence the term “ascending cholangitis”), but may also enter from above via the portal vein or from periductular lymphatics. In acute bacterial cholangitis, particularly if severe, the classical Charcot’s triad of intermittent fever and chills, jaundice and abdominal pain may be followed by septic shock. Most cases are less severe and life-threatening; jaundice may be absent. Mild cases may respond to antibiotics and conservative measures. Investigation and decompression of the biliary system are mandatory in all patients, whether by ERCP, PTC or surgery. The duration of antibiotics needed after successful biliary drainage can be as short as three to five days, unless bacteremia coexists.

4.2.2. Sclerosing Cholangiopathies

Primary sclerosing cholangitis:

Primary sclerosing cholangitis (PSC) is a chronic cholestatic syndrome, distinguished by progressive inflammation and fibrosis of the intra- and extrahepatic bile ducts. PSC is uncommon (incidence of 0.9 per 100,000). It predominantly affects men aged 35-50 years. The entity may appear either alone (20%) or in association with inflammatory bowel disease (80%), particularly ulcerative colitis and less commonly, Crohn’s colitis. PSC may precede inflammatory bowel disease (especially ulcerative colitis) and runs a separate course, not being cured by colectomy. The basis for the patchy scarring (sclerosis) that leads to fibrotic narrowing and eventually obliteration of the bile ducts is unknown. In a genetically predisposed individual, biliary epithelial damage likely begins with exposure to an infectious agent and/or enterohepatic toxin. In inflammatory bowel disease with defective intestinal permeability, this might originate from transmigration of bacteria and toxins. An autoimmune process might then perpetuate the attack.



PSC is insidious; most patients are asymptomatic at presentation, particularly in those with inflammatory bowel disease who are identified by having cholestatic liver enzymes on routine testing. Clinical symptoms begin with fatigue and pruritus. Progression leads to jaundice, weight loss, chronic cholestatic features. Complications include episodes of bacterial cholangitis with upper abdominal pain, fever and worsening cholestasis. Secondary biliary cirrhosis with portal hypertension supervenes and progressive liver failure. Those with ulcerative colitis have a heightened risk of colon and hepatobiliary cancers.

The liver biochemistry is cholestatic with elevated alkaline phosphatase and GGT. Serology often includes antoantibodies like ANA, SMA and p-ANCA (80% of cases) at low levels, but not antimitochondrial antibodies, an important distinction from primary biliary cirrhosis. Diagnosis requires high-resolution bile duct imaging to show diffuse strictures and dilation of both the intra- and extrahepatic bile ducts. MRCP is quite accurate for PSC. ERCP is reserved for equivocal cases, or for biliary intervention: stones, sludge and a dominant biliary stricture. Liver biopsy is not usually necessary except for difficult cases: 1. Small-duct PSC - these have a sclerosing cholangitis with the clinical and biochemical features of PSC, but have a normal cholangiogram (as small ducts are involved). Some will progress to classic (large duct) PSC; and 2. Autoimmune hepatitis overlapping with PSC.

Management includes that for chronic cholestasis: treating the pruritus with bile-salt binding resins (cholestyramine) and using ERCP to dilate any dominant strictures; preventing metabolic bone disease (calcium, vitamin D) and nutritional management of steatorrhea including use of fat-soluble vitamins. Therapeutic trials of corticosteroids, immunosuppressive agents (for the presumed immunologically mediated inflammatory process), ursodeoxycholic acid (to theoretically displace any toxic bile acids and be anti-inflammatory) and proctocolectomy in patients with inflammatory bowel disease have all failed to change outcomes. As some patients may be asymptomatic for a decade, only careful observation is probably warranted early on. Recurrent bacterial cholangitis requires antibiotics and sometimes ERCP to remove extrahepatic sludge/stones. Extrahepatic “dominant”, large-duct strictures, associated with symptoms or significant cholestasis warrant ERCP balloon dilation, generally avoiding stenting because of the risk of contamination of upstream, poorly draining biliary segments.

Prognosis from diagnosis to death or liver transplantation is about 10 years. The development of jaundice, intractable pruritus and features of cirrhosis (ascites, portal hypertension with esophageal bleeding) are indications for liver transplantation (with a Roux-en-y choledochojejunostomy). The outcome is quite good with a 5-year survival exceeding 80%. PSC recurs in 20%. Some 10-15% of patients develop cholangiocarcinoma, creating a diagnostic challenge. Unexplained weight loss, a rising CA19-9 serum tumor marker (e.g. >100IU), or recent worsening of cholestasis should raise suspicion. MRCP imaging and/or ERCP with biliary brushings or other sampling/cholangioscopy are then warranted. . The development of cholangiocarcinoma prior to transplantation has a poor prognosis; the cancer progresses with immunosuppression, and is generally a contraindication to transplantation.



Other Sclerosing Cholangitides

Secondary sclerosing cholangitis causes diffuse stricturing. It complicates biliary obstruction from a common duct stone, ischemia, biliary stricture or cholangiocarcinoma, or some HIV-related infections. An infiltrative process (e.g., diffuse liver metastases, lymphoma, prominent regenerative nodules, and sarcoidosis) can also give a beaded appearance to the intrahepatic ducts that can mimic PSC.

IgG4-associated cholangiopathy is an autoimmune, steroid-responsive, sclerotic process manifest by IgG-4-positive plasma cell infiltration producing segmental stricturing in the larger bile ducts. Half of the strictures are confined to the intrapancreatic portion of the bile duct. The condition was originally described as a variant of autoimmune pancreatitis (AIP) and can be associated with various other autoimmune diseases. It is most common in older males, typically 60 years. IgG4-related cholangitis differs from PSC in several other ways: not commonly associated with inflammatory bowel disease; characteristically has elevated serum IgG-4 levels, and the strictures respond to corticosteroids (e.g. prednisone 30-40mg/d for 4-6 weeks). Hence, serum IgG-4 should be assessed in those with suspected PSC (which is not steroid-responsive). To aid the diagnosis, IgG4 immunostaining tissue can be obtained from the ducts, ampulla or pancreas (e.g. by EUS-guided core) in serology-negative cases. Characteristic changes in the pancreas and duct wall can be seen on EUS and ERCP. Recurrence after treatment is common. Associated autoimmune pancreatitis with inflammatory masses, and associated weight loss, can sometimes make this difficult to differentiate from malignancy.

4.3. Neoplasia

Benign tumors (adenomas, papillomas, cystadenomas) are rare causes of mechanical biliary obstruction. Ampullary adenomas can be associated with colonic polyposis syndromes. Localized adenomas of < 2 cm are amenable to endoscopic removal. Ampullary adenocarcinomas should be considered for a Whipple's pancreaticoduodenectomy.

The most common malignant stricture of the bile duct is due to invasion from to pancreatic cancer.

Cholangiocarcinoma, the most frequent primary biliary tract malignancy, is rather uncommon in the Western world. Predisposing factors are chronic parasitic infestations of the biliary tract (e.g., a liver fluke, such as *Clonorchis sinensis* or *Opisthorchis viverrini*), congenital ectatic lesions (anomalous pancreaticobiliary junction, Caroli's disease, choledochal cyst) and primary sclerosing cholangitis.

Painless jaundice is the hallmark presentation, but the presentation is varied. Cholestasis and weight loss eventually develop. There may be a deep-seated, vague discomfort - a feeling of fullness localized in the right upper quadrant of the abdomen. Indeed, cholangitis is uncommon (10-15%) if biliary manipulations, such as an ERCP-placed stent, have not been performed. A distended, non-tender gallbladder may rarely be palpated, feeling like a small rubber ball, if the common duct is obstructed below the insertion of the cystic duct ("Courvoisier's sign"). Obstruction produces dilation of the biliary tree that can be readily detected on ultrasound or CT scan. MRCP/ERCP often



shows an irregular, shouldered (as opposed to smoothly tapering) stricture; EUS shows bile duct wall thickening or a mass centered on the duct or at the liver hilum. A discrete mass is often not appreciated on cross-sectional imaging (CT/MR). An elevated prothrombin time/INR can occur due to cholestasis and anorexia, and needs to be corrected prior to ERCP/PTC. Tissue diagnosis is problematic. ERCP brushings for cytology have a relatively low yield for malignant cells (<40%). EUS and fine needle aspiration can help, especially in hilar tumors, or with the tumor is >2cm (yield > 70%). This slow-growing tumor unfortunately presents late.

Surgery for distal bile duct tumors is similar to a head of pancreas cancer (i.e. a Whipple pancreatoduodenectomy). For hilar/intrahepatic tumors, surgical decisions are more complicated and depend on stage (like vascular and bilateral liver involvement). If non-invasive imaging reveals a resectable non-hilar lesion in a young surgical candidate, it may be reasonable to go straight to surgery avoiding stenting, but generally a tissue diagnosis is pursued preoperatively in most patients. Palliation of distal tumors using biliary stents placed across strictures helps improve quality of life via alleviating jaundice, pruritus. Plastic stents are removable/exchangable but occlude after an average of 3-4 months, whereas self-expandable metal stents (both removable and non-removable varieties now available) can last longer (6-12 mos), but are much more costly (5-10 times).

Hilar tumors are managed differently (both surgically and endoscopically) and should be suspected when the characteristic painless jaundice of cholangiocarcinoma occurs in the presence of intrahepatic biliary dilatation, but without extrahepatic biliary dilatation. MRCP is non-invasive and quite accurate at staging these tumors (Bismuth classification) and determining their resectability. If not resectable, the MRCP also determines the feasibility of endoscopic/percutaneous drainage. Only 30% of the biliary tree needs be drained to alleviate jaundice. Draining one lobe is often sufficient for palliation although occasionally both sides may require drainage, especially if both sides are contaminated with dye at a procedure, or if cholangitis develops after stenting one side.



Chapter 19: Pancreas

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1. Anatomy

The pancreas is located retroperitoneally in the upper abdomen overlying the spine and adjacent structures, including the inferior vena cava, aorta and portal vein and parts of their major tributaries. Its retroperitoneal location makes the pancreas relatively inaccessible to palpation. The head and uncinate process lie within the curvature of the duodenum, while the body and tail extend to the hilus of the spleen. The arterial supply of the pancreas is from the major branches of the celiac artery, including the splenic and gastroduodenal arteries, and the superior mesenteric artery, as well as an arborization of smaller branches (i.e., the superior and inferior pancreatico- duodenal arteries) arising from these main arterial trunks. Venous supply comes from the superior mesenteric and splenic veins, which join together to become the portal vein (Figure 1). The pancreas does not have a capsule, and therefore pancreatic cancer often invades vascular structures, particularly the superior mesenteric vessels located directly posterior to the angle between the head and body of the pancreas. Nervous supply comes from parasympathetic branches of the vagus nerve, which provide a major secretory stimulus, and the sympathetic branches of the intermediolateral column of the thoracic spinal cord. Pain fibers are believed to accompany these sympathetic branches, which overlap those supplying the posterior abdominal wall structures, and which thereby account for the back pain experienced with pancreatic diseases.

The exocrine pancreas is drained by two duct systems. The major duct (duct of Wirsung) originates from the embryonic ventral pancreas and traverses the pancreas from the head of the pancreas to the tail. At the head it turns caudal and posterior to approach the infraduodenal portion of the common bile duct at the ampulla of Vater. The ampulla's opening is regulated by the sphincter of Oddi. The minor duct (duct of Santorini) originates from the embryonic dorsal pancreas, which supplies part of the anterior head, and enters the duodenum as a separate minor ampulla several centimeters above the ampulla of Vater. The minor duct fuses with the major duct in > 90% of people. In the minority, a lack of fusion of these two ducts results in the drainage of the head and body of the pancreas into the minor duct at the smaller ampulla, causing relative outflow obstruction. This anatomical variation, called pancreas divisum, is believed by some to be a cause of pancreatitis.



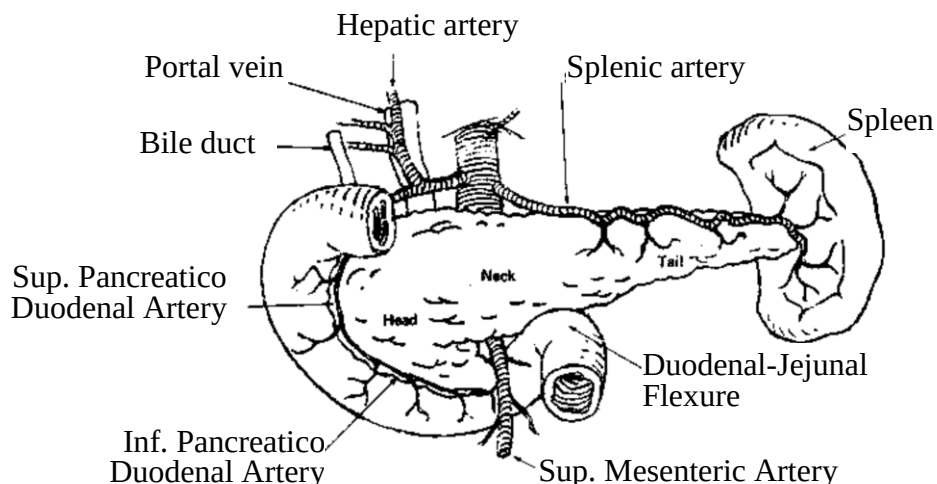


Figure 1. Relationships and blood supply of the pancreas.

The pancreatic tissue consists of endocrine and exocrine portions. The islets of Langerhans are islands of cells scattered throughout the pancreas. The majority of the islet cells are beta cells, which secrete insulin, whereas the non-beta cells secrete glucagon, pancreatic polypeptide and somatostatin. The exocrine portion (Figure 2) accounts for over 80% of the pancreatic mass. It is composed of primarily 1) acinar cells that secrete digestive enzymes and 2) centroacinar and ductal cells that secrete fluid and electrolytes, particularly bicarbonate.

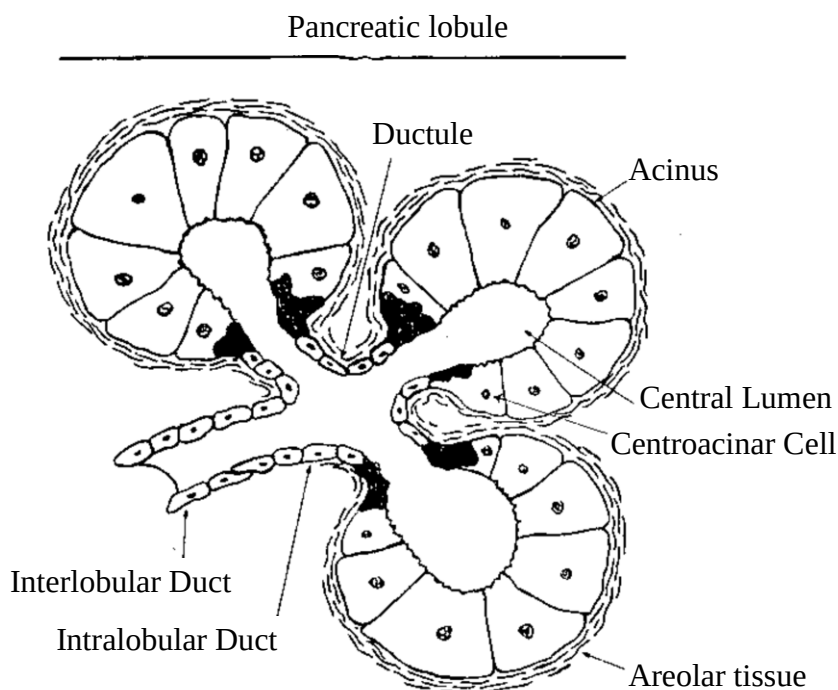


Figure 2. Schematic representation of acinar structure of exocrine pancreas.



2. Physiology

Pancreatic acinar and ductal secretions are regulated by neural and endocrine stimuli. The major peptide hormones stimulating acinar and ductal cells, respectively, are cholecystokinin (CCK) and secretin. Some peptide hormones such as somatostatin and pancreatic polypeptide, *inhibit* secretion.

2.1 Enzyme Secretion

The acinar cells secrete about 20 digestive enzymes, the vast majority of which are proenzymes later activated in the intestinal lumen. The pancreas has a great capacity for enzyme secretion, such that at least 90% of the gland must be destroyed before clinically significant maldigestion, leading to malnutrition, would be observed.

The pancreatic acinar cell secretes proenzymes, and enzymes that digest proteins, carbohydrates and lipids. Of these, amylase, and lipase are of particular clinical relevance. Other secretory products include ribonucleases, proteases and glycoprotein-2 (GP-2). All the digestive enzymes are packaged in zymogen granules within the acinar cell in their inactive proenzyme forms, except for amylase and lipase. The digestive enzymes synthesized in the rough endoplasmic reticulum are packaged within the Golgi apparatus and specifically targeted into the zymogen granules, which undergo a series of maturation steps involving condensation of the protein contents and shedding of excess membranes of the secretory vesicle. Each zymogen granule becomes very densely packed with digestive enzymes (they are called “dense core granules”) and lodges at the apical pole of the acinar cell, waiting for a stimulus to induce exocytotic fusion at the apical plasma membrane, which releases the granule’s contents. These vesicular transport processes could be blocked in a manner that causes fusion of the zymogen granule with lysosomes, allowing lysosomal hydrolytic enzymes to activate the digestive enzymes, or alternatively, causes pathologic fusion of the zymogen granule with the lateral side of the acinar cell. These pathologic processes have been hypothesized to play a role in the development of acute pancreatitis. Certainly, it is widely accepted that the inappropriate/uncontrolled activation of trypsin within the acinar cell is one of the most important pathological steps in acute pancreatitis.

Glycoprotein-2 (GP-2), which plays a role in stabilizing the zymogens, has the tendency to form protein plugs when excreted in excess into the ducts. These protein plugs serve as a nidus for calcium deposition and result in pancreatic ductal obstruction and smoldering inflammation leading to fibrosis and atrophy. This mechanism has been implicated in alcohol-induced chronic pancreatitis. A recently discovered relationship between ductal bicarbonate secretion and acinar GP-2 secretion also implicates GP-2 in chronic pancreatitis of patients with cystic fibrosis.

Under normal conditions, upon release of digestive proenzymes into the intestinal lumen, trypsinogen is activated by enterokinase to active trypsin, which in turn activates all the other digestive enzymes. (Figure 3). Appropriate conditions, most importantly an alkaline pH brought about by the ductal bicarbonate secretion, should be present for digestive enzymes to be active. The optimal pH of these digestive enzymes ranges from 7 to 10.



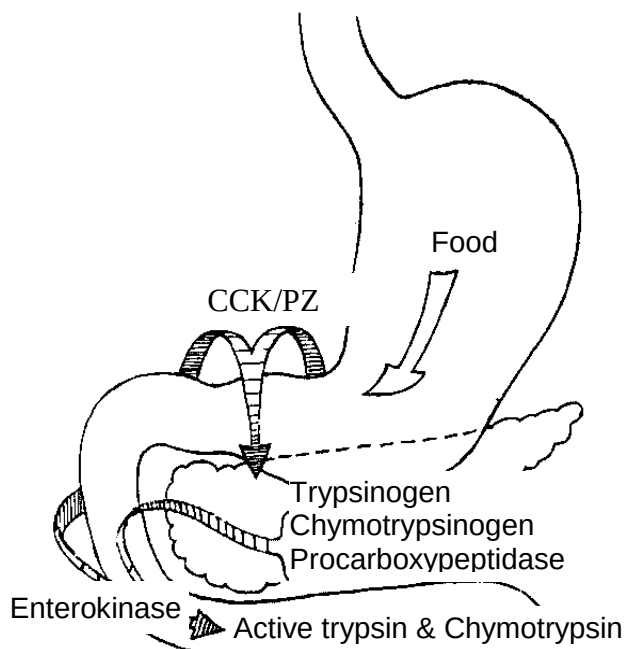


Figure 3. Role of cholecystikinin (CCK), pancreaticozymn (PZ) and enterokinase activation in pancreatic secretion.

The proteases are components of pancreatic secretions that break down specific protein peptide bonds to form amino acids. Endopepsidases such as trypsin and chymotrypsin cleave peptide bonds in the middle of the protein whereas carboxypeptidases act at the carboxyl terminus. The essential amino acids liberated by these mechanisms effect pancreatic secretion and upper GI motility.

Importantly, both amylase, and lipase, are secreted into the small intestine in their active forms. Amylase hydrolyzes starch to maltose, maltotrioses and dextrans. The effective action of lipase is more complex than that of either pancreatic proteases and amylase. This complexity accounts for the relatively low survival of lipase among the digestive enzymes. In fact, in pancreatic exocrine insufficiency, frequently only fat maldigestion is evident. Among these enzymes, lipase has the highest optimal pH (> 8) requirement, is most susceptible to inactivation by low pH, and requires a cofactor, colipase, for its optimal activity. Lipase acts at the oil–water interface of fat droplets. Its action results from emulsification of the food bolus, which is effected by the churning motion of the stomach and the action of bile acids. The bile salts then solubilize the fat into micelles. Colipase binds to lipase, stabilizes it, and prevents it from being inhibited and removed from the oil–water interface by bile salts. Perturbation of any of these processes will adversely affect the action of lipase on fats.



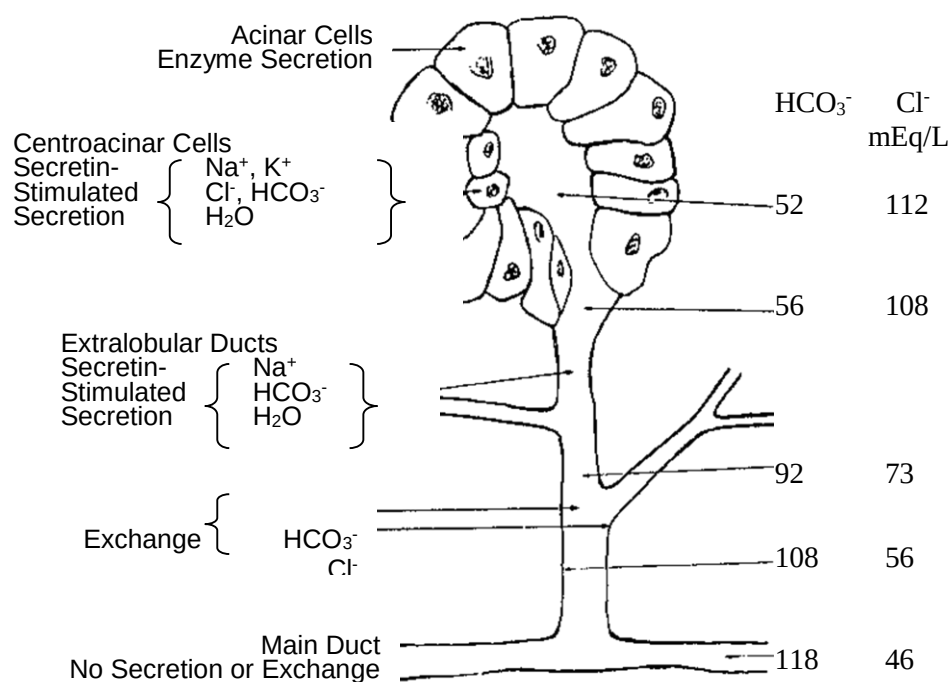


Figure 4. Secretion by centroacinar cells and by cells of the extralobular ducts of the pancreas. Chloride concentrations (right) were determined on fluid collected by micropuncture, and the bicarbonate concentrations were inferred from the fact that the fluid is isotonic. These data are for the cat pancreas, but other species seem to be similar.

Source: Adapted from Lightwood R, Reber HA. Micropuncture study of pancreatic secretion in the cat. *Gastroenterology* 1977;72:61.

2.2 Bicarbonate Secretion

The ductal and centroacinar cells contribute to a total secretion of 2.5 L of pancreatic juice per day. The pancreatic juice is isotonic with a pH of 8–9. The anion concentration exceeds 150 mEq/L, consisting of Cl^- and HCO_3^- (Figure 4). At high flow rates such as after a meal, HCO_3^- secretion predominates over Cl^- secretion, and the reverse is true at low flow rates. This change in $\text{HCO}_3^- / \text{Cl}^-$ ratio is effected by a ductal plasma membrane $\text{HCO}_3^- / \text{Cl}^-$ exchanger, which is activated by secretin-mediated cAMP pathways. The HCO_3^- is necessary to neutralize the acidic (pH < 2) gastric chyme entering the duodenum to a pH level (> 6) that is optimal for enzymatic digestion.

2.3 Regulation of Pancreatic Secretion

There are two patterns of pancreatic secretion. The first pattern is *basal secretion*, which is punctuated every 1 or 2 hours by bursts of increased bicarbonate and enzyme secretion that last 10 to 15 minutes. The second pattern is the



postprandial stage, which results from a complex interaction of neural and hormonal mechanisms.

The postprandial stage is divided into three phases. The *cephalic phase* occurs in response to the sight, smell and taste of food and is mediated by the vagus cholinergic nerves. Cholinergic stimulation has a primary stimulatory effect on acinar enzyme secretion, and a secondary potentiating effect on secretin-mediated ductal HCO_3^- secretion. The *gastric phase* occurs in response to distention of the stomach, which affects vagovagal neural reflexes and stimulates the release of gastrin. Both vagal reflexes and gastrin stimulate pancreatic enzyme secretion and gastric parietal cell acid secretion.

The *intestinal phase*, which is initiated in the duodenum, accounts for the major stimulation of both enzyme and bicarbonate secretion. The presence of products of fat and protein digestion in the duodenum stimulates the release of CCK, which in turn stimulates acinar enzyme secretion. When gastric acid entering the duodenum decreases the duodenal pH to < 4.5 , secretin is released, which stimulates ductal bicarbonate secretion. CCK acting via calcium pathways and secretin acting via cAMP pathways potentiate each other's effects on enzyme and bicarbonate secretion. Vasoactive intestinal polypeptide (VIP), like secretin, also acts on cAMP pathways to stimulate bicarbonate secretion, and is present and released at vagal nerve endings.

As the chyme reaches further into the small intestine, a number of hormones are released which are capable of inhibiting both basal and stimulated pancreatic secretion, and therefore serve as feedback inhibitory mechanisms on enzyme and bicarbonate secretion. These hormones, including pancreatic polypeptide (PP), peptide YY, glucagon, and somatostatin, are released not only by the small intestine, but also by the stomach and pancreatic islets, reflecting the complexity of feedback inhibitory pathways.

3. Pancreatic Function Test

The diagnosis of pancreatic insufficiency is strongly suggested by the clinical triad of pancreatic calcification, steatorrhea and, less commonly, diabetes.

Pancreatic calcification along with other structural abnormalities of the pancreas, including pancreatic atrophy and ductal irregularities, can be diagnosed by radiological imaging (plain x-ray, ultrasound and computerized tomography [CT scan], MRI/MRCP or endoscopic retrograde cholangiopancreatography (ERCP). These radiological tests demonstrating characteristic structural abnormalities of the pancreas, coupled with steatorrhea and or diabetes, are so strongly suggestive of pancreatic insufficiency that often a clinician will not proceed to functional testing of the gland itself for diagnosis.

Steatorrhea resulting from fat malabsorption has typical clinical features (foul-smelling floating stools, oil droplets). It appears earlier than protein malabsorption (azotorrhea) in pancreatic exocrine insufficiency, because of the low survival of lipase. Nonetheless, development of steatorrhea and azotorrhea requires the destruction of at least 90% of the pancreas.



Diabetes is less common in pancreatic diseases, since the islets are remarkably resistant to damage during the inflammatory process. However, when diabetes is present, it follows a more brittle course, since the nonbeta cells producing the counter-regulatory hormones glucagon and somatostatin are also affected.

Pancreatic function tests were initially divided for diagnosis of pancreatic dysfunction. They are now used with more frequency in the research realm. They can be divided into two main groups: direct or indirect tests requiring duodenal intubation, and non-invasive, indirect tests. (Table 1). Of the pancreatic function tests, the direct invasive tests are the gold standard.

Table 1. Exocrine pancreatic function tests

Intubation tests

CCK/secretin stimulation

Lundh meal

ERCP and pancreatic aspiration

Noninvasive tests

Stool fats and nitrogen

Stool trypsin and chymotrypsin

Breath tests

Oral function tests (bentiromide test and pancreolauryl test)

Blood determination

Trypsinogen

Lipase

Pancreatic amylase

Adapted from: Pandol SJ. *Sleisenger & Fordtran's Gastrointestinal and Liver Disease: Pathophysiology/Diagnosis/Management* 2006; page 1197-1199; and 2010, page 928.

3.1 Intubation Tests

“Tube”/Intubation tests require an oroduodenal tube positioned at the level of the ampulla of Vater to aspirate pancreatic secretion in response to stimuli, including a specific (Lundh) meal or intravenous administration of secretin, with or without CCK. These tests are based on the principle that as pancreatic flow increases with stimulation, there is a progressive increase in bicarbonate concentration (> 80 mEq/L) and a corresponding decrease in chloride concentration. When CCK is infused in conjunction with these tests, trypsin secretion can also be measured. This hormonal stimulation (secretin-CCK) test is believed to be the most sensitive ($> 90\%$) pancreatic function test. The Lundh test meal, although slightly less sensitive, is more physiologic since it also assesses the normal release of CCK and secretin in response to a meal containing protein, fat and carbohydrates. However, the accuracy of the Lundh test is affected by small bowel mucosal disease, rate of gastric emptying and surgical interruption of the gastroduodenal anatomy. Neither test is frequently used because of their disadvantages, including the prolonged (2–3 hours) and unpleasant intubation,



and the difficulty of accurate tube positioning. They are therefore not widely available.

Finally, cannulation of the pancreatic duct during ERCP has been combined with direct stimulation of the pancreas to measure pure pancreatic secretion uncontaminated by biliary or intestinal secretion. This method has not been shown to be more sensitive than other tests in the diagnosis of pancreatic diseases.

3.2 Indirect Pancreatic Function (Tubeless) Tests

The standard indirect pancreatic function test is the 72-hour fecal fat determination. Here, the patient is placed on a 100 g/day fat diet and the stool is collected daily for three days. Individuals with normal pancreatic function excrete less than 7% of the total amount of fat ingested, whereas those with pancreatic exocrine insufficiency excrete more than 20%. Only a few other conditions, such as extensive small bowel mucosal disease and short bowel syndrome, could cause such a degree of fat malabsorption. The major drawbacks of stool fat estimations are the lack of specificity and the inconvenience of collecting and analyzing the specimens. Measurements of stool nitrogen and stool chymotrypsin have not proved superior to fecal fat determinations. Attempts to screen for steatorrhea with less offensive tests (such as urine oxalate levels, ^{14}C -triolein/ ^3H -oleic acid assimilation test, and tripalmitate or palmitic acid breath tests) are promising but not generally accepted. (which test is the rice flour test referring to? Could we delete the rice-flour referral?)

Two oral function tests are available for assessing pancreatic functions: the bentiromide test and the pancreolauryl test. The bentiromide test is a urinary test that directly determines pancreatic chymotrypsin secretion. Bentiromide (N-benzoyl-L-tyrosyl-p-aminobenzoic acid [NBT-PABA]) is given orally, and hydrolyzed by chymotrypsin to release PABA. PABA is absorbed by the intestinal mucosa, conjugated by the liver, and excreted in the urine. Fifty percent of the PABA ingested should be recovered in the urine during a six-hour urine collection in normal subjects; less than this indicates pancreatic exocrine insufficiency. Intestinal mucosal, liver and kidney diseases understandably adversely affect the accuracy of the bentiromide test; measuring plasma levels of PABA could circumvent the problem. A number of medicines can also interfere with urine measurement of free PABA, including acetaminophen, sulfonamides and thiazide diuretics.

The pancreolauryl test, using fluorescein dilaurate, has been extensively evaluated in Europe. However, it can detect only severe pancreatic insufficiency and is therefore rarely used.

Chronic pancreatitis may give rise to an abnormal Schilling test, but rarely causes clinical B₁₂ deficiency. Vitamin B₁₂ is initially bound to an R factor present in saliva, which stabilizes B₁₂ in acidic gastric pH. Pancreatic enzymes release the R factor from B₁₂ to allow B₁₂ to bind to the intrinsic factor secreted by the stomach, which is required for B₁₂ absorption at the terminal ileum.

3.3 Miscellaneous Tests

Differentiating pancreatic carcinoma from chronic pancreatitis can at times be difficult. Many tests have been described to aid diagnosis, but none are of proven



value. Assay of carcinoembryonic antigen (CEA) in serum or from pure pancreatic juice obtained during ERCP has not proved to be a useful discriminator. The pancreatic oncofetal antigen has proved to be of uncertain significance. Serum galactosyl II transferase activity has recently been shown to be a reasonably specific indicator of pancreatic carcinoma in some patients. A sophisticated assay, it is unlikely to be suited to widespread use.

Trypsinogen, a proteolytic proenzyme, is exclusively produced in the pancreas. This enzyme can be detected by radioimmunoassay. It is elevated during an attack of pancreatitis and in renal failure, and is decreased in severe pancreatic insufficiency, cystic fibrosis and insulin-dependent diabetes without exocrine insufficiency. The levels of trypsinogen in cystic fibrosis decrease with age if the pancreas is involved. Low levels are found in about 60% of patients with pancreatic insufficiency. Patients with pancreatic insufficiency who have ongoing inflammation may have normal or raised levels. This fact, in addition to low levels in non-insulin-dependent diabetes, casts some doubt on the usefulness of this test in diagnosing pancreatic insufficiency. It may be useful in patients with steatorrhea that is due to nonpancreatic causes.

Table 2. Causes of elevated serum amylase/lipase

-
- GI causes
 - Small bowel obstruction
 - Intestinal ischemia
 - Bowel perforation
 - Cholecystitis
 - Salivary gland disease, e.g. mumps
 - Peptic ulcer disease with penetration
 - Pancreatic cancer
 - Pancreatic trauma/surgery
 - Cystic fibrosis
 - Celiac disease
 - Appendicitis
 - Pancreatitis
 - Liver disease
 - Non-GI causes
 - Tubo-ovarian disease, e.g. fallopian tube inflammation (salpingitis), ectopic pregnancy
 - Pregnancy
 - Renal failure
 - Diabetic ketoacidosis
 - HIV infection
 - IgA deficiency
 - Anorexia, bulimia
 - Neoplasia
-

Adapted from: Vissers RJ, et al. *J Emerg Med* 1999;17(6):1027-37.



3.4 Tests Suggestive of Active Disease

When faced with a patient with hyperamylasemia, it is necessary to exclude disease involving many organs other than just the pancreas (Table 2).

Amylase is produced and released from a variety of tissues, including the salivary glands, intestine and genitourinary tract. Normal serum contains three types of isoamylases as identified by isoelectric focusing. The pancreatic gland secretes one amylase at an isoelectric point of 7.0 that constitutes 33% of the total normal serum amylase. The parotid secretes several isoamylases with isoelectric points of about 6.4 and 6.0. Electrophoresis on polyacrylamide gel can separate five isoamylases on the basis of electrode mobility. Amylases originating in the fallopian tubes, tears, mucus and sweat have the same mobility as salivary amylase. All amylases have similar molecular weight and amino acid composition, but vary in terms of their glycosylation or deamination.

Amylase is filtered through the glomerular membrane and is reabsorbed in the proximal tubule. In healthy individuals, the amylase clearance parallels creatinine clearance. During acute pancreatitis, there is an increase in amylase clearance as opposed to creatinine clearance. Although this ratio was once thought to be specific to acute pancreatitis, other conditions that produce hyperamylasemia (such as diabetic ketoacidosis, burns, renal failure and perforated duodenal ulcer) may demonstrate a similar elevation. Occasionally, the serum amylase may be markedly increased in the absence of pancreatic or salivary diseases, whereas the urinary amylase is normal. In this instance, one must suspect either renal disease or macroamylasemia. In the latter condition normal serum amylase is bound by an immunoglobulin A (IgA), forming a complex that is too large to be filtered by the glomerulus. Affected individuals have an elevated serum amylase and a low to normal urinary excretion rate.

Frequently physicians are faced with a patient who has no overt salivary gland disease but has hyperamylasemia and no specific abdominal findings. As a rule, the level of amylase in pancreatitis usually is elevated to greater than 3 times the upper limit of normal and returns to normal within 2 to 10 days. If the amylase continues to be elevated in the absence of pancreatic complications, other causes (such as malignancy and macroamylasemia) should be investigated.

A rapid rise and fall in serum amylase in a patient with abdominal pain suggests the passage of a stone through the ampulla of Vater. When the serum amylase remains elevated for several days, the gallstone disease is usually complicated by pancreatitis.

Marked hyperamylasemia has been observed in patients with metastatic disease with ovarian cysts and tumors, and in ruptured ectopic pregnancy. Isoamylase analysis reveals that the amylase has the same electrophoretic mobility as salivary-type isoenzyme. Macroamylase consists mostly of salivary amylase complexed with globulins, being therefore too large to be filtered at the glomerulus. Therefore these individuals have elevated serum amylase and low urinary amylase, with a low amylase-to-creatinine clearance ratio.

While the amylase levels in serum and urine are usually used as a measure of acute pancreatitis, measurements of lipase may be more specific and sensitive than total serum amylase. The assay of lipase is as accurate as the pancreatic isoamylase assay, and is likely to replace the amylase assay. Measuring both offers no advantage.



Amylase and lipase measurements are readily available clinically, whereas radioimmunoassays are still being developed for other pancreatic enzymes (such as trypsin, chymotrypsin and elastase). Their role in the diagnosis of pancreatic disease needs to be established.

A recently developed urinary test for trypsinogen-2, which can be done with a urinary dipstick, appears to be quite promising in detecting patients with acute pancreatitis. It has a sensitivity of 94% and a specificity of 95%, as compared to serum amylase assay which has a sensitivity of 85% and a specificity of 91%. A negative test rules out acute pancreatitis with a high probability. A positive result usually identifies patients in need of further evaluation.

4. Pancreatitis

4.1 Etiology and Pathogenesis

Inflammatory disease of the pancreas is a common problem in North America, with gallstones and alcohol being the major causes. Pancreatitis tends to present with abdominal pain, which may improve with no sequelae or may run a more severe course that can lead to death. When the pancreas is continuously injured, such as with alcohol, a chronic condition results in obstruction and fibrosis of the gland, which leads to pancreatic insufficiency and chronic pain. Even one attack of pancreatitis from alcohol use can lead to some residual pancreatic damage.

Inadvertent activation of trypsin and chemotrypsin in the pancreas is normally prevented by several protective mechanisms; these are overwhelmed in acute pancreatitis, resulting in autodigestion. Pancreatic digestive enzymes (including proelastase, procollagenase and phospholipases), vasoactive materials, and other toxic materials extravasate out of the pancreas into the surrounding areas, leading to a widespread chemical irritation. Trypsin damages endothelial cells and mast cells, resulting in the release of histamine. This major inflammatory mediator enhances vascular permeability, leading to edema, hemorrhage and the activation of the kallikrein system, which in turn results in the production of vasoactive peptides or kinins. The latter are thought to cause pain and further aggravate the inflammatory response. The other released enzymes destroy the supporting matrix of the gland and the plasma membrane of the acinar cell, precipitating further release of digestive enzymes, which in turn leads to further damage. Lysolecithin, which is released by the action of phospholipase on lecithin (a phospholipid found in bile), has also implicated in pancreatic damage, because of its cytotoxic and haemolytic properties.

Although the action of these enzymes results in pancreatic damage, the triggering mechanism is not well known. In the case of gallstone pancreatitis, major theories include (1) reflux of bile into the pancreatic duct (2) distal obstruction of the pancreatic duct by stones or oedema from recent stone passage. Here, continued pancreatic secretion results in increased ductal pressure.

When the pancreas is inflamed but remains viable, the condition is termed *interstitial pancreatitis*; this may occur in up to 80% of cases. In the remaining cases, there is a significant pancreatic necrosis resulting from disruption of the microcirculation,



destruction of the pancreatic parenchyma and peripancreatic necrosis. This latter condition, necrotizing pancreatitis, follows a more protracted course.

Although alcohol has been implicated as a cause of acute pancreatitis in at least 30% of cases, there is no evidence that an occasional bout of excessive alcohol intake can lead to an acute attack. It is suggested that chronic ingestion may lead to chronic damage and sensitization, which may lead to acute pain even with small amounts of alcohol. Alcohol can cause direct damage to acinar cells in a manner similar to that in which it damages liver cells.

Hyperlipoproteinemia types I, IV and V are associated with the majority of lipid-associated cases of pancreatitis. The incidence of pancreatitis varies from 15-40% of patients. Hyperlipidemia has been suggested to be the cause of pancreatitis; however, recent evidence suggests that mild to moderate elevation of serum triglyceride levels is likely to be an epiphenomenon of the pancreatitis rather than the primary etiology. Hypercalcemia and hyperparathyroidism may also induce pancreatitis. Although the incidence of pancreatitis in patients with hyperparathyroidism was at one time shown to vary from 7-19%, recent findings suggest this variation to be closer to 1.5 % or less. This discrepancy can be accounted for by the difference in the degree or duration of the hyperparathyroidism and by the earlier treatment of hypercalcemia.

Other less common but important causes of acute pancreatitis include iatrogenic, through prescribed medications or following ERCP, ductal obstruction secondary to neoplasm, pancreas divisum, abdominal trauma, viral/parasitic infections, and hereditary causes. There is also a condition of Sphincter of Oddi dysfunction, which is associated with a higher risk of pancreatitis following ERCP.

4.2 Acute Pancreatitis

4.2.1 CLINICAL MANIFESTATIONS

The clinical spectrum of acute pancreatitis ranges from mild, self-limiting disease to fulminant lethal disease. Up to 80% of patients will have an uneventful recovery; the remainder will have serious complications with a high mortality rate. Objective measurements such as Ranson's criteria (Table 4) or APACHE II score, show a good correlation with the risk of major complications and death. Other methods of risk stratification have been developed for acute pancreatitis in the context of ERCP (Table 5). The overall mortality rate of acute pancreatitis ranges from 7–20%. The mortality rate correlates well with complications such as shock and hemorrhage.



Table 4. Poor prognostic indicators in acute pancreatitis*First 24 hours*

Age >55

Leucocytosis >16,000

Hyperglycemia, serum glucose >11.1 mmol/L

LDH >350 units/L

AST >250 U/L

After 24 hours

Decrease in hematocrit by >10%

Hypocalcemia (<2.0 mmol/L)

Hypoxemia pO₂ <60 mmHg

Hypovolemia

Base deficit >4.0 meq/L

(Ranson's criteria, 1978, modified by Hollander et al., 1983)

Table 5. Risk factors associated with the development of post-ERCP pancreatitis

- Operator related
 - Lower ERCP volume
- Patient related
 - Suspected sphincter of Oddi dysfunction (SOD)
 - History of recurrent pancreatitis/post ERCP pancreatitis
 - Younger age
 - Normal bilirubin
 - Prior post-ERCP pancreatitis
 - Female sex (possible)
- ERCP method related
 - Difficult cannulation
 - Pancreatic duct injection
 - Pancreatic sphincterotomy
 - Precut sphincterotomy (by endoscopists of mixed experience)
 - Balloon dilation of biliary sphincter
 - Acinarization (possible)
 - Absent common bile duct stone (possible)

Abbreviation: CCK, cholecystokinin

Adapted from: Slivka A. *AGA Institute Postgraduate Course* 2006; page 211-213.

4.2.2 SYMPTOMS

Pain from acute pancreatitis is a knife-like, steady, sharp pain that starts suddenly and reaches its zenith rapidly. It is commonly localized to the epigastric area and may radiate directly to the back. It improves on leaning forward and is frequently associated with nausea or vomiting. Depending on the location of the inflammation, the pain may be referred to either the left upper quadrant or the right upper quadrant. Frequently the pain is dyspeptic in quality and aggravated by food. This is due partially to the fact that eating stimulates secretion. Classically the pain lasts between three and four days. When the pancreatitis is severe, it may result in peripheral circulatory failure; under these conditions, the mortality rate approaches 60%.

Recurrent nausea and vomiting may be due to a reflex mechanism secondary to pain and occurs in over 90% of the cases. Other causes include pseudo- obstruction secondary to ileus and distention or obstruction secondary to a pancreatic mass or pseudocyst. Since the common bile duct traverses the pancreatic head before entering the duodenum, jaundice may occur, often transiently.

4.2.3 SIGNS

Depending on the severity of pancreatitis, the patient may appear in distress or be in shock. Jaundice may be caused by edema of the head of the pancreas or by an obstructing stone. Tachycardia could be secondary to pain, volume depletion or the inflammatory process. Low-grade fever could be secondary to the inflammation in the pancreas or result from such complications as abscess formation.

Abdominal examination may reveal epigastric and abdominal tenderness with guarding or rigidity. Bluish discoloration of the flanks (Grey Turner's sign) or of the periumbilical area (Cullen's sign) indicates that blood from hemorrhagic pancreatitis has entered the fascial planes. The signs are not specific and may occur in any condition that causes retroperitoneal hemorrhage. Tender red and painful nodules that mimic erythema nodosum may appear over the extremities. These are often due to circulating lipases.

4.2.4 COMPLICATIONS

Local involvement of pancreatitis includes phlegmon (18%), pancreatic pseudocyst (10%), pancreatic abscess (3%) and thrombosis of the central portal system. Phlegmon is an area of edema, inflammation and necrosis without a definite structure (unlike an abscess). A phlegmon results from acute intrapancreatic inflammation with fat necrosis and pancreatic parenchymal and peri- pancreatic necrosis. This arises from the ischemic insult caused by decreased tissue perfusion and release of the digestive enzymes. When this damage is not cleared, further inflammation ensues, declaring itself by increased pain, fever and tenderness. In severe cases a secondary infection ensues, a process termed *infected necrosis of the pancreas*, which occurs within the first one to two weeks of the illness and carries a high mortality. This diagnosis can be made by CT and percutaneous aspiration of the area with subsequent bacterial staining and appropriate cultures. In 3% of acute pancreatitis cases an abscess develops, usually several weeks into the illness. An abscess is a well-defined collection of pus occurring after the acute inflammation has subsided.



A pseudocyst develops as a result of pancreatic necrosis and the escape of activated pancreatic secretions through pancreatic ducts. It contains blood and debris. This fluid coalesces and becomes encapsulated by an inflammatory reaction and fibrosis. These patients usually have pain and hyperamylasemia, but may be asymptomatic. They may present with an abdominal mass, causing compressive symptoms.

Systemic complications of acute pancreatitis are numerous (Table 6) and correlate well with the severity of the inflammatory process. They may be manifested by shock (circulatory collapse secondary to sequestration of retroperitoneal fluid or hemorrhage), respiratory and renal failure and profound metabolic disturbances.

Table 6. Complications of pancreatitis

- Local
 - Sterile necrosis
 - Infected necrosis
 - Abscess
 - Pseudocyst
 - Gastrointestinal bleeding
 - Pancreatitis-related:
 - Splenic artery rupture or splenic artery pseudoaneurysm rupture
 - Splenic vein rupture
 - Portal vein rupture
 - Splenic/portal vein thrombosis, leading to gastroesophageal varices with rupture
 - Pseudocyst or abscess hemorrhage
 - Postnecrosectomy bleeding
 - Non-pancreatitis-related:
 - Mallory-Weiss tear
 - Alcoholic gastropathy
 - Stress-related mucosal gastropathy
 - Splenic injury
 - Infarction
 - Rupture
 - Hematoma
 - Fistulization to or obstruction of small or large bowel
 - Right-sided hydronephrosis
-



-
- Systemic (systemic cytokine response, aka “cytokine” storm)
 - Respiratory failure
 - Renal failure
 - Shock (circulatory failure)
 - Hyperglycemia
 - Hypoglycemia
 - Hypocalcemia
 - Hypomagnesemia
 - Disseminated intravascular coagulation
 - Subcutaneous nodules due to fat necrosis
 - Retinopathy
 - Psychosis
 - Malnutrition
 - Death
-

Adapted from: Keller J, et al. *Best Practice & Research Clinical Gastroenterology* 2007; 21(3): page 524.

Although acute pancreatitis may run a mild self-limiting course, severe pancreatitis occurs in up to 25% of acute attacks, with a mortality approaching 10%. The majority of deaths occur within the first week of hospital admission and are caused by local and systemic complications, including sepsis and respiratory failure. Most clinical studies in the adults cite pancreatic infection as the most common cause of death, accounting for 70–80% of deaths.

4.2.5 DIAGNOSTIC EVALUATION

Since the signs and symptoms of acute pancreatitis may mimic those of surgically correctable intra-abdominal disorders, knowledge and consideration of the differential diagnosis for acute pancreatitis is an important part of the initial evaluation. This includes: perforated

peptic ulcer, mesenteric ischemia/infarction, intestinal obstruction, dissecting aneurysm, peritonitis, acute cholecystitis, biliary colic, inferior wall myocardial infarction, ectopic pregnancy, and appendicitis. The diagnostic process is complicated by the fact that hyperamylasemia can occur in disorders other than pancreatic inflammation (such as ectopic pregnancy, parotiditis, carcinoma of the lung, posterior penetrating ulcer, ruptured aortic aneurysm and opiate administration: see table 2). Although amylase values greater than 1,000 units have been said to occur principally in conditions requiring surgery (e.g., biliary tract disease), this distinction is not absolute.

The diagnosis of acute pancreatitis is based on consideration of the above mentioned symptoms and signs, and the use of laboratory and radiographic techniques. Elevation of serum amylase in acute pancreatitis is short-lived. Amylase is rapidly cleared by the renal tubules and although it can stay elevated for several days, it may return to normal within 24 hours from the time of onset. Lipase levels appear to be a more sensitive and specific method of diagnosing acute pancreatitis and may

remain elevated longer than serum amylase. Immunologic assays for trypsinogen or immunolipase are experimental and do not add any more information than the serum lipase.

Although not diagnostic, it is important to complete lab workup of a patient with pancreatitis. A CBC should be ordered, as white blood count may be elevated in these patients, hemorrhagic pancreatitis may occur, and a high MCV may point to alcohol as a cause of pancreatitis. Liver enzymes may also be elevated; particularly in the setting of gallstone pancreatitis.

4.2.6 RADIOLOGIC EVALUATION

A plain film of the abdomen is very helpful. It may reveal calcification of the pancreas (indicative of a chronic process) or it may reveal gallstones (if calcified). The presence of free air suggests perforation, whereas the presence of thumb-printing in the intestinal wall may indicate a mesenteric ischemic process. A localizing ileus of the stomach, duodenum or proximal jejunum (all of which are adjacent to the pancreas) is highly suggestive of pancreatic inflammation. Similarly, when the transverse colon is also involved, air filling the transverse colon but not the descending colon (colon “cut-off” sign) may be seen. The chest x-ray can show atelectasis or an effusion, more often involving the left lower lobe.

Although clinical, biochemical and simple radiographic evaluation suffice for the diagnosis of pancreatitis, ultrasonographic and computerized tomography imaging are essential. Additional imaging such as MRCP, ERCP, or EUS, may also be indicated. These tests provide clues as to etiology, detect the presence/location of stones, help delineate relevant anatomy, provide an early assessment regarding severity, and detect complications such as phlegmon, pseudocyst and abscess formation. A pseudocyst or an abscess may also be drained percutaneously under CT or ultrasound guidance.

- The most common ultrasonographic and CT finding in patients with acute pancreatitis is diffuse glandular enlargement. Ultrasonographically there is a decrease in echogenicity of the organ; on CT scan there is decreased attenuation from edema of the tissues. Frequently intravenous contrast is given, and this may demonstrate a uniform enhancement in the pancreatic parenchyma. Contrast enhanced CT useful to grade pancreatitis, and to detect necrosis as well as neoplasm. In this regard, it is equivalent to gadolinium-enhanced dynamic MRCP. However, both contrast-enhanced MRCP and EUS are superior to contrast enhanced CT to detect CBD stones. (Arvanitakis M, et al. *Gastroenterology* 2005:715-23.
- A normal CT examination does not rule out the presence of acute disease. In up to 30% of uncomplicated cases of acute pancreatitis CT scan may be normal; these patients usually have a mild form of pancreatitis. (ie: grade “A”, see below) When a stone or an obstruction of the distal common bile duct is present, CT may demonstrate dilatation of the common bile duct, or of the intrahepatic biliary tree. Ultrasound is able to diagnosis dilated common bile duct 55-91% of the time, and is



able to pick up common bile duct stones 20-75% of the time. This is in contrast to detection rate of gallstones, where the accuracy of ultrasound in detection is greater than 90%. Ultrasound is, however, not useful to ascertain severity of pancreatitis.

This is best done with CT or MRI.

- Accepted criteria for grading severity of pancreatitis on CT have been established. These criteria, termed the “Balthazar severity index” use a grading scale of A to E, where grade A is normal appearing pancreas, grade C involves peripancreatic inflammation, and grades D and E involve peripancreatic fluid collection or several collections/evidence of pancreatic or retroperitoneal gas.

ERCP is an invasive diagnostic and therapeutic procedure that involves the cannulation of the ampulla of Vater and then injection of contrast material into the pancreatic duct and the biliary tree. This procedure is usually contraindicated during the acute phase, except when the pancreatitis is caused by an impacted common bile duct stone. Under those conditions, a sphincterotomy and stone removal may be performed. If performed as early as 24 hours following admission, this procedure may result in significant improvement in morbidity and mortality.

Table 7. Tests use for the detection of large and small duct disease in persons with chronic pancreatitis

Diagnostic test	Possible findings in ‘big duct’ disease	Findings in ‘small duct’ disease
➤ Fecal elastase	○ Usually low (<100/g of stool)	○ Usually normal
➤ Serum trypsin	○ Usually low (<20 ng/mL)	○ Usually normal
➤ Abdominal ultrasonography	○ Pancreatic atrophy, pancreatic duct dilation, pancreatic calcifications pseudocyst	○ Usually normal
➤ Computerized tomography	○ Pancreatic atrophy, pancreatic duct dilation, pancreatic calcifications, pseudocyst	○ Usually normal or equivocal
➤ MRCP	○ Pancreatic atrophy, pancreatic duct dilation, irregularity or stricture, pancreatic calcifications, pseudocyst	○ Usually normal or equivocal



Diagnostic test	Possible findings in 'big duct' disease	Findings in 'small duct' disease
➤ Endoscopic ultrasonography	○ Abnormal (>4 features of chronic pancreatitis)	○ May be abnormal
➤ ERCP	○ Abnormal	○ Normal or minimally abnormal
➤ Diagnostic test	Possible findings in 'big duct' disease	Findings in 'small duct' disease
➤ Direct hormonal stimulations test (e.g. secretin test)	○ Abnormal	○ Usually abnormal

Abbreviations: MRI, magnetic resonance imaging, MRCP, magnetic resonance cholangiopancreatography.

Printed with permission: Lieb JG II, and Forsmark CE. Review article: Pain and Chronic Pancreatitis. *Aliment Pharmacol Ther.* 2009;29(7):706-19.

4.2.7 TREATMENT

The aims of therapy of acute pancreatitis are (1) hemodynamic stabilization, (2) alleviation of pain, (3) stopping the progression of the damage, and (4) treatment of local and systemic complications. As yet there are no specific medical therapies capable of reducing or reversing the pancreatic inflammation. Hence therapeutic interventions are aimed at the complications of the disease.

Once the diagnosis is established with certainty, the patient's intravascular volume is replenished, and electrolytes, calcium, magnesium and blood sugar are closely monitored. Depending on the severity of the attack, an indwelling urinary catheter and close monitoring of urinary output may be necessary. Analgesics should be administered regularly during the first several days of the attack. This may alleviate the pain, decrease the patient's apprehension and improve respiration, thus preventing pulmonary complications such as atelectasis. The risk of narcotic addiction is minimal during the first days; most patients settle within 72 hours. The patient is kept off oral feeding; nasogastric suctioning is maintained only if the disease is severe and complicated by intractable vomiting and ileus. The rationale behind nasogastric suctioning is to place the pancreas at rest by removing the acidic gastric juices. This suppresses secretin release and decreases pancreatic stimulation. The validity of this postulate has not been substantiated. Similarly, the use of acid-suppressive medications has failed to show benefit in the treatment of acute pancreatitis. The use of enzyme inhibitors such as soy- bean trypsin inhibitor to prevent further damage is controversial, as is the use of prostaglandins and corticosteroids.

The routine administration of antibiotics does not improve the course of mild to



moderate disease. However, when the development of pancreatic abscess is suspected from an increase in fever and abdominal pain, antibiotic therapy should be instituted. The use of prophylactic antibiotics in the setting of necrotizing pancreatitis is controversial.

Respiratory insufficiency may occur in up to 40% of the cases, usually in patients with severe or recurrent pancreatitis. In such patients, arterial oxygen saturation should be monitored and corrected. Fluid overload should be avoided. Intubation and ventilation may be required.

Peritoneal lavage has been advocated in patients with severe disease, such as those with marked hypovolemia or hypotension or those who continue to deteriorate despite appropriate medical therapy. Although this technique reduces the circulatory and renal complications, it does not seem to alter the local complications.

Intravenous alimentation has been advocated in patients who continue to have pain and whose symptoms are aggravated postprandially. Several studies have documented equally effective results with nasoenteric alimentation.

If during a trial of six weeks or longer, complications develop (such as an abscess or an enlargement of phlegmon), a surgical debridement may be warranted, albeit as a last resort.

4.3 Chronic Pancreatitis

Chronic pancreatitis is defined as a continued inflammation characterized by irreversible morphologic changes. These changes include fibrosis, ductal abnormality, calcification and cellular atrophy. Alcohol is the major etiologic factor, accounting for about 75% of the cases. Repeated attacks of gallstone-related pancreatitis rarely if ever result in chronic pancreatitis. Other causes include diabetes, protein-calorie malnutrition, hereditary pancreatitis, cystic fibrosis, hypertriglyceridemia, hypercalcemia, tropical pancreatitis, autoimmune pancreatitis, and idiopathic causes.

Recent evidence suggests the possibility that some patients with chronic pancreatitis have a mutation of the CFTR or SPINK 1 gene that predisposes them to this complication. These cases may explain some of the cases of idiopathic or familial pancreatitis.

Alcohol presumably causes pancreatic injury by the intraductal formation of protein plugs secondary to increased protein concentration and precipitation, with or without calcification. These plugs lead to obstruction and secondary pancreatic damage caused by autodigestion. In developed countries chronic pancreatitis occurs after a long history (6 to 17 years) of alcohol ingestion of 150 to 170 g per day. Alcoholic pancreatitis is known to occur with much less consumption of alcohol, as low as 50 g per day. The mean age of a patient with new onset of disease is around 32 years, with a male predominance. Despite heavy drinking only a small percentage of alcoholics develop chronic pancreatitis, suggesting other factors that potentiate the injurious side effects of alcohol. Potential cofactors include smoking (very high association with alcohol pancreatitis and may be independent risk factor), high-protein diet with either very high or very low fat content, genetic mutations, and type of alcohol/manner of ingestion.



Table 8: Causes of Chronic Pancreatitis

-
- Duct obstruction
 - Benign pancreatic duct obstruction
 - Traumatic stricture
 - Stricture after severe acute pancreatitis
 - Duodenal wall cyst
 - Pancreas divisum
 - Sphincter of Oddi Dysfunction (SOD)
 - Malignant pancreatic duct stricture
 - Ampullary or duodenal carcinoma
 - Pancreatic adenocarcinoma
 - Intraductal papillary mucinous neoplasm
 - Hereditary
 - CT (cationic trypsinogen) gene
 - Autosomal dominant
 - Hereditary pancreatitis (PRSS1 mutations)
 - Autosomal recessive or modifier genes
 - CFTR mutations
 - SPINK1 mutations
 - IgG4 associated
 - Autoimmune
 - Associated with autoimmune diseases (eg. Sjögren's syndrome, primary biliary cirrhosis, primary sclerosing cholangitis)
 - Tropical
 - Tropical calcific pancreatitis
 - Fibrocalculous pancreatic diabetes
 - Metabolic
 - Diabetes
 - Alcohol
 - Hypercalcemia
 - Hyperlipidemia
 - Hypertriglyceridemia
 - Lipoprotein lipase deficiency
 - Apolipoprotein C-II deficiency
 - Postnecrotic chronic pancreatitis
 - Idiopathic
 - Early-onset
 - Late-onset
-



-
- Asymptomatic pancreatic fibrosis
 - Chronic alcoholism
 - Old age
 - Chronic renal failure
 - Radiotherapy
-

Adapted from: Chari ST. *Mayo Clinic Gastroenterology and Hepatology Board Review*; pg 470.; Forsmark CE. *Sleisenger & Fordtran's gastrointestinal and liver disease: Pathophysiology/Diagnosis/Management* 2006: page 1274.; and 2010, page 988; and Keller J, and Laver P. *Best Practice & Research Clinical Gastroenterology* 2008; 22(1): page 106.

4.3.1 CLINICAL MANIFESTATIONS

Chronic pancreatitis is characterized by irreversible injury to the pancreas and clinically by intractable abdominal pain and loss of exocrine and endocrine pancreatic function. The pain is localized to the upper abdomen, with radiation to subcostal regions and to the back. The pain is aggravated by meals and improves with fasting.

When more than 90% of exocrine pancreatic function is lost, maldigestion and malabsorption ensue. This is manifested by steatorrhea (fat malabsorption) associated with diarrhea and bloating, azotorrhea (protein malabsorption) and progressive weight loss. In addition, they manifest muscle wasting and edema, indicating protein deficiency. Latent fat-soluble vitamin deficiency (vitamins A, D, E and K) in addition to deficiencies of magnesium, calcium and essential fatty acids may occur and are closely related to dysfunction of fat digestion. Endocrine insufficiency presenting as diabetes mellitus may present at the same time as exocrine insufficiency or years later.

One exceptional presentation is that of autoimmune pancreatitis, which, although a cause of chronic pancreatitis, can initially present as painless jaundice mimicking pancreatic cancer. In this setting, both diagnoses must be carefully considered. (see table 9).

4.3.2 COMPLICATIONS

4.3.2.1 Pancreatic pseudocyst

Pancreatic pseudocyst is localized fluid collection occurring within a pancreatic mass or in the peripancreatic spaces following acute or chronic pancreatitis (Figure 5). The pseudocyst is usually surrounded by a non-epithelial-lined fibrous wall of granulation tissues. Its frequency varies from 10–50% of patients experiencing severe pancreatitis. When a pseudocyst is present for less than six weeks, it is considered acute; after that it becomes chronic. The pseudocyst may be asymptomatic or may present as an acute exacerbation of pancreatitis, with abdominal pain, nausea, vomiting and weight loss. These pseudocysts may obstruct intra-abdominal viscera, cause pancreatic ascites, rupture into viscera or the abdominal cavity, hemorrhage or become infected.



Spontaneous resolution occurs in 20% of the cases within the first six weeks of the pseudocyst's development. Chronic pseudocysts or pseudocysts greater than 5 cm rarely improve. Asymptomatic patients with persistent pseudocysts should be observed and intervention may be considered if symptoms appear. Successful percutaneous catheter drainage may be accomplished by CT- or ultrasound- guided drainage techniques. The catheter may be required for up to six weeks and is frequently associated with infections. Surgical drainage is sometimes necessary for failed percutaneous drainage or for complicated pseudocysts. If the pseudocyst is in the head of the pancreas, drainage can be done via ERCP.

4.3.2.2 *Pancreatic ascites*

Pancreatic ascites results from the leakage of pancreatic juices into the peritoneal cavity through a fistula or a ruptured pseudocyst. It presents with gradually increasing massive ascites, with high levels of amylase, abdominal pain and weight loss. Painful areas of subcutaneous fat necrosis result from the high levels of circulating pancreatic lipase.

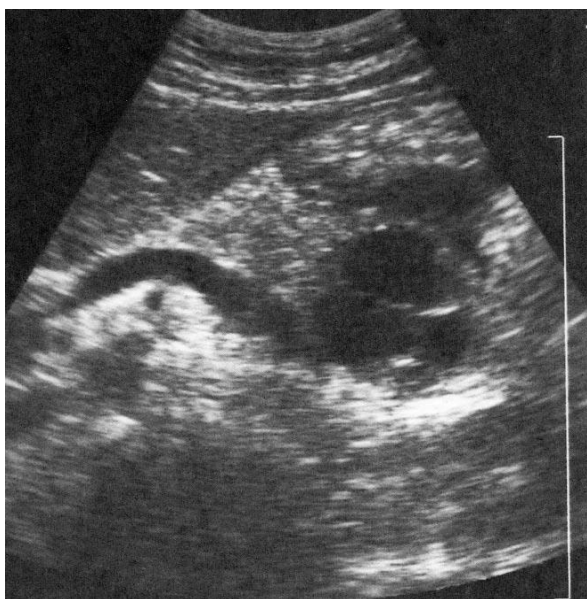


Figure 5. Pancreatic foil pseudocyst. Transverse sonogram showing a cystic septated well-defined mass in the pancreatic tail. It is touching and compressing the line of the splenic vein.

4.3.2.3 *Common bile duct stricture*

Common bile duct compression is another manifestation of chronic pancreatitis, but it rarely results in significant obstruction. As the distal common bile duct traverses the head of the pancreas, it may be narrowed secondary to inflammation, edema or fibrosis of the gland.

Pancreatic carcinoma, a cause of common bile duct stricture, was formerly thought to be increased in chronic pancreatitis. The incidence is now believed to be the same as in the general population. Importantly however, pancreatic carcinoma may present as pancreatitis.



4.3.2.4 Other complications

Gastric outlet obstruction can result during an acute flare. Similarly, inflammation can result in splenic vein thrombosis, which in extreme cases can lead to left sided portal hypertension and gastric variceal bleeding.

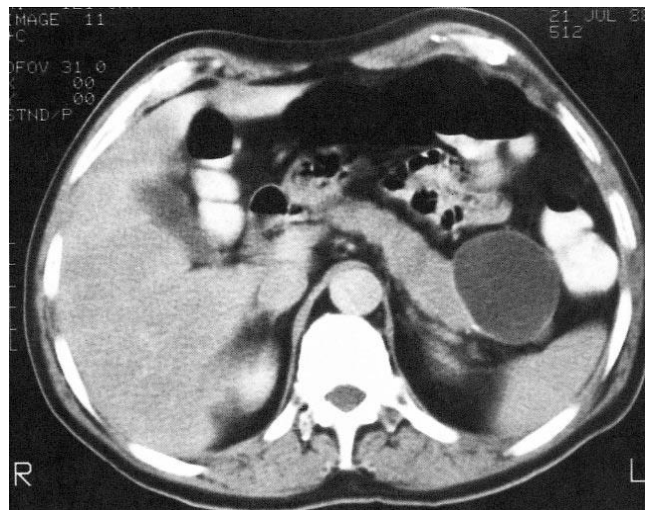


Figure 6. Computerized tomography of a pancreatic pseudocyst in the tail of the pancreas.

4.3.3 DIAGNOSTIC AND RADIOGRAPHIC EVALUATION

The diagnosis of chronic pancreatitis is straightforward in patients with advanced pancreatic disease. This can be demonstrated by the presence of calcification seen exclusively in the ductal system on plain radiographic abdominal films, by ultrasonography or on computerized tomography. However, radiologic evidence is only seen in up to 30% of patients with chronic pancreatitis.

Although ultrasonography may demonstrate pancreatic enlargement, ductal dilatation or pseudocysts, these findings are better seen on computerized tomography (Figure 6).

The role of Endoscopic ultrasound (EUS) in evaluation of chronic pancreatitis is evolving. The advantage of EUS, is the ability to provide information about the pancreatic parenchyma, as well as the ducts. Problems of interpretation may arise in these patients, particularly in older adults or alcoholics whose senile or fibrotic changes may be misinterpreted as a reflection of underlying chronic pancreatitis.

MRCP can provide detailed information about the pancreas and surrounding tissues. Large dilated ducts, as well as structural abnormalities, can be detected. However, small duct changes and calcifications are not well visualized.

ERCP is quite sensitive and specific for diagnosis of moderate to severe pancreatitis. In more severe disease there is narrowing and dilation of the ducts, stenosis, and filling of side ductules. Examination may reveal a tortuous main duct



containing stones or protein plugs, or obstruction of the common bile duct (Figure 7). In mild to moderate disease, however, ERCP findings may be subtle and even normal. Also, ERCP changes may not be closely related to the degree of pancreatic insufficiency; hence the rationale for pancreatic function studies in evaluating chronic pancreatitis.

The only pancreatic function test that appear to accurately measure pancreatic function in chronic pancreatitis are the direct tube tests that measure the response of the pancreas to various stimuli. The commonest manifestation is a decreased bicarbonate concentration ($< 50 \text{ mEq/L}$) and decreased volume of secretion.

When no cause of the pancreatitis is found, the condition is considered to be "idiopathic". Microlithiasis (stones $< 3\text{mm}$) occur in 37-89% of persons with idiopathic acute pancreatitis, and some experts recommend cholecystectomy for associated symptoms. Biliary crystals, crystals of calcium bilirubinate, calcium carbonate, or cholesterol monohydrate, can contribute. The use of duodenal drainage to assess the presence of biliary crystals has a sensitivity of 65%, and a specificity of 94-100%

Overall, extensive investigation of the patient is necessary before the diagnosis of idiopathic chronic pancreatitis is made (Table 8).

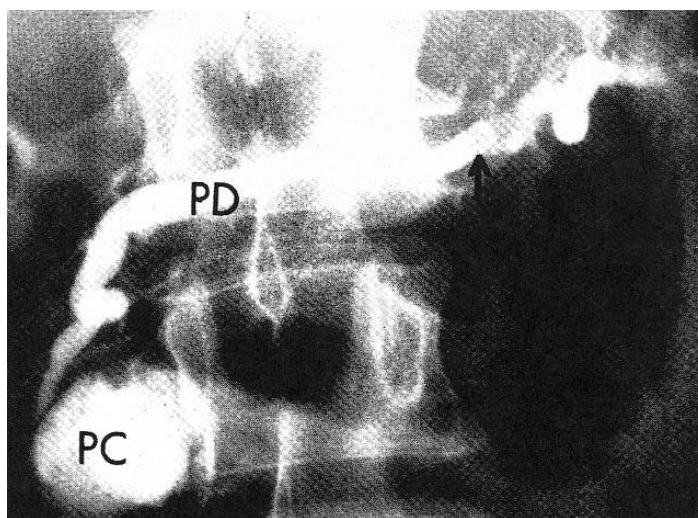


Figure 7. ERCP of a patient with a chronic pancreatitis demonstrating dilation of the duct (PD) with filling of side branches in the tail. This is complicated by pancreatic pseudocyst (PC).



Table 8. Workup: Chronic Pancreatitis

-
- Structural (ERCP/MRCP, CT)
 - Pancreas Divisum, chronic pancreatitis, ampullary stenosis, juxta-ampullary diverticulum, or other anatomic abnormalities.
 - ERCP with bile aspiration, centrifugation and examination of pellet for biliary crystals
 - SOD (Sphincter of Oddi) dysfunction (pressure measurement)
 - Hereditary
 - CFTR gene
 - cationic trypsinogen (CT) gene
 - SPINK gene
 - Tests for autoimmune pancreatitis: (for details, see Table 9)
-

Printed with permission: Dite P, et al. *Best Pract Res Clin Gastroenterol.* 2008;22(1):131-43.

Table 9. Criteria for the diagnosis of autoimmune pancreatitis (AIP), and the features characteristic for the diagnostic groups

-
- Diagnostic criteria
 - Clinical
 - More frequently males (80%), over 50 years (80%)
 - Pain is not a prominent feature
 - Histology
 - Periductal lymphoplasmacytic infiltrate with obliterative phlebitis (LPSP) in pancreatic tissue
 - High (>10 cells/hpf) IgG4 positive cells in the pancreas
 - Lymphoplasmacytic infiltrate with fibrosis in the pancreas
 - Imaging
 - Typical: diffusely enlarged gland with delayed 'rim' enhancement, diffusely irregular, attenuated main pancreatic duct
 - CT/MRI shows "sausage-shaped" enlargement of pancreas, peripheral (RIM) enhancement, and delayed enhancement; ERCP shows characteristic diffusely irregular and narrowed pancreatic duct.
 - Other: focal pancreatic mass/enlargement, focal pancreatic ductal stricture, pancreatic atrophy, calcification, pancreatitis
 - Focal, but usually diffuse involvement of pancreas with irregular narrowing of pancreatic duct, swelling of parenchyma, from periductive lymphoplasmacytic, infiltration, storiform fibrosis, obliterative phlebitis (infiltrative surrounds venules but not arteriols), and IgG4 positive immunostaining of $\geq$ IgG4 positive cells per HPF
 - Serology
 - Elevated serum IgG4 level (normal 8-140 mg/dl)
-



- Other organ involvement
 - ISD may affect pancreas, bile ducts, salivary glands, kidneys, retroperitoneum, and lymph nodes
 - Hilar/intrahepatic biliary strictures, persistent distal biliary stricture, parotid/lacrimal gland involvement, mediastinal lymphadenopathy, retroperitoneal fibrosis
 - Response to steroid therapy
 - Resolution or marked improvement of pancreatic /extrapancreatic manifestation with corticosteroid therapy
 - Consistent response to 30-40 mg prednisone, tapering with improvement in serum IgG4 and imaging
-

Abbreviations: HPF, high power field; IgG4, immunoglobulin G4; AIP, autoimmune pancreatitis; ISD, IgG4-associated systemic disease

Printed with permission: Dite, Petr., et al. *Best Practice & Research Clinical Gastroenterology* 2008; 22(1): page 138.

4.3.4 MANAGEMENT

The ultimate goals of treatment in chronic pancreatitis are to alleviate pain, maintain adequate nutritional status, and reduce symptoms associated with steatorrhea such as abdominal pain, bloating and diarrhea.

The mechanism of pain in chronic pancreatitis is not known. There are numerous approaches to the management of pain in chronic pancreatitis which need to be carefully considered (Table 10). Endoscopic procedures play an important role in the management of patients with acute or chronic pancreatitis (Table 11). Despite the many positive uses of endoscopic management, there are clear indications for surgery (Table 12).

Table 10. Approaches to the management of pain in the patient with chronic pancreatitis

- General measures
 1. Manage associated/causative factors
 2. Cessation smoking and alcohol intake
 3. Analgesics
 4. Gabapentin, SSRIs, TCAs
 5. Low-fat diet
- Neural interruption
 - Percutaneous or endoscopic (EUS) nerve blocks (data promising)
 - Surgical (thorascopic) splanchnic nerve resection



- Reduction of intrapancreatic pressure
 - Suppression of enzyme secretion
 - Anticholinergics, PPI, somatostatin, pancreatic enzyme replacement
 - Decompression techniques
 - Sphincterotomy, endoscopic dilation and stenting
 - Stone removal (endoscopic or ESWL)
 - Surgical drainage, if pancreatic duct dilated
 - Organ resection
 - Partial for persistent inflammatory mass, complete for refractory cases, with/without pancreatic islet cell transplant

Adapted from: Forsmark CE. *Sleisenger & Fordtran's gastrointestinal and liver disease: Pathophysiology/Diagnosis/Management* 2006: pg 1288-1294.

Some of the methods found to help relieve the pain from chronic pancreatitis involve endoscopic procedures (Table 11) or the use of nasogastric drainage of the duodenal lumen.

Table 11. Roles of endoscopic procedures in the management of acute/chronic pancreatitis

- ERCP
 - Sphincterotomy
 - Dilation and stenting of pancreatic strictures
 - Removal of pancreatic duct stones
 - Pancreatic duct disruption and pseudocyst
 - Biliary strictures from chronic pancreatitis
 - Pancreas divisum
 - Aspirate cyst fluid
 - EGD
 - Jejunal tube placement for enteral feeding
 - EUS
 - Diagnosis of CBD stones
 - Celiac nerve block and neurolysis
-



Table 12. Indications for surgery in persons with chronic pancreatitis

-
- Intractable pain
 - Suspicion of malignancy
 - Common bile duct obstruction
 - Symptomatic duodenal obstruction
 - Symptomatic pseudocysts^a
 - Vascular obstruction^b
 - Pancreatic duct obstruction^b
-

^aBoth surgical and endoscopic drainage procedures are possible

^bIf present with other complications

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Abstinence from alcohol may decrease the frequency and severity of painful attacks in patients with alcoholic pancreatitis. Large meals with foods rich in fat should be avoided. Analgesics should be given prior to meals, since the pain is maximal postprandially. The continuous use of narcotics often leads to drug addiction, which makes the management of pain more difficult. Large doses of pancreatic extracts may reduce the frequency and severity of the pain in patients with no demonstrable duct obstruction. These enzymes appear to suppress pancreatic exocrine output, thus putting the pancreas at rest and resulting in pain relief. Pancreatic replacement is given with meals and at bedtime. Patients who respond to this therapeutic regimen tend to be middle-aged women with idiopathic pancreatitis who suffer from mild or moderate disease. These patients tend to have a bicarbonate output greater than 55 mEq/L and normal fat absorption. Patients with more severe disease, whose peak bicarbonate output is less than 50 mEq/L, tend not to respond to this regimen.

Patients with intractable pain who fail to respond to medical therapy may benefit from surgical intervention. When there is a dilated pancreatic duct with obstructive areas, longitudinal pancreatojejunostomy may induce immediate pain relief. When the duct is small, partial surgical resection of the pancreas may control the pain in a certain percentage of patients. Although pain alleviation with surgery may be achieved in certain patients, its long-term benefit is limited since pain recurs in the majority of patients. An alternative to surgical drainage may be achieved by endoscopic insertion of an endoprosthesis (stent) into the pancreatic duct. Although this approach is promising, its long-term benefit has not been proven.

Octreotide, a long-acting somatostatin analogue, appears to decrease the pain of chronic pancreatitis. Its action is mediated by suppressing pancreatic secretion, hence resting the pancreas. The role of octreotide remains uncertain.

Administration of high-potency, enteric-coated pancreatic enzymes remains the main therapy for the treatment of steatorrhea in the majority of patients with idiopathic and alcoholic pancreatitis. This will improve fat digestion, increase absorption and allow weight gain, although it will not correct the steatorrhea completely. Azotorrhea is more easily



reversed than steatorrhea, since trypsin is more resistant to acid inactivation than lipases. It seems that the most important barrier preventing correction of steatorrhea is the destruction of enzymes in the stomach, which prevents the delivery of enough active enzyme into the duodenum.

Replacement pancreatic enzymes are made from hog pancreas and contain a mixture of proteases, lipase and amylase, along with a variety of enzymes normally present in pancreatic secretions. Different preparations vary in the amount of lipase activity and the method of enzyme delivery (e.g., tablets, capsules or enteric-coated microspheres). Treatment with these enzymes is lifelong. Pancreatic enzymes are inactivated by pH 4 or below; hence, enteric-coated preparations such as Pancrease® or Cotazym® may be appropriate. In patients who do not respond well, the use of proton pump inhibitors or antacids with meals may overcome the detrimental effect of acid on the enzymes. The causes of failure to respond to pancreatic enzyme supplementation are shown in Table 13.

Table 13. Causes of failure of pancreatic replacement

-
- Incorrect diagnosis (nonpancreatic causes of steatorrhea, such as sprue, bacterial overgrowth)
 - Poor compliance
 - Incorrect timing of the medication (should be given with meals)
 - Variability in the enzyme content of the pancreatic replacement or loss of potency of the enzyme (inadequate amount of enzymes)
 - Inactivation of the enzymes by gastric juices or by sunlight
-

Hypersensitivity to pancreatic enzymes has been reported in patients who have hypersensitivity to pork proteins. Hyperuricosuria may occur in patients receiving high doses of pancreatic extracts, although recent reports have questioned this relationship. There appears to be a relationship between urinary urate concentration and the severity of pancreatitis. It appears that oral pancreatic enzymes may bind to folic acid, thereby impairing its absorption, but the clinical significance of this is not clear. Fat-soluble vitamins (e.g., vitamins A and E) are poorly absorbed when steatorrhea exceeds 20 g of fat loss per day. Vitamin K is also malabsorbed, but bleeding is rare. Malabsorption of vitamin B₁₂ occurs up to 40% of patients with chronic pancreatitis, although vitamin B₁₂ deficiency is rare. This malabsorption is thought to be due to the failure of R factor to cleave from the vitamin B₁₂-intrinsic factor complex, resulting in failure to absorb vitamin B₁₂. Thus, multiple and lifelong vitamin supplementation may be necessary in these patients.

If a patient is found to have chronic pancreatitis relating to autoimmune pancreatitis disease management involves the use of glucocorticoids. There are no clear recommendations for glucocorticoid dose, although 30 to 40 mg of prednisone orally per day for four to eight weeks is reasonable. Repeat pancreatic imaging at one month to assess response. Once a response is observed, prednisone is tapered. Normalization of IgG4 may not be apparent for several months, although decreases may be seen within four weeks. Between 30% and 40% of patients experience a relapse after glucocorticoid therapy. If so, a repeat course of prednisone is indicated,



but patient should be tapered to a lower maintenance dose. Immunomodulators, such as azathioprine, have been used in a few steroid-dependent patients with success

5. Pancreatic Cysts

It is important to recognize and to treat pancreatic cysts to relieve the patient's symptoms, and to remove any premalignant conditions. While there are many causes of cystic or cyst-like lesions in the pancreas (Table 14), the cystic lesions of major interest and concern are serous, mucinous, intrapapillary mucinous tumour (IPMT) and pseudocyst (Table 15 and 16).

Table 14. Classification of cystic and cystic-appearing lesions of the pancreas

-
- Congenital true cysts
 - Polycystic disease
 - Von Hippel-Lindau disease
 - Cystic fibrosis
 - Dermoid cysts
 - Inflammatory
 - Pseudocysts
 - Abscess
 - Hydatid cyst
 - Angiomatous cysts
 - Cystic neoplasms
 - *Mucinous tumors*
 - Mucinous cystadenoma (macrocytic adenoma) and cystadenocarcinoma
 - Intraductal mucin hypersecreting neoplasm; "Mucinous ductal ectasia"
 - *Non-mucinous tumors*
 - Serous cystadenoma (microcystic adenoma)
 - Papillary cystic tumor
 - Cystic cavitation of pancreatic adenocarcinoma or lymphoma
 - Acquired cysts
 - Central cavitory necrosis
 - Pseudocyst
 - Parasitic cyst
 - Misdiagnosed non-pancreatic lesions
 - Splenic artery aneurysm
 - Choledochal cyst
 - Mesenteric cyst
 - Duodenal duplication cyst or diverticulum
 - Lesser sac biloma
 - Lymphangioma
 - Hypoechoic solid tumor
 - Metastases, with cystic component

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Table 15. Characteristics of pancreatic serous cystadenoma (SCA), mucinous cystadenoma (MCN), IPMT (Intraductal papillary mucinous tumor) and pseudocyst (PC)

Characteristic	SCA	MCN
○ Sex	- Female (2-3:1)	- Female (~100%)
○ Age	- 60s	- Adenocarcinoma (50s-60s) - Carcinoma (60s-70s)
○ Ethanol abuse	- No association	- No association
○ Pancreatic history	- Yes (uncommon)	- Yes (uncommon)
○ Malignant potential	- No (rare)	- Yes
○ Location	- Evenly distributed body/tail	- Body/tail
○ Locularity	- Multiple small	- multilocular
○ Calcifications	- Yes (central sunburst or stellate)	- Yes (peripheral, curvilinear)
	IPMT	PC
○ Sex	- Male (3-4:1)	- Male
○ Age	- 60s	- Variable
○ Ethanol abuse	- no association	- Yes
○ Pancreatic history	- yes (uncommon)	- Yes (uncommon)
○ Malignant potential	- yes	- No
○ Location	- head	- Head
○ Locularity	- multilocular	- Unilocular
○ Calcifications	- no	- No, unless associated with chronic pancreatitis

Adapted from: Scheiman JM. *AGA Institute Postgraduate Course* 2006: page 586.

Depending upon the type of cyst and their location in the pancreas, cysts may be treated by continued monitoring, drainage or pancreatic resection (Table 16).



Table 16. The therapeutic approach (monitor, drain, resect) for cystic lesions in the head, body, and tail of the pancreas

	Mucinous	Malignant	Serous	Pseudocyst
➤ Head	Monitor	Resect	Monitor	Drain
➤ Body	Resect	Resect	Monitor	Drain
➤ Tail	Resect	Resect	Resect	Resect

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6. Carcinoma of the Pancreas

The incidence of cancer of the pancreas has increased steadily over the past 25 years. In males it is the fourth commonest cancer causing death, exceeded only by cancers of the lung, colon and rectum, and prostate. In females it is the fifth commonest cause of death, with only cancers of the breast, colorectum, lung, and ovary/uterus being more frequent. The incidence is higher in males, with a sex ratio of two males to each female; peak incidence occurs in the fifth through seventh decade.

The overall five-year survival rate is less than 3%, and most patients who develop carcinoma of the pancreas die within six months of diagnosis. The poor prognosis in this condition is secondary to the inability to diagnose the carcinoma at an early stage. When symptoms present, the tumor is far advanced and often has metastasized to regional lymph nodes and to adjacent and distant organs, as shown in Table 17.

Table 17. Most common sites of metastases from pancreatic carcinoma

○ Local nodes ○ Liver ○ Peritoneum ○ Adrenal glands ○ Lung ○ Kidneys ○ Spleen ○ Bone

Ductal cell adenocarcinoma accounts for 90% of pancreatic tumours. Approximately 5% of pancreatic carcinomas are of islet cell origin; the rest consist of cystadenocarcinoma, giant cell carcinoma and epidemoid carcinoma. The head of the pancreas is the most common site of involvement, accounting for 70% of the cases, whereas the body and tail account for 20% and 10% of the cases, respectively. Hereditary pancreatitis appears



to carry a 40-fold increased risk of developing pancreatic cancer by 70 years of age; the risk seems to be associated with a paternal mode of inheritance.

Several etiological agents have been invoked in the pathogenesis of pancreatic carcinoma (Table 18), although most of the studies have not yielded consistent results. Epidemiologically, long-term cigarette smoking is a well-established risk factor. Two tobacco-specific nitrosamines have been proposed as causative agents in the pathogenesis of carcinoma. Little is known of the role of the pancreas in the metabolism of carcinogens involved in exocrine pancreatic carcinoma. High-fat or high-protein diets tend to stimulate CCK release from the duodenum, which in turn can cause pancreatic hypertrophy and may predispose to carcinoma, although the evidence is not convincing. Diabetics are at twice the risk of developing carcinoma of the pancreas as the general population. The mechanism of this is not known. There is no evidence to suggest that alcoholic chronic pancreatitis predisposes to carcinoma. A recent study has shown a four- to five-fold increase in pancreatic carcinoma in individuals exposed to DDT (dichlorodiphenyltrichloroethane). Some epidemiological studies have suggested an increased rate of pancreatic carcinoma in patients who drank chlorinated water; this remains to be proven.

Table 18. Putative causes/associations of pancreatic cancer

-
- Hereditary pancreatitis
 - Cationic trypsinogen (CT)
 - CF
 - SPINK
 - Polyp syndromes
 - FAP
 - HNPCC-Lynch mismatch MLH1, MSH2, BRCH2
 - HNPCC
 - Peutz-Jeghers syndrome
 - Cowden syndrome
 - Genetic abnormalities
 - Familial atypical mole and multiple melanoma (FAMMM): germline p16 mutation
 - Hereditary breast cancer: germline BRCA2 mutation
 - Oncogenes - K-RAS mutations (90%) and p53 (70%) indicate tumor induction by exogenous carcinogens
 - Inactive tumor suppression gene (p59, p16 [DKN2A])
 - Familial pancreatic cancer
 - Familial ovarian and breast cancer
-



-
- Drugs/Diet
 - Risk factors are smoking, alcohol, and high-saturated fat/low vegetable/low vitamin diet
 - 7-fold increased risk after exposition to dichlorodiphenyltrichloroethane or deviates (e.g. ethylene)
 - Metabolic
 - Chronic pancreatitis
 - Diabetes
 - Partial gastrectomy
 - Miscellaneous
 - Diabetes mellitus
 - Cystic fibrosis
 - Fanconi anemia
 - Familial adenomatons polyposis
 - Ataxia telangiectasia
 - Neurendocrine tumors
-

Adapted from: Keller J, et al. *Best Practice & Research Clinical Gastroenterology* 2007; 21(3): page. 522.

Genetic defects such as K-ras oncogene, and tumor-suppressor genes including p16, DPC4 and p53 have been proposed to be involved in the pathogenesis of pancreatic carcinoma. Attempts to use the presence of these gene mutations in the diagnosis of occult pancreatic carcinoma seem to be vulnerable to a high false-positive rate.

6.1 Clinical Manifestations

The major symptoms of pancreatic carcinoma include pain, jaundice and weight loss. Rapid and progressive weight loss is probably the commonest symptom of carcinoma of the pancreas, and is not related to the location or to the extent of the tumor.

Most (up to 90%) of the patients suffer from pain during the course of the disease. The pain frequently is a dull aching or boring. Located in the epigastrium, it radiates to the back and increases in severity at night. Depending on the site of the tumor, the pain may radiate to the right or left upper quadrant. Unrelenting pain results from retroperitoneal extension, with invasion of the neural plexuses around the celiac axis.

Jaundice may be the presenting symptom in up to 30% of the patients, and the incidence increases as the disease progresses. It may be associated with pain and pruritus. Jaundice is more common when the head of the pancreas is involved, but obstruction or jaundice can occur secondary to spread to the liver or to lymph nodes around the bile duct. Other nonspecific symptoms include bloating, nausea and vomiting, weakness and fatigue, and diarrhea.



6.2 Signs

The commonest finding in carcinoma of the head of the pancreas is jaundice, with abdominal tenderness and an enlarged liver. Less common signs include a palpable gallbladder, abdominal mass, and edema. Thrombophlebitis occurs in less than 10% of the patients.

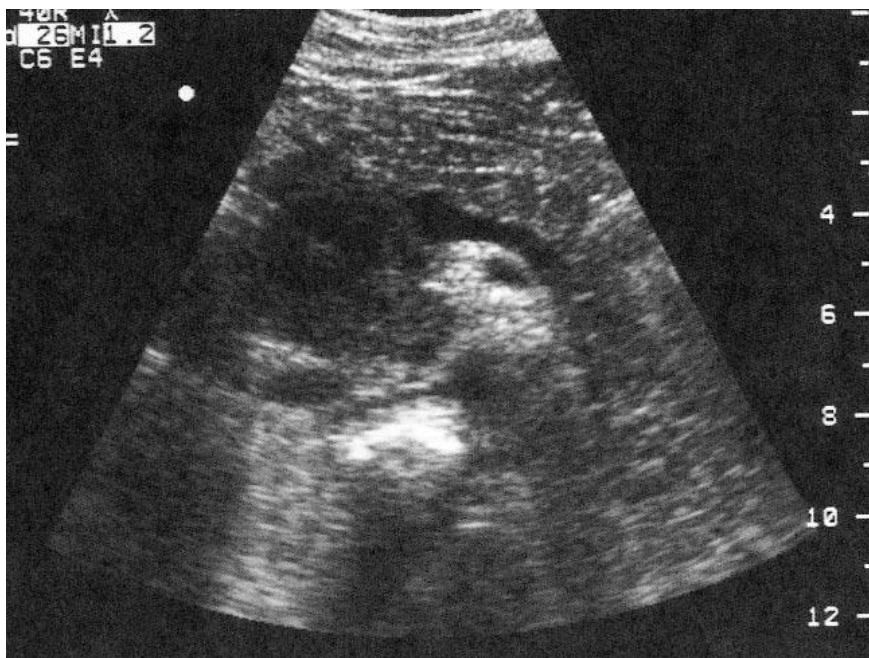


Figure 8. Pancreatic head carcinoma. Transverse sonogram shows the confluence of splenic vein and portal vein. The pancreatic body and tail are normal. The head is enlarged and bulbous with an abnormal texture, appearing hypoechoic on the image.

The development of diabetes in a middle-aged man or elderly patient with no family history of diabetes should suggest pancreatic carcinoma, especially when this is associated with abdominal pain or weight loss.

6.3 Diagnostic Evaluation

Laboratory tests are often normal or nonspecific. Serum alkaline phosphatase and bilirubin are elevated when the bile duct is obstructed or there are hepatic metastases. Serum amylase may be moderately elevated but also may be normal. Pancreatic secretory studies are not often helpful, since findings overlap with those of chronic pancreatitis.

Several tumor markers have been detected in the sera of patients with pancreatic carcinoma. CA19-9 is the most widely studied pancreatic tumor marker. Its importance and significance in the management of pancreatic cancer are unclear. This marker may be useful as an adjunct in the diagnosis, selection of therapy and postoperative follow-up of patients with pancreatic cancer. Other serum markers include pancreatic



oncofetal antigen (POA), α -fetoprotein (AFP), carcinoembryonic antigen (CEA), and pancreatic cancer-associated antigen. These tests are nonspecific and not sensitive enough for screening purposes. Cytologic specimens can be obtained by percutaneous needle aspiration under ultrasound or CT guidance and by aspiration of duodenal or pancreatic juices at ERCP or EUS. Positive cytology may guide further management; on the other hand, negative cytology does not rule out the disease.

Ultrasonography is the initial procedure of choice for detecting pancreatic cancer (Figure 8). However, its usefulness is dependent on the examiner's expertise. Examination may be less than optimal in the presence of increased bowel gas. The sensitivity of this test in pancreatic cancer is reported to be 76–94%, with a specificity of 96%. Once a lesion is detected, a guided biopsy may be helpful in establishing the diagnosis. When obstructive jaundice is present, ultrasound may reveal the presence of hepatic lesions or obstruction of the biliary tree. This procedure is simple and involves no radiation exposure.

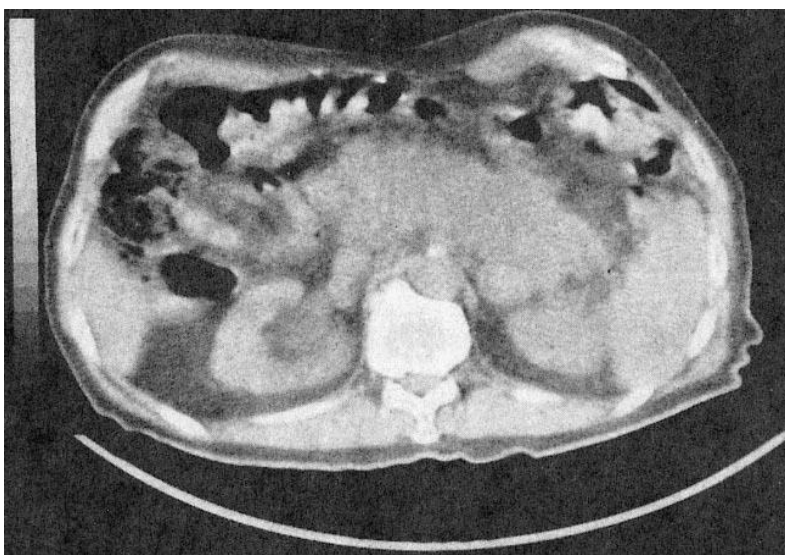


Figure 9. Computerized tomography showing a cancer in the head and body of the pancreas. The tumour is overlapping the superior mesenteric artery posteriorly.

CT is more accurate and gives more information than ultrasonography for diagnosis and staging pancreatic carcinoma (Figure 9). In contrast to ultrasonography, with this technique bowel gas does not interfere with the resolution. Unfortunately, CT has limitations in detecting early small cancer and small metastases to lymph nodes, liver and peritoneum. Helical CT scan, has the capability of producing precise images of the major pancreatic vessels (celiac, superior mesenteric arteries and their branches, and the superior mesenteric veins and their tributaries). This technique detects vascular involvement with great accuracy, hence predicting tumor resectability and retroperitoneal invasion (Figure 10). A guided biopsy of the lesion is also possible. Endoscopic ultrasonography (EUS) in combination with guided fine-needle aspiration has become a useful tool in the evaluation of focal pancreatic



lesions. Its overall accuracy in detecting parenchymal lesions and lymph node involvement is about 84%.

When there is a clinical suspicion of a pancreatic lesion and the ultrasound or CT scan is normal, an ERCP is helpful. It has the advantage of combining gastroduodenoscopy, cholangiography and pancreatography. The papilla may also be examined and cytologic sampling may be obtained. When obstruction is present, therapeutic drainage via stents may be attempted. Angiography is no longer used for diagnosing pancreatic carcinoma, but is still useful to evaluate patients who have known carcinoma for resectability, outlining vascular anatomy. Endoscopic ultrasound may further improve selection of patients who might benefit from curative surgery. Magnetic resonance imaging has no apparent advantage over CT.

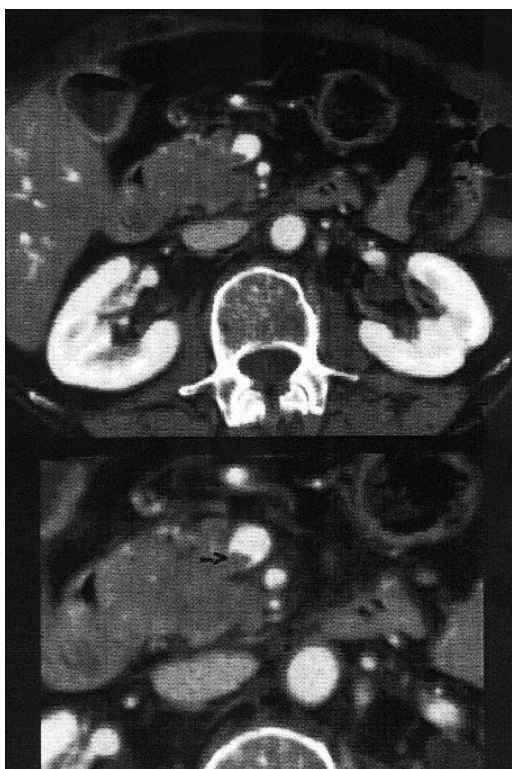
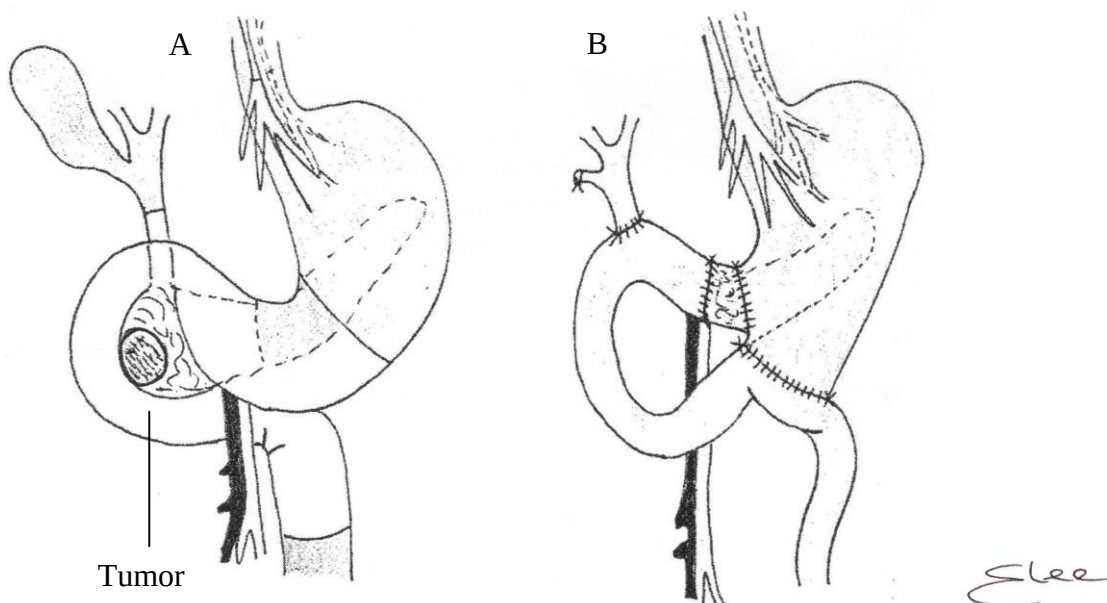


Figure 10. Pancreatic adenocarcinoma in the head with direct invasion into the superior mesenteric vein (Courtesy of Dr. A. Hanbridge).

6.4 Treatment

For localized cancers, surgical resection alone, such as pancreatectomy or pancreatoduodenal resection, offers the potential for long-term survival. Unfortunately, at the time of presentation, 75–80% of patients have an unresectable tumor. Despite this intervention, the disease carries a poor long-term prognosis, with a survival rate of 3% at five years. Factors that lead to a poor prognosis in pancreatic carcinomas include the presence of tumor in the lymph nodes and neural tissues, vascular invasion, tumor encasement of celiac or superior mesenteric artery, tumor size greater than 2.5 cm and histologically poorly differentiated tumor. Pancreatic surgery using the Whipple procedure should be done only in specialized centers where such an operation is performed by highly trained surgeons.





- A.
 - An en bloc resection of the distal stomach, duodenum, common duct, and head of the pancreas containing the pancreatic neoplasm is performed (areas removed are not shaded).
 - A cholecystectomy and truncal vagotomy are also done.
- B.
 - Gastrointestinal continuity is restored by performing a pancreaticojejunostomy, a choledochojejunostomy, and a gastrojejunostomy.

Adapted from: Reber, H.A and Way, L.W: The pancreas. In Dunphy, J.E, and Way, L.,W [eds.]. *Current Surgical Diagnosis and Treatment*, 3rd Ed. Los Altos, Calif. Lange Medical Publications, 1977.

In such centers the mortality rate approaches 6%, as compared to nonspecialized centers where the mortality rate reaches 28%. The five-year survival rate in some recent studies appears encouraging.

Complications can occur in up to 20% of patients following pancreatoduodenectomy. These include delayed gastric emptying (20%), pancreatic fistula (14%), wound infection (10%), pancreaticojejunal leak, intra-abdominal sepsis, biliary anastomotic leak, gastrointestinal bleeding and other intra-abdominal hemorrhage. Factors favoring longer survival include jaundice at presentation, a small tumor mass, early tumor stage and a well-differentiated tumor. Palliative operations for unresectable tumor, such as alleviating biliary or duodenal obstruction, offer some relief. Surgery is frequently associated with high morbidity and mortality; hence, nonsurgical intervention may be preferable. Biliary obstruction can be relieved by percutaneous drainage or by endoscopic stenting of the bile duct. Unfortunately these stents tend to occlude and may require frequent changes.

Adjuvant chemotherapy in combination with radiotherapy, (5-fluorouracil (5-FU), has shown minimal effect in long-term survival. Irradiation therapy has been



advocated in treating larger tumors it may offer local control and pain management, although its benefit in longterm survival has not been proven.

For palliative chemotherapy of pancreatic cancer, Gemcytabine has shown a small statistically significant benefit over 5FU in overall survival, and an approximate 15% improvement in one year survival for advanced pancreatic cancer. It is the recommended palliative chemotherapy in advanced pancreatic cancer.

7. Pancreatic Islet Cell Tumors

There are numerous types of pancreatic neuroendocrine tumors (Table 19). The most common of these rare tumors is insulinoma and gastrinoma, with an annual incidence of approximately $1/10^6$. The rate of malignancy is over 50% in these pancreatic islet cell tumors, except for insulinoma (~10%) and GRFoma (>30%).

Table 19. A comparison and contrast of the incidence, symptoms and signs, rate of malignancy, hormone causing symptoms and signs, and frequency of Multiple Endocrine Neoplasia (MEN-1) in insulinoma, gastrinoma, VIPoma, glucagonoma, somatostatinoma, GRFoma ACTHoma and PEToma

Tumor syndrome	Primary symptoms/signs (approximate frequency, %)
➤ Insulinoma	○ Hypoglycemic symptoms (100)
➤ Gastrinoma, Zollinger-Ellison syndrome	○ Abdominal pain (75) ○ Diarrhea (65) ○ Dysphagia/pyrosis GERD (20)
➤ VIPoma, (Verner-Morrison syndrome, WDHA, pancreatic cholera)	○ Diarrhea, dehydration (100) ○ Hypokalemia (95) ○ Hypochlorhydria (30) ○ Flushing (20)
➤ Glucagonoma	○ Dermatitis (80) ○ Weight loss (70) ○ Diarrhea (15)
➤ Somatostatinoma	○ Diarrhea (70)
➤ GRFoma	○ Acromegaly ○ Abdominal pain
➤ ACTHoma	○ Cushing's syndrome
➤ PTHoma causing hypercalcemia	○ Malignant tumor ○ Hypercalcemia



- Tumor syndrome
 - Primary symptoms/signs (approximate frequency, %)
- Carcinoid syndrome
 - Diarrhea
 - Flushing
 - Hypertension
- PEToma (secreting: rennin)
- Erythropoietin
 - Polycythemia

Abbreviation: GRF, growth hormone releasing factor.

Adapted from: Jensen, Robert T and Horton, Jeffrey A. *Sleisenger & Fordtran's gastrointestinal and liver disease: Pathophysiology/Diagnosis/Management* 2006: 626.

Pancreatic islet cell tumors are divided into two types: (1) an endocrine type that elaborates excessive gastrointestinal tract hormones, causing specific clinical syndromes, and (2) a nonfunctioning type that is characterized by symptoms related to the size, location and invasion of the tumor mass. Patients with multiple endocrine neoplasm type 1 (MEN-1) and von Hippel-Lindau disease (VHL) are predisposed to develop pancreatic endocrine tumors. Pancreatic islet cell tumors have a better prognosis than those associated with ductal cell adenocarcinoma. They may be diagnosed by the classic clinical manifestation, by the detection of hormones in the serum and by dynamic CT scan with intravenous and oral contrasts.

Several pancreatic islet cell tumors have been identified. These tumors tend to elaborate a variety of biologically active peptides, resulting in a variety of clinical presentations. These peptides include glucagon, insulin, gastrin, vasoactive intestinal peptide (VIP), somatostatin and pancreatic polypeptide (PP).

Insulinoma is the most common neoplasm of the endocrine pancreas. The insulinoma syndrome is associated with Whipple's triad, which includes symptoms of (1) fasting hypoglycemia (confusion, seizures, personality changes, in addition to palpitation, tremulousness and diaphoresis), with (2) a low serum glucose level, and (3) a relief of symptoms by the administration of glucose. The diagnosis can be made by the demonstration of high serum insulin and low blood sugar, and an elevation in the insulin-to-glucose ratio (IG). The tumor may be localized by dynamic CT scan. Treatment includes surgery to remove the tumor if it is well localized or amenable to surgery, and prior to that, diet and medical therapy with diazoxide or octreotide to combat hypoglycemia.

Glucagon-secreting tumors (*glucagonomas*) arise from the alpha cells of the pancreas. Patients commonly present with mild diabetes, dermatitis, delayed gastric emptying, stomatitis, ileus and constipation. The dermatitis is manifested by a skin rash termed *necrolytic migratory erythema*, commonly appearing over the lower extremities. The diagnosis is established by the demonstration of elevated plasma glucagon levels



that increase, paradoxically, with challenge by intravenous tolbutamide. Glucagonoma tends to present with large tumors and can be demonstrated by dynamic CT scan.

Gastrin-secreting tumors (*gastrinomas*; Zollinger-Ellison syndrome) arise from nonbeta islet cells. They are frequently malignant and tend to be multiple. They commonly present with recurrent severe peptic ulceration accompanied by marked gastric acid hypersecretion and occasionally diarrhea. The diagnosis is established by the demonstration of marked fasting hypergastrinemia and marked gastric acid hypersecretion. In patients who have borderline increases in gastrin, provocative testing with secretin is indicated. Following secretin stimulation, gastrin levels increase in patients with gastrinoma, whereas in patients with common duodenal ulcer, gastrin levels may show a minimal increase, a decrease or no change. High levels of gastrin may be present in a condition known as G-cell hyperplasia. This can be distinguished from gastrinoma by the sharp rise in gastrin level ($> 200\%$) in response to meals. Patients with gastrinoma show minimal or no rise in gastrin level.

Vasoactive intestinal peptide-secreting tumors (*VIPoma*; Werner-Morrison syndrome) produce the pancreatic cholera syndrome, which is characterized by severe diarrhea, hypokalemia and hypochlorhydria or achlorhydria. Fluid secretion may exceed 3–5 L, with a loss of 200–300 mEq of potassium daily. Although the diagnosis is established by the demonstration of high levels of VIP, other substances, such as prostaglandins and secretin-like substances, may contribute to this syndrome.

Somatostatin-producing tumors (*somatostatinomas*) are the least common of pancreatic islet cell tumors, so by the time of diagnosis they tend to be malignant and have usually metastasized. They commonly present with mild diabetes mellitus, gallstones with a dilated gallbladder, anemia, hypochlorhydria and malabsorption. The diagnosis is established by the demonstration of high serum levels of somatostatin.

Pancreatic polypeptide-producing tumors have not been shown to produce any clinically defined syndrome.

7.1 Treatment

Pancreatic endocrine tumors are ideally treated by resection. Unfortunately, despite all our available techniques, up to 40% of these tumors tend to escape localization. These tumors tend to be single or multiple and may be located in any portion of the pancreas or ectopically in the duodenum or any other part of the gastrointestinal tract. **Both** octreotide scintigraphy, and more recently, endoscopic ultrasound have shown promise in detecting endocrine islet cell tumors, which appear to have somatostatin receptors. In octreotide scintigraphy, radiolabeled somatostatin analogues bind to these receptors and can be demonstrated by gamma camera scintigraphy. This test offers some hope in differentiating endocrine versus ductal cell tumors. It may assist the surgeon in delineating and removing the tumor and possibly the metastatic lesions.



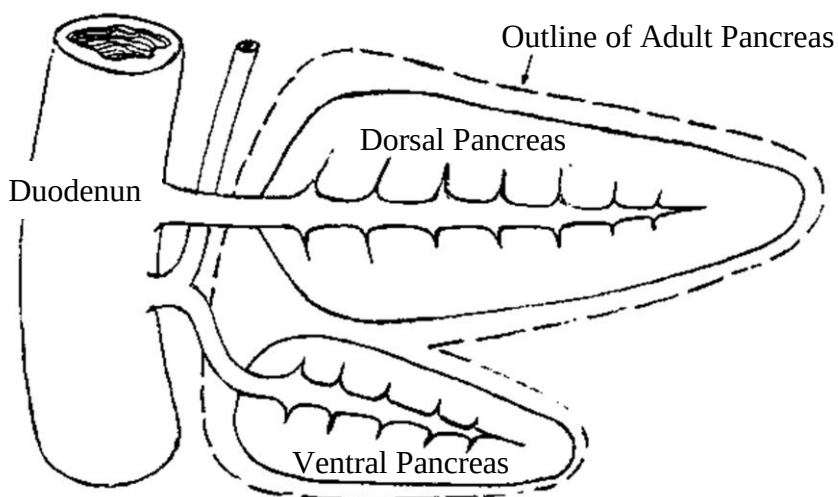


Figure 11. Pancreas at approximately 7 weeks fetal life.

8. Pancreatic Divisum

Pancreas divisum is the most common variant of human pancreas, occurring in nearly 10% of the population. This anomaly results from the failure of fusion of the dorsal and ventral pancreatic ducts, which usually occurs in the second month of fetal life. This results in the drainage of the main pancreatic duct (including the superior-anterior aspect of the head, the body and the tail) into the dorsal duct via the accessory papilla. The ventral duct, which drains the posterior-inferior aspect, joins the common bile duct and empties into the major papilla (Figure 11). The diagnosis of this condition is made by ERCP.

Most patients having this anomaly are symptom-free, although some reports have suggested a high incidence of abdominal pain and pancreatitis. It has been suggested that the relative stenosis of the accessory papillary orifice, the major outflow tract for pancreatic secretions, is the cause of problems.

Endoscopic minor papilla sphincterotomy as well as dorsal duct stent placement have been studied and shown promise as therapy for this developmental anomaly.

9. Cystic Fibrosis in The Adult

Cystic fibrosis (CF) is no longer solely a paediatric disease. CF is the most common potentially lethal genetic disease affecting Caucasians. Its incidence shows regional variations, but overall incidence in Caucasians is approximately 1 per 2,500 live births; it is inherited as an autosomal recessive trait. CF is also the most common cause of chronic lung disease and pancreatic insufficiency in patients under the age of 20. It is practically unknown among North Americans of African origin, with an incidence of less than 1 in 99,000 among Asian Americans.

Over the past decade the fundamental biochemical defect in CF has been identified. The gene has been cloned and up to 300 alleles have been discovered. The



gene product is a protein called the cystic fibrosis transmembrane conductance regulator (CFTR) and is present on the long arm of chromosome 7. This regulator, the main chloride transport system, is defective in individuals with CF. The regulator is synthesized within the epithelial cell, then transported to the apical cell membrane of the epithelial duct cells of the proximal pancreatic duct. The commonest mutation in CF is that of a three-nucleotide base pair deletion that results in a missing phenylalanine at position 508 in the first nucleotide binding fold. This mutation is often referred to as delta F508. Its main function is to act as a chloride channel that is activated through cAMP-mediated phosphorylation, thus allowing secretion of chloride ions into the pancreatic duct or to the skin through the sweat glands. In addition to CFTR, these cells contain $\text{Cl}^-/\text{HCO}_3^-$ exchangers, which are responsible for bicarbonate secretion and are dependent on luminal chloride, which is supplied by cAMP-activated chloride channels. Thus, in CF, altered chloride secretion results in decreased bicarbonate production and ultimately failure to adequately hydrate and alkalinize the concentrated protein secretions of the acinar cells. This proteinaceous material becomes inspissated, resulting in ductal obstruction and ultimately acinar cell destruction, fibrosis and malabsorption. The decrease in bicarbonate secretion also results in failure to neutralize duodenal acid, thus leading to further malabsorption by decreasing lipase activity and altering the bioavailability of enteric-coated enzyme supplement.

The “classic” picture of a chronically malnourished child with progressive lung disease and pancreatic dysfunction culminating in early death is an oversimplification. CF should now be regarded as a syndrome with a heterogeneous assortment of presentations involving variable degrees of organ dysfunction and damage. Pulmonary disease and its complications still dominate the clinical picture in most patients, and are the primary determinants of overall morbidity and mortality. However, as many as 20% of CF patients are not diagnosed until after the age of 15 because they have atypical presentation (e.g., recurrent sinusitis, nasal polyps, chronic bronchitis, recurrent abdominal pain, loose, foul-smelling stools, cirrhosis and infertility).

The advent of vigorous physiotherapy, more effective antibiotics, improved pancreatic extracts and continuing care in specialized CF clinics has resulted in a median survival of at least 18 years. Indeed, in many CF centers, half the patients survive 26 years, and up to 90% of patients may live more than 18 years after the diagnosis has been made. With such increased survival, gastrointestinal complications are becoming increasingly common.

Abnormalities have been identified in glycoproteins, mucus secretions, circulating proteases and cell transport mechanisms. Liver and biliary tract disease may occur in individuals with CF. The incidence of biliary cirrhosis reaches 14% during the second decade of life in those who have pancreatic insufficiency. In these individuals subclinical hepatic involvement, manifested as biochemical or ultrasound abnormalities of the liver, is common. High losses of sodium and chloride through sweating during periods of heat in the summer months can lead to sodium depletion, dehydration, cardiovascular collapse and death. The abnormally thick mucus produced obstructs ductules and tubules, and results in distal organ damage, which leads to chronic



obstructive lung disease, pancreatic insufficiency, hepatic fibrosis and intestinal obstruction. The mucosal and submucosal glands of the small intestine are dilated, with acidophilic concretions. Steatorrhea and enteral protein loss result from exocrine pancreatic failure, low duodenal pH and perhaps also impaired absorption of fatty acids. These patients require supplementation with fat-soluble vitamins A, D, E and K.

Abdominal pain is common in CF patients. It may be related to steatorrhea, constipation, meconium ileus equivalent, intussusception, cholelithiasis, duodenal ulcers or pancreatitis. In contrast to infants and children, adults are less affected by malabsorption, although close questioning may reveal that they experience cramps, flatulence and frequent, greasy, foul-smelling, bulky stools.

8.1 Complications

There are a number of gastrointestinal, hepaticopancreaticobiliary as well as non-GI manifestations of cystic fibrosis (Table 20). Most CF patients have height and weight levels that are less than the mean for their age and sex. Although during adulthood nutritional status declines progressively with advancing age, not all patients are malnourished at the time of diagnosis or in early adulthood. In early adulthood, some 10% of patients are above the 90th percentile, while others are even overweight.

Table 20. GI and Hepatobiliary clinical manifestations of CF

- Gastrointestinal
 - Gastroesophageal reflux
 - Peptic ulcer disease
 - Fat malabsorption
 - Meconium ileus
 - Volvulus
 - Ileal atresia
 - Distal intestinal obstruction syndrome (meconium equivalent)
 - Fecal masses
 - Intussusception
 - Constipation
 - Impaction
 - Rectal prolapse
 - Hemorrhoids
 - Peritonitis
- Pancreas
 - Nutritional failure caused by pancreatic insufficiency
 - Diabetes
 - Calcification
 - Maldigestion
 - Fat soluble vitamin deficiencies
 - Steatorrhea and azotorrhea



- Hepatobiliary
 - Mucus hypersecretion
 - Gallstones, atrophic gallbladder
 - Focal biliary cirrhosis
 - Cirrhosis
 - Portal hypertension
 - NAFLD
 - Hepatomegaly
 - Premature death

Non-GI/Hepatobiliary manifestations of cystic fibrosis in the adult.

- Respiratory
 - Sinusitis
 - Nasal polyposis (secondary to mucous membrane hypertrophy)
 - Lower respiratory infections
 - Bronchiectasis
- GU
 - Male infertility (sterility; congenital absence of vas deferens, epididymis, and seminal vessels)
 - Female infertility (increased viscosity of vaginal mucous)
- Nutrition
 - Clubbing
 - Short stature
- Premature death
- Reproductive
 - Female gender
 - Increased viscosity of vaginal mucus and decreased fertility
 - Male gender
 - Sterility: absence of ductus deferens, epididymis and seminal vesicles
- Skeletal
 - Retardation of bone age
 - Demineralization
 - Hypertrophic pulmonary osteoarthropathy
- Ophthalmic
 - Venous engorgement
 - Retinal hemorrhage
- Other
 - Salt depletion through excessive loss of salt via the skin
 - Heat stroke
 - Hypertrophy of apocrine glands



There is no correlation between the patient's nutritional status and the severity of the steatorrhea or gastrointestinal symptoms, or age at diagnosis. The height and weight attained seem to correlate only with the severity of the pulmonary disease; those individuals with the least pancreatic insufficiency tend to have better preservation of pulmonary function.

Pancreatic insufficiency markedly overshadows the other GI complications of CF. In spite of the clinical impression of a voracious appetite, overall energy intake in the CF patient is usually inadequate. Maldigestion and malabsorption, along with the increased energy requirements associated with pulmonary disease, further compound the energy problem.

CF patients also show biochemical evidence of essential fatty acid deficiency. Improvement may be achieved with oral linoleic acid monoglyceride or with total parenteral nutrition. Essential fatty acid deficiency is associated with impaired intracellular oxygenation, decreased membrane fluidity and impaired transport mechanisms. It has not yet been established, however, what benefit will be derived by treating and preventing essential fatty acid deficiency.

In addition to the problems of essential fatty acid and energy deficiency, there is a third major problem in the nutrition of the CF patient: deficiency of fat-soluble vitamins. Even with a standard supplementation of vitamin A 4,000 IU/day, vitamin A levels, retinol binding protein levels and serum carotene may remain low. Approximately 25% of patients have evidence of vitamin D deficiency. Otherwise, the management of pancreatic insufficiency in adults with CF is similar to the management of pancreatic insufficiency due to other conditions. About half of the adults with CF show some degree of glucose intolerance. Diabetes mellitus in this instance is controlled with insulin, and because glucagon levels are decreased, ketoacidosis is extremely uncommon. The presumed pathogenesis of the pancreatic islet cell dysfunction is fibrosis-induced islet cell disarray and strangulation.

Meconium ileus is seen in approximately 10% of neonates with CF and is primarily related to the secretion of abnormal mucinous (glycoprotein) material by the intestinal glands. Children, adolescents and adults have a counterpart, termed *meconium ileus equivalent*, that is characterized by recurrent episodes of intestinal obstruction. Typically, there is colicky abdominal pain, a palpable, indentable right lower quadrant mass and evidence of mechanical obstruction. Constipation is considered a milder form of this disorder, and must be differentiated from intussusception, which occurs in a small number of CF patients. There is usually a history of precipitating cause, such as immobilization, use of antidiarrheal agents, dietary indiscretions, or reduction or abrupt discontinuation of oral enzyme therapy.

The diagnosis of meconium ileus equivalent is suggested by the presentation. Plain abdominal radiographs may show an empty colon with bubbly granular material proximally, and ileal distention with air fluid levels. It is necessary to confirm the diagnosis by early fluoroscopy guided Gastrografin® enema studies because of the high mortality of this condition and the need to rule out intussusception. Nasogastric suction and correction of electrolyte imbalance result in resolution of the obstruction in 80% of cases. Decompressive surgery may be necessary if medical management fails.



Pancreatitis is relatively uncommon in CF patients, but tends to occur in those patients (some 15%) whose pancreatic function is initially normal. The pathophysiology of the pancreatitis is presumably related to precipitation of abnormal secretions in the tubules, with subsequent damage. Biliary tract disease and alcohol are other possible causes of pancreatitis in these patients.

An increase in the incidence of duodenal ulcer might be expected in CF patients because of the loss of pancreatic bicarbonate buffer, but in fact duodenal ulcer is uncommon.

Patients with untreated pancreatic insufficiency commonly have profound malabsorption of bile acids in the terminal ileum and fecal losses of bile acids. This interrupts the normal enterohepatic circulation of bile acids. The etiology of bile acid wastage is unknown, but it probably relates to the presence of steatorrhea, with bile acid binding to undigested fat, fiber and other intraluminal contents. As a result of the excessive fecal bile acid loss, there is a decrease in the total bile acid pool; the bile becomes saturated with cholesterol. Up to 60% of adolescents and adults with CF have gallbladder abnormalities (e.g., cholelithiasis, nonvisualization, microgallbladder, and marginal filling defects or septation). There is a high incidence of both gallbladder abnormalities and abdominal pain in these patients, but there is not necessarily a cause-effect relationship between the cholelithiasis or gallbladder abnormalities and the clinical symptoms. The hazards of surgery must be weighed against the hazards of nonoperative intervention. The structure and function of the gallbladder may be evaluated by ultrasonography and oral cholecystography.

Treatment of pancreatic insufficiency with oral enzymes will decrease bile acid loss, thus correcting the lithogenic nature of the bile. However, the abnormal glycine:taurine ratio and the preponderance of cholic and chenodeoxycholic acid persist despite enzyme replacement. Ursodeoxycholic acid therapy remains experimental.

With increased age and survival, liver disease is becoming increasingly prevalent in CF patients. The most common hepatic lesion in CF is steatosis, secondary to decreased circulating lipoprotein levels and decreased hepatic triglyceride clearance. Other hepatic lesions seen include nonspecific portal changes, excessive biliary ductal mucus, mild ductal proliferation and focal biliary cirrhosis. A small number of these patients will develop multilobular biliary cirrhosis, the progression remaining clinically silent until portal hypertension supervenes with classical presentation of ascites, hypersplenism or variceal bleeding. Hepatic decompensation and portosystemic encephalopathy are extremely uncommon because of the relative hepatic parenchymal integrity and the overall focal nature of the pathology. The only clinical clue is the development of a hard, knobby liver, while liver biochemical tests remain relatively normal. The results of therapeutic portacaval anastomoses are encouraging, with no development of portosystemic encephalopathy.



9.2 Diagnosis

Classical CF in infants and children is easy to diagnose. However, diagnosis of CF is more difficult in adults and in mild or atypical cases. The cornerstone of diagnosis is the quantitative pilocarpine iontophoresis sweat chloride test. This should be performed on two separate occasions, using a sample of 100 mg of sweat or more. Chloride levels that are continually above 60 mEq/L are virtually diagnostic. Such levels are not found with other chronic pulmonary or gastrointestinal tract diseases. Sweat chlorides may, however, occasionally reach 60 mEq/L or more in a variety of other disorders, including untreated adrenal insufficiency, hereditary nephrogenic diabetes insipidus, hypothyroidism, and a variety of genetic mucopolysaccharide disorders.

Sweat chloride testing should be performed in infants and children with chronic pulmonary disease, meconium ileus, steatorrhea, rectal prolapse, failure to thrive, heat prostration or pansinusitis, and in siblings of affected individuals. In addition, children, adolescents and young adults should be screened if they have any type of chronic liver disease, long-standing gastrointestinal complaints, childhood or cryptogenic cirrhosis, aspermia or malabsorption.

9.3 Treatment

Pancreatic enzyme replacement is the mainstay of treatment in patients with CF who suffer from pancreatic insufficiency. Enteric-coated enzymes ideally should be used, since they are not inactivated by gastric acids. Ultimately these enzymes could be used in combination with an H₂ blocker. At least 30,000 USP units of lipase should be administered and taken together with food.

Hyperuricosuria may occur in these patients secondary to the large purine content in the enzyme preparation. This complication can be controlled by decreasing the dose of the enzymes.



Chapter 20: Nutrition in Gastrointestinal Disease

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1. Introduction

Food assimilation is the major function of the gastrointestinal tract. Many gastrointestinal diseases have important nutritional effects. Digestion and absorption of nutrients are discussed elsewhere. This chapter reviews physiologic considerations that are essential for planning proper nutritional management. The focus will be on the role of the liver in regulating the supply of carbohydrate and lipid fuels as well as ensuring the availability of essential substrates to peripheral tissues. The clinical features of malnutrition and specific effects of malnutrition on the gastrointestinal tract and liver will be discussed along with diet therapy in gastrointestinal disease. Finally, an approach to clinical nutrition will be presented, including nutritional assessment and the rational use of enteral and parenteral nutritional support.

2. Essential Physiologic Concepts in Nutrition

To maintain a continuous supply of nutrients in the bloodstream in the face of intermittent dietary intake, a complex set of regulatory mechanisms have evolved. These allow the storage of nutrients during feeding, and their release from storage pools during the interdigestive period so as to maintain nutrient levels in the bloodstream within remarkably narrow limits. Short-term regulation between the fed state and the interdigestive state is mediated principally by (Goldwasser 1997) the concentration of several key substrates and (Klein 2002) a set of regulatory hormones, which include insulin, glucagon, catecholamines and corticosteroids (Table 1).

Table 1. Hormonal regulation of nutrient metabolism

Hormone	Principal metabolic actions
➤ Insulin	○ Increases glucose uptake in peripheral tissues ○ Stimulates protein synthesis ○ Inhibits lipolysis and glycolysis ○ Increases amino acid uptake into muscle (particularly important post-exercise)
➤ Glucagon	○ Increases cyclic AMP levels in the liver and adipose tissue, with stimulation of fatty acid mobilization, glycogenolysis, glycolysis and gluconeogenesis, thereby increasing plasma glucose
➤ Catecholamines	○ Increase cyclic AMP levels in the liver, skeletal muscle and adipose tissue, with release of glucose, free fatty acids and lactate
➤ Corticosteroids	○ Increase gluconeogenesis ○ Increase amino acid mobilization from the periphery (chiefly skeletal muscle) ○ Increase fatty acid release from extremities ○ Decrease glucose utilization by peripheral tissues by increasing post-receptor insulin resistance ○ Increase glucagon release



Taken together, the actions of glucagon, catecholamines and corticosteroids work to increase plasma glucose and free fatty acid levels in direct opposition to insulin. Therefore, the release of these hormones, which occurs in response to low glucose levels and/or stress, leads to insulin resistance.

Glucose is rapidly absorbed following ingestion as starch, disaccharides or a monosaccharide. The glucose is transported via the portal system to the liver, which extracts a considerable fraction of portal venous glucose. The remainder enters the systemic circulation and causes pancreatic secretion of insulin. The high portal vein insulin and glucose concentrations lead to hepatic glucose uptake with conversion to glycogen and fatty acids. The peripheral rise in insulin, which occurs in association with the rise in plasma glucose concentration, causes a large peripheral uptake of glucose, first by muscle cells, and second by adipocytes. Glucose is the essential substrate for brain, renal medulla and red cell metabolism; other organs mainly use fatty acids for energy. The rise in plasma insulin also leads to amino acid uptake by muscle and has an antiproteolytic effect. These effects on muscle protein have led to the designation of insulin as an “anabolic hormone.” In the postabsorptive or interdigestive state, plasma glucose is low, with low plasma insulin levels. The low plasma insulin influences the metabolism of all three macronutrients (i.e., carbohydrates, fat and protein). Glycogenolysis occurs in the liver to maintain plasma glucose levels. The low plasma insulin also allows lipolysis to take place, such that fatty acids can be utilized as the major energy substrate. Finally, the low plasma insulin leads to proteolysis, particularly of muscle protein, which leads to release of alanine and glutamine, which can be used for gluconeogenesis in the liver. This gluconeogenesis occurs in concert with glycogenolysis to ensure an ongoing supply of glucose for the body.

Other hormones, such as glucagon, catecholamines and growth hormone, play less important roles in macronutrient metabolism, but in general have been termed the “stress hormones,” since they are released during times of stress and have anti-insulin effects. In particular, if for any reason there is a low blood sugar, all these hormones are released and will promote an elevation in plasma glucose.

The flux of lipid nutrients in the fed and the interdigestive states is contrasted in Figure 2. In the fed state, fat enters the circulation from the intestine as chylomicrons, which are large droplets of triglyceride emulsified by a surface mono-layer of phospholipid and apolipoproteins. Additional apolipoproteins are transferred onto the chylomicrons from HDL. The artificial fat emulsions used for parenteral nutrition are very similar to chylomicrons in that they contain a core of triglyceride with a surface monolayer of phospholipid. They initially contain no apolipoproteins, but acquire these from HDL very rapidly once they have entered the circulation. One of the apolipoproteins, apolipoprotein C-II, is particularly important in that it is an essential cofactor for the action of lipoprotein lipase. This enzyme is attached to the capillary endothelium in tissues, such as the heart and adipose tissue, that are active in utilizing fatty acids. Chylomicrons bind to the enzyme and the core triglyceride is rapidly hydrolyzed. The released fatty acids are then taken up and utilized in the peripheral tissues. As the chylomicron particle shrinks in size, the excess surface material is transferred back to HDL, and ultimately the remnant particles are cleared via a specific receptor in the liver. The process of lipolysis is extremely efficient, and the half-life of chylomicron triglyceride in the circulation is normally less than 15 minutes in the postabsorptive or interdigestive state. Chylomicrons are absent, but triglyceride fuels are available in the circulation in the form of VLDL, which are secreted by the liver. The substrates for triglyceride assembly include free fatty acids



released from adipose tissue through the action of a hormone-sensitive lipase, and fatty acids synthesized in the liver from acetyl-CoA. The newly secreted VLDL acquire apolipoproteins and cholesterol ester from HDL. Lipolysis of VLDL in peripheral tissues is mediated by lipoprotein lipase. As the particle decreases in size, free cholesterol transfers to HDL, where it is esterified through the action of lecithin-cholesterol acyltransferase (LCAT), and the resultant cholesterol ester is then transferred back to the lipolyzed particle, where it forms part of the core. When lipolysis is completed, what is left behind is termed an LDL particle. This is smaller and denser than VLDL, has lost all apolipoproteins except apolipoprotein B, and has a core of cholesterol ester rather than triglyceride. LDL is cleared relatively slowly, with a half-life of several days. The uptake of LDL is mediated by a specific membrane receptor, termed the LDL receptor, whose activity in turn is regulated by intracellular cholesterol levels. The most active tissues (on a weight basis) for LDL clearance are steroidogenic tissues, such as the adrenals, gonads and the liver; because of its size, the liver accounts for over half of total LDL catabolism. As peripheral tissues cannot degrade cholesterol, excess cholesterol is returned to the liver via HDL, where it is used for bile acid synthesis or excreted in the bile.

Starvation leads to a number of adaptive responses. There is a depletion of liver glycogen within 24 to 48 hours, with stimulation of gluconeogenic enzymes to allow the production of glucose from amino acids released through protein breakdown in skeletal muscle. Lipolysis in adipose tissue leads to increased fatty acid levels and activation of enzymes responsible for β -oxidation of fatty acid in the liver (acyl-CoA-carnitine acyltransferase). In addition to acetyl-CoA, fatty acid oxidation generates ketone bodies. One important adaptive response to starvation is the induction of 3-hydroxybutyrate dehydrogenase in the brain, which allows this organ to utilize ketone bodies as a fuel. Decreased dependence on glucose reduces the need for excess gluconeogenesis and spares muscle protein. In a relatively lean 70 kg man with 12% body fat, survival without food can be expected to be about 60 days or longer.

3. Clinical and Laboratory Features of Protein- Energy Malnutrition

Protein-energy malnutrition may result from a number of causes. These are shown in Table 2. Intake or assimilation may be impaired or, alternatively, losses may be increased, as occurs with excessive enteric protein loss in protein-losing enteropathies. In some disorders, multiple causes may be present. Moreover, requirements may be significantly increased in some patients as a result of growth, pregnancy, tissue injury or a superimposed disease process. In some patients with chronic debilitating diseases, multiple factors may be responsible.



Table 2. Causes of protein-energy malnutrition

-
- Impaired intake
 - Insufficient quantity or quality
 - Impaired intake due to systemic disease (e.g., cerebrovascular accident, chronic infections)
 - Impaired intake due to localized gastrointestinal disease (e.g., benign or malignant esophageal stricture)
 - Impaired digestion and/or absorption
 - Selective enzyme defect (e.g., enteropeptidase deficiency, trypsinogen deficiency)
 - Generalized enzyme defect (e.g., pancreatic exocrine insufficiency)
 - Impaired small intestinal assimilation (e.g., celiac disease)
 - Excessive enteric protein loss
 - Gastric or intestinal mucosal disease (e.g., Ménétrier's disease, intestinal lymphangiectasia)
 - Extraintestinal disease with lymphatic blockage (e.g., pericarditis, lymphoma)
 - Disorders with multiple causes
 - Advanced malignancy
 - Chronic renal failure with uremia
 - Other chronic debilitating diseases
-

Malnutrition has been classically divided into kwashiorkor (protein restricted) and marasmus (protein-calorie restricted). In kwashiorkor, the subject ingests a moderate number of calories, usually as complex carbohydrate (e.g., rice), but very little protein. The carbohydrate is absorbed as glucose, causing rises in plasma glucose and insulin, and leading to decreased lipolysis and proteolysis. The liver is therefore supplied with inadequate amino acids, with little oral intake and little peripheral mobilization from skeletal muscle stores. Transport of triglyceride made from ingested glucose is impaired since there is inadequate production of apoprotein, which is needed for the formation of VLDL. The liver becomes fatty and enlarged. Furthermore, other proteins, including albumin, are inadequately produced by the liver in kwashiorkor, and serum albumin falls, with resulting peripheral edema. With marasmus the subject takes inadequate amounts of protein and calories. The low caloric intake means that only small amounts of carbohydrate are taken; plasma glucose and insulin are low. Hence, lipolysis and proteolysis occur, with adequate delivery of amino acids from muscle to the liver for protein production. Fatty liver does not occur, and serum albumin levels tend to be normal, with no peripheral edema. Often patients fall between these two extremes of nutritional states, but there are examples of kwashiorkor and marasmus in Western clinical practice. Anorexia nervosa is a classic example of marasmus. Marked muscle wasting and loss of subcutaneous tissue (adipose tissue) occur with normal-sized nonfatty livers and no peripheral edema. In contrast, the intensive care unit patient who has received intravenous dextrose (glucose) without amino acids for a prolonged period will often show a fatty liver and marked hypoalbuminemia and edema. Other changes in the liver that may occur in nutritional disorders are listed in Table 3.



Table 3. Effects of specific nutritional disorders on the liver

Nutritional disorders	Effects on the liver
➤ Common conditions	
○ Alcoholism	– Steatosis, alcoholic hepatitis and cirrhosis
○ Obesity	– Steatosis, steatohepatitis and cholelithiasis
○ Uncontrolled diabetes	– Glycogenosis, steatosis and steatohepatitis
○ Protein deficiency	– Pigment stones
○ Kwashiorkor	– Steatosis and decreased protein synthesis
○ Fasting	– Mild unconjugated hyperbilirubinemia, especially in Gilbert's syndrome
➤ Uncommon conditions	
○ Jejunioileal bypass	– Steatosis and steatohepatitis
○ Gross dietary iron excess	– Bantu siderosis/hemochromatosis
○ Senecio alkaloids	– Veno-occlusive disease
○ Dietary aflatoxins	– Hepatocellular carcinoma (?)
○ Chronic arsenic ingestion	– Noncirrhotic portal hypertension, angiosarcoma and hepatocellular carcinoma
○ Hypervitaminosis A	– Hepatic fibrosis and cirrhosis

Clinical vitamin deficiencies are listed in Table 4. Except for cheilosis and glossitis, which are seen with multiple vitamin B deficiencies, physical findings of vitamin deficiencies are seldom observed in protein-calorie malnourished patients in developed countries. Trace elements are elements that are required in small quantities (milligram amounts or less) for normal growth and/or function. Essential trace elements for humans include iron, iodine, zinc, chromium, copper, selenium, cobalt (as vitamin B12), molybdenum, manganese and possibly vanadium. Except for iron deficiency due to blood loss and/or poor intake, deficiency states of trace elements are rare in subjects with some oral intake, since only minute amounts are required.

4. Effects of Malnutrition on the Gastrointestinal Tract and Pancreas

Protein-energy malnutrition may produce major structural and functional changes in the gastrointestinal tract and pancreas, which, in turn, may aggravate the underlying poor nutritional condition. In severe protein-energy malnutrition, for example, acinar cell atrophy occurs and exocrine cells have decreased numbers of zymogen granules. Pancreatic secretion may be reduced following stimulation with cholecystikinin and/or secretin. With malnutrition, the activities of enzymes contained in pancreatic juice (i.e., trypsin, chymotrypsin, lipase and amylase) are reduced. With reversal of malnutrition these can return to normal levels, but this may require several weeks.

In addition to pancreatic exocrine changes, the entire wall and mucosal lining of the stomach and intestine may be reduced in thickness. Microscopically, marked changes may develop, including severe “flattening” of the small intestinal mucosa, similar to celiac



disease. In contrast to celiac disease, however, reduced numbers of crypt mitoses are seen. Changes may be present throughout the small intestine in an irregular patchy distribution, although the jejunum appears to be most severely affected. Some brush-border enzymes (e.g., disaccharidases) may be reduced; as a result, malabsorption of a variety of substances (e.g., lactose) may be observed. Altered uptake of glucose and D-xylose has also been reported, and steatorrhea may be present with impaired absorption of fat and some fat-soluble vitamins. In addition, there may be increased protein loss from the gut, leading to increased fecal nitrogen loss. Finally, specific nutrients may be deficient and cause alterations in certain tissues. In particular, folic acid and vitamin B12 deficiencies may lead to subtotal villous atrophy in association with crypt hypoplasia (Table 4).

Table 4. Effects of depletion of specific nutrients on the intestine

Nutrient	Effects
➤ Protein-energy malnutrition (e.g., especially, kwashiorkor)	○ Total or subtotal villous atrophy and crypt hypoplasia
➤ Folic acid deficiency	○ Total or subtotal villous atrophy and crypt hypoplasia; macrocytic and/or “megaloblastic” enterocytes
➤ Vitamin B12 deficiency	○ Total or subtotal villous atrophy and crypt hypoplasia; macrocytic and/or “megaloblastic” enterocytes
➤ Vitamin E deficiency	○ (?) Small intestinal ceroidosis (i.e., “brown bowel syndrome”)
➤ Vitamin A deficiency	○ Reduced numbers of intestinal goblet cells

Restitution of small bowel mucosa occurs after renutrition. There is growing evidence that mucosal atrophy occurs during total parenteral nutrition with associated increased intestinal permeability, especially in stressed metabolic states, and that atrophy is absent or minimal in patients fed enterally. Therefore, whenever possible, intestinal (i.e., enteral) feeding is preferred to parenteral feeding. When refeeding occurs after a period of malnutrition, however, it should be appreciated that gut function may be impaired, with resultant malabsorption and diarrhea, and that total refeeding via the gut may not initially be achieved. In this circumstance, partial enteral refeeding with parenteral supplementation is usually given, provided there are no contraindications to enteral feeding (e.g., bowel obstruction).

There is evidence that the colonic mucosa uses short-chain fatty acids (especially butyrate) as an energy source. In patients who undergo a colostomy, the bowel that is left distally does not have a fecal stream. The mucosa of this bowel may develop inflammation, called “diversion colitis.” Some improvement in the colitis has been reported with administration of short-chain fatty acid enemas or with irrigation of fiber. A major source of the short-chain fatty acids in the colon is fermented dietary fiber, and thus fiber may be considered a “nutrient.”



5. Dietary Therapy in Gastrointestinal Disease

5.1. General Principles

A number of specific diets are useful in different gastrointestinal disorders. These may involve diet restriction or supplementation, or alternatively, a change in the consistency or content of specific nutrients. In patients with steatorrhea, for example, luminal fatty acids are present and involved in the pathogenesis of diarrhea. In these patients, reduction in diarrhea can be accomplished, in part, by a reduction in the oral intake of triglycerides; a low-fat diet may be beneficial. In some patients with steatorrhea, supplementation with medium-chain triglycerides may be useful because these are hydrolyzed more rapidly by pancreatic enzymes, do not require bile acid micelles for absorption, and are primarily directed to the portal rather than the lymphatic circulation. Because medium-chain triglycerides undergo ω -oxidation to metabolically nonutilizable dicarboxylic acids, the effective caloric content of medium-chain triglycerides is less than expected. Medium-chain triglycerides in a daily dose of 60 mL will provide approximately 460 calories. Low-fat dietary supplements may be provided in the form of a number of commercially available products prepared as complete nutritional supplements. Fat-soluble vitamins can be replaced using oral water-miscible formulations, if steatorrhea is present. For vitamin K, a water-soluble form is available. Fat-soluble vitamins require bile acid micelles for absorption; thus, if steatorrhea is due to bile acid depletion (as might occur in the short bowel syndrome following surgical resection for extensive Crohn disease), increased amounts of vitamins may be required.

Bloating and cramping pain may follow ingestion of lactose-containing foods. This may be due to lactase deficiency (e.g., small bowel disease, "ethnic" lactase deficiency). Dietary lactose restriction may be indicated in patients if there is a history of lactose intolerance or a positive lactose tolerance test (i.e., rise in blood sugar less than 20 mg/dL [1.1 mmol] after 50 g of lactose) accompanied by characteristic symptoms. An alternative test is the lactose breath hydrogen test, in which 2 g/kg (up to 25 g) of lactose is ingested and breath hydrogen is measured. An increase in breath hydrogen of greater than 20 ppm is considered diagnostic of lactose intolerance.

Lactose may be found in milk, including buttermilk, even if it has been naturally fermented. Commercial yogurt should also be avoided, since this often has milk or cream added after fermentation to avoid the sour taste produced by fermenting lactose. Ice cream and sherbets have high lactose concentrations and should be avoided. Cheese or desserts made from milk or milk chocolate as well as sauces or stuffings made from milk, cream or cheese should also be avoided. Calcium supplements may be necessary with dairy product restriction, particularly in postmenopausal women. Liquid dairy products may be used to a limited extent by patients who have lactose intolerance; in these patients, an enzyme preparation (prepared from yeast or bacteria) added to milk at 4°C (15 drops/L) can hydrolyze up to 99% of the lactose in 24 hours. Nonliquid dairy products cannot be treated with enzyme preparations, although lactase tablets may be chewed prior to eating solid food.

5.2. Celiac Disease

Celiac disease, also known as gluten-sensitive enteropathy or celiac sprue, is a malabsorption disorder resulting from ingestion of proteins derived from certain cereal grains of the grass family, Gramineae: wheat, rye, barley. Although oats is not directly related, this grain is believed to be often contaminated with others so that it is usually



restricted, although oats certified to be gluten-free are available. It is believed that the alcohol-soluble gliadin fraction of wheat gluten or similar alcohol-soluble proteins from the other grains (termed *prolamins*) cause the intestinal damage. Consequently, absolute restriction is required for life. Table 5 provides some dietary guidelines for celiac disease patients. Gluten, however, is a particularly ubiquitous substance and can be found in coffee, catsup, dip, frozen TV dinners, ice cream and even in the capsules of medications! Although wheat, rye, barley and possibly oats are important, corn and rice do not appear to activate celiac disease. Data on other grains are not as clear. Buckwheat is not derived from the grass family and is usually permitted. Millet and sorghum are often allowed, but have not been thoroughly evaluated. Triticale, a hybrid of wheat and rye, should be avoided. Rye whiskey, Scotch whiskey and other cereal-derived alcohols can be consumed, since gluten is not present in distilled spirits. Similarly, brandy and wine made from fruit pose no difficulties. Beer and ale are produced from barley; it is not entirely clear if they can activate disease and would best be avoided. Malt made from barley should be avoided, as well as hydrolyzed vegetable proteins used as flavor enhancers in processed foods, since they may be made from soy, wheat and other cereal proteins.

Table 5. Dietary guidelines for celiac disease patients

-
- Foods to avoid
 - Wheat, rye, barley, oat products Triticale (wheat–rye hybrid) Millet and sorghum
 - Malt and hydrolyzed vegetable protein

 - Acceptable foods
 - Corn, rice, buckwheat products
 - Wine and distilled alcoholic beverages
 - Fruits and vegetables
 - Meat
 - Nuts
 - Dairy products (unless lactose-intolerant)
-

For both symptomatic and asymptomatic patients with celiac disease, a lifelong gluten-free diet is recommended. Multivitamin supplements are frequently required and specific vitamin, mineral and trace element deficiencies should be corrected. Iron and folate supplementation may be needed and poor absorption of oral iron may sometimes necessitate parenteral administration. Supplements of calcium and vitamin D may be required to prevent mobilization of skeletal calcium, and in some patients magnesium may be needed.

5.3. Inflammatory Bowel Disease

Malnutrition in patients with inflammatory bowel disease, especially Crohn disease, is a frequent problem. Weight loss may be seen in over 65% of patients and growth retardation may be observed in up to 40% of children. As shown in Table 6, there are multiple causes for malnutrition, especially in patients with Crohn disease with small bowel involvement. The goal of nutritional management is to ensure adequate nutrient intake with modifications that reduce symptoms. Although only limited studies are available, evidence suggests that energy expenditure in quiescent Crohn disease and



ulcerative colitis is no greater than one would predict for a healthy individual. If the disease is quite active, or is accompanied by fever or sepsis, resting energy expenditure increases. Interestingly, patients, even with quiescent Crohn disease, have evidence of increased fat oxidation at rest, similar to findings in starved individuals. There may be increased caloric as well as nutrient requirements, particularly if gastrointestinal losses are substantial and malabsorption is significant. Attention should also be placed on micronutrient deficiencies in these patients, particularly if concomitant malabsorption is present. For example, patients with significant ileal disease or resection require regularly administered parenteral vitamin B12.

Table 6. Malnutrition in inflammatory bowel disease

-
- Reduced oral intake
 - Disease-induced (e.g., postprandial abdominal pain and diarrhea, sitophobia, anorexia, nausea and vomiting)
 - Iatrogenic (e.g., restrictive diets, “fad” diets)
 - Malabsorption
 - Reduced absorptive surface (e.g., shortened small intestine due to prior resection, diseased segments)
 - Bacterial overgrowth (e.g., associated with strictures and bypassed loops, stasis)
 - Bile salt deficiency after ileal resection (e.g., impaired micelle formation and steatorrhea)
 - Lactase deficiency (e.g., associated with small bowel disease)
 - Drug-induced malabsorption
 - Increased nutrient loss
 - Protein-losing enteropathy
 - Diarrhea with losses of electrolytes, minerals and trace elements (e.g., potassium, zinc)
 - Gastrointestinal blood loss (e.g., iron loss)
 - Drug-induced malabsorption
 - Cholestyramine (e.g., bile acids; fat; fat-soluble vitamins, including vitamins D and K)
 - Sulfasalazine (e.g., folic deficiency associated with reduced absorption and increased requirement related to hemolysis)
 - Steroids (e.g., calcium absorption and mobilization)
 - Increased requirements
 - Chronic inflammatory disease, fever, superimposed infection
-

Lactose intolerance is no more common in patients with ulcerative colitis than in healthy individuals. Furthermore, lactose intolerance is also probably no more common in patients with Crohn disease. Owing to the problems with malnutrition in Crohn disease, a lactose-restricted diet should not be recommended unless there is clear-cut improvement in diarrhea with lactose restriction.

Specific drugs may also alter nutrient absorption. Cholestyramine is the classic



example of an agent that interferes with nutrient (especially cations such as zinc) and drug absorption.

6. Dietary Therapy in Liver Disease

Two important manifestations of chronic liver disease, ascites and portosystemic encephalopathy, have dietary modification as a cornerstone of treatment. The prime dietary objective in the treatment of ascites is sodium restriction. Severe dietary sodium restrictions are no longer recommended since such restrictions will likely promote malnutrition. Restricting dietary sodium to 80 to 120 mmol per day is felt to be appropriate.

Patients with advanced liver disease, including cirrhosis, have a high prevalence of protein-calorie malnutrition which adversely affects the underlying liver disease and results in poor clinical outcome. These patients should take a diet high in protein (1.2 – 1.5 g/kg) and calories (35 – 40 kcal/kg). Restricting protein intake in patients with portosystemic encephalopathy has not been shown to be beneficial in several randomized trials and is therefore not generally recommended. Vegetable protein may be less ammoniagenic than meat, postulated to be due to a number of factors. Factors cited include a vegetarian diet increased dietary fiber in the vegetarian diet leading to increased elimination of nitrogen in the gut and increased levels of plasma arginine and citrulline leading to increased ammonia removal via the Krebs-Henseleit cycle. Patients with portosystemic encephalopathy have increased levels of aromatic amino acids and decreased levels of branched chain amino acids (BCAA). However, the efficacy of BCAA-enriched formulas in treating portosystemic encephalopathy remains controversial due to conflicting trial results and cost.

Cholestatic liver diseases, including primary biliary cirrhosis (PBC), secondary biliary cirrhosis, sclerosing cholangitis and biliary atresia, may be accompanied by malabsorption of fat-soluble vitamins. Vitamin K deficiency can be easily confirmed with the demonstration of a prolonged INR that corrects with administration of parenteral vitamin K. Assays for vitamins D, A and E may also be performed. If confirmatory tests are not available and if there are strong clinical grounds for suspecting a deficiency state, appropriate replacement therapy should be initiated. Table 7 lists a number of hereditary liver diseases for which appropriate therapy includes specific dietary interventions.

Table 7. Diet therapy for hereditary liver diseases

Disorder	Dietary intervention
○ Tyrosinemia	– Low-phenylalanine diet
○ Hereditary fructose intolerance	– Low-fructose, low-sucrose diet
○ Galactosemia	– Galactose-free diet
○ Glycogen storage disease	– Continuous glucose feeding
○ Cerebrotendinous xanthomatosis	– Deoxycholic acid supplementation
○ Wilson's disease	– Low-copper diet, zinc supplementation (together with chelating agent)



Disorder	Dietary intervention
○ Hemochromatosis	– Avoidance of excess dietary iron, selection of foods containing phytates or tannins to reduce iron absorption (together with appropriate phlebotomy treatment)
○ Cystic fibrosis	– Low-fat diet, pancreatic enzyme supplements, fat-soluble – vitamin supplements

7. Nutrition Intervention

7.1. Introduction

The decision to intervene nutritionally is based on a number of disparate factors, including the current nutritional status of the patient (well-nourished versus malnourished), the duration of the time the patient will be expected to be unable to eat, the underlying medical condition and the prognosis for recovery. Once the decision to intervene has been made, the next decision is the method of intervention: oral, enteral or parenteral.

7.2. Nutritional Assessment

Malnutrition can affect patient morbidity and mortality. It is thus important to detect malnourished patients and improve their nutritional status by providing nutritional support. There are several methods to assess nutritional status; the best method would be the one that predicts clinical outcome. In particular, the best method would predict nutrition-associated complications that increase the risk of morbidity and mortality in the absence of nutritional intervention.

However, since it is often difficult to dissect out the effects of malnutrition from the effects of disease, nutritional assessment cannot rely on a single parameter or simple model. Furthermore, disease can affect several parameters used for nutritional assessment independently of nutritional status.

7.2.1 Methods of Assessing Nutritional Status (Table 8)

7.2.1.1. Body composition

Several methods can be used to measure various body compartments and most are used within a research protocol. The ones most frequently used clinically are based on a two compartment model: body fat and lean body mass (muscle, bones). This can be assessed, for example, by anthropometry, where triceps and subscapular skinfold thicknesses provide an index of body fat, and mid-arm circumference provides a measure of muscle mass. This method is mostly used in population studies and is less reliable in the individual patient because of inter- and intra-observer variability and the effect of hydration status, age and physical activity.



Table 8. Methods of nutritional assessment

-
- Laboratory determinations
 - albumin, pre-albumin, transferrin, retinol-binding protein lymphocyte count, WBC
 - 24-hour urinary urea nitrogen, nitrogen balance creatinine-height index
 - delayed cutaneous hypersensitivity
 - Anthropometric measurements
 - height, weight, ideal body weight (IBW), usual body weight (UBW), BMI weight as percent IBW or UBW, % weight loss triceps skinfold thickness, mid-arm circumference and others
 - Techniques to assess body composition
 - bio-impedance imaging: DEXA, CT scan dilution radioisotope methods, whole body counting
 - Dietary intake
 - Miscellaneous
 - muscle function
 - indirect calorimetry
-

7.2.1.2. Body weight and weight loss

This is a simple measure and is compared to an ideal weight for height, usually by calculating body mass index (BMI). BMI is the weight in kilograms divided by height in meters squared. A normal BMI is 18.5 to 25 kg/m². An ideal weight should give a BMI in that range. On the other hand, a BMI less than 18.5 suggests undernutrition and it is associated with significant morbidity and mortality.² A BMI over 25 but below 30 suggests overweight. When BMI reaches 30 or above, the patient is obese and high BMI is also associated with increased risk of morbidity and mortality.² A history of weight loss is also important. Studies have shown that unintentional weight loss of > 10% is a good predictor of adverse clinical outcome.

7.2.1.3. Creatinine-height index (CHI)

The excretion of creatinine in the urine is related to muscle mass. Normalized for height, the 24-hour creatinine excretion is an index of muscle mass and can be compared to published tables. However, in a hospital environment, this is not used because of frequent underlying renal disease and use of diuretics.

7.2.1.4. Plasma proteins

Albumin is one of the most studied proteins and several studies have demonstrated that low serum albumin concentration correlates with an increased incidence of medical complications and mortality.¹ However, serum albumin may be inappropriate as a measure of nutritional status because it represents the summation of many events: synthesis, degradation, losses, exchange between intravascular and extra-vascular compartment and volume of distribution. Therefore, hospitalized patients may have lower albumin levels for several reasons: inflammatory disorders cause a decrease in albumin



synthesis, an increase in albumin degradation and trans-capillary losses; gastrointestinal, cardiac and renal diseases as well as wound, burns and peritonitis can cause significant albumin losses and during serious illness, vascular permeability increases dramatically (with loss of albumin into the interstitial space). On the other hand, protein-calorie malnutrition causes a decrease in the rate of albumin synthesis, but a short-term reduction in albumin synthesis will have little impact because of albumin's low turnover rate (half-life: 20 days) and large pool size. Even during chronic malnutrition, plasma albumin concentration is often maintained because of compensatory decrease in albumin degradation and transfer of extravascular albumin to the intravascular compartment. Another plasma protein, prealbumin, is more responsive to nutritional changes because its turnover rate is rapid with a half-life of 2–3 days. However, it is also influenced by underlying diseases such as inflammation, infections, renal and liver failure. Therefore, it is also an unreliable index of nutritional status in patients.

7.2.1.5. Immune competence

As measured by delayed cutaneous hypersensitivity is affected by severe malnutrition. However, other diseases and drugs may also influence the measurements making it a poor predictor of malnutrition in sick patients.

7.2.1.6. Global assessment techniques

Several global assessment techniques exist. A prognostic nutritional index depending largely on albumin and transferrin was shown to provide a quantitative estimate of postoperative complication (Blackburn, 1977). Subjective global assessment (SGA) is a clinical method that has been validated and is able to identify patients who are at risk of developing complications due to malnutrition (Baker 1982). It categorizes the patients as being well nourished (A) or as having moderate or suspected malnutrition (B) or severe malnutrition (C) (Table 10). The use of SGA in evaluating hospitalized patients gives reproducible results and can predict complications in several patient populations such as surgical, dialysis and liver transplant patients.

At present, there is no gold standard for evaluating nutritional status. It is important to recognize the multiple facets of malnutrition to detect the patient at risk of nutrition-related complications. Subjective global assessment combined with selective objective parameters defined above is the best clinical way to detect the patients at risk.

7.3 Nutritional Requirements

7.3.1 Nitrogen Requirements

In a well-nourished adult in steady state, total nitrogen intake will equal nitrogen output in urine, stool, skin and body fluids. This is termed (zero) “nitrogen balance.” Nitrogen is assimilated almost exclusively as protein, and, on average, 6.25 g protein is equivalent to 1 g nitrogen. The nitrogen is excreted predominantly as urea in the urine, but stool and skin losses account for about 2–3 g daily. In the steady state, ingestion of more nitrogen will merely result in excretion of more nitrogen in the urine, with the excess protein oxidized in the liver and used as an expensive energy source. In growing children or in malnourished adults, the nutritional goal is a positive nitrogen balance, meaning that body tissue is being formed in excess of what is being broken down (i.e., there is net growth). It is less clear that patients with conditions associated with protein loss, such as nephrotic syndrome and protein-losing enteropathy, benefit from extra protein intake.



Indeed, there remains concern with nephrotic syndrome that extra protein may contribute to a fall in glomerular filtration rate (GFR), as has been reported in other renal conditions.

If energy requirements are met or exceeded, studies have shown that well-nourished adults can maintain nitrogen balance when given as little as 0.6 g/kg protein intake. In order to allow for biologic variability, the standard recommendation for protein intake is 0.75 g/kg. It is important that the protein supplied be of high quality; it should include all essential amino acids and a balanced mix of nonessential amino acids. Malnourished, septic, injured or burned patients will require more protein, in the order of 1.0–2.0 g/kg daily. Pregnant patients should also be given 1.5 g/kg protein daily. It is not clear that patients with conditions associated with protein loss, such as protein-losing enteropathy, benefit from extra protein intake. Indeed, patients with nephrotic syndrome may even benefit from protein restriction, though this is not firmly established.

7.3.2 Energy Requirements

Resting energy requirements in average weight healthy subjects can be accurately predicted with reasonable accuracy by the Harris-Benedict equation:

MALES: Energy (kcal/d) = $66 + (13.75 \times W) + (5.00 \times H) - (6.78 \times A)$

FEMALES: Energy (kcal/d) = $655 + (9.56 \times W) + (1.85 \times H) - (4.68 \times A)$ where W = weight in kg, H = height in cm and A = age in years.

The Harris-Benedict equation may be less accurate in malnourished or obese individuals. Malnourished patients exhibit resting energy requirements about 10% to 20% below predicted. The resting energy requirements of obese patients will also be below predicted since adipose tissue is less metabolically active than other tissues. In overweight patients, it has been proposed that an adjusted weight be used in the Harris-Benedict equation based on actual and ideal body weight, using the following formula:

Adjusted weight = $[(\text{actual body wt} - \text{ideal wt}) \times 0.25] + \text{ideal wt}$.

The Mifflin-St. Joer (also called Mifflin) formula may be a better choice for calculating resting energy expenditure in the obese patient. The formula is as follows:

For males, REE = $10 \times \text{weight (kg)} + 6.25 \times \text{height (cm)} - 5 \times \text{age (y)} + 5$

For females, REE = $10 \times \text{weight (kg)} + 6.25 \times \text{height (cm)} - 5 \times \text{age (y)} - 161$

Formulas applied to individuals may be inaccurate for a variety of reasons. The population of subjects upon which the formula is based needs to be understood. Race, age, disease state and BMI are several factors which might profoundly affect the REE of an individual, so the formula used must be considered only a guideline in deciding energy requirements.

Basal energy requirements, as predicted by these equations, increase in the presence of fever (13% per °C), sepsis or injury (up to 20–30%), and burns (up to 100%). Modest physical activity usually requires about 30% above basal requirements.

7.4. Types of Nutritional Intervention

The options for refeeding include oral refeeding, tube feeding and total parenteral nutrition. An assessment by a dietitian regarding current food intake and food preferences



is essential. It may well be possible by determining food preferences to provide a well-balanced, nutritionally complete diet. In addition, supplements of high-calorie, high-protein foods such as milkshakes or commercially prepared liquid formula diets may allow for adequate intake. If the patient will not or cannot eat, however, nutritional intervention may be indicated. Examples of patients who will not eat include those with anorexia due to tumor or chemotherapy, and those with anorexia nervosa. Such patients generally have a normal or near-normal nonobstructed bowel, and can be fed enterally. Patients who cannot eat because of severe gastrointestinal illness include those with bowel obstruction or ileus. If nutritional intervention is required in these patients, parenteral (intravenous) nutrition will be necessary.

7.4.1 Enteral Nutrition

7.4.1.1 Methods of delivery

Enteral nutrition generally refers to nutrition provided through a tube that has been inserted into the gastrointestinal tract. Usually the tube is a fine-bore (10 French [3.3 mm] or less) silicone, polyvinylchloride or polyurethane tube placed via the nose into the stomach, duodenum or jejunum. When long-term feeding is required, it is often preferable for cosmetic and comfort reasons to perform a gastrostomy radiologically or endoscopically, the latter commonly referred to as a PEG (percutaneous endoscopic gastrostomy). These tubes can be placed through the pylorus to feed into the jejunum with only local anesthetic and mild sedation. Despite convincing evidence of efficacy of post-pyloric placement of tubes in reducing pulmonary aspiration, the tube is usually placed in the jejunum if aspiration is a concern.

7.4.1.2 Enteral formulas

A multitude of commercial enteral formulas are available for infusion. The formulas have been traditionally divided into polymeric, oligomeric, monomeric, modular and disease-specific formulas. Polymeric formulas (also called defined formula diets) provide nitrogen as whole protein, often casein, egg white solids or soy protein. Carbohydrate is often provided as corn syrup, maltodextrins or glucose oligosaccharides, with sucrose added for sweetness in oral formulas. Fat is usually provided as soy oil, although corn oil and safflower oil may be used. Medium-chain triglycerides (MCT oil) are rarely used. Protein may be provided as milk (usually dry or skim), with lactose as a major carbohydrate. These formulas are contraindicated in patients with lactose intolerance.

Specialized polymeric formulas are available for a variety of disease states, including kidney and lung disease as well as diabetes. The efficacy of these products has generally not been well established. Products also vary in caloric density (usually between 1.0 and 2.0 kcal/mL) and protein content. Some contain fiber and others are prepared for oral consumption (generally sweeter with a higher osmolality than those meant primarily for tube feeding).

Oligomeric formulas (also called semi-elemental diets) provide nitrogen as peptides from partially hydrolyzed whole protein. Monomeric formulas (also called elemental diets) provide nitrogen as crystalline amino acids. Carbohydrate tends to be provided as glucose oligosaccharides. Fat is usually present in small quantities, enough to meet the requirement for linoleic acid (an essential fatty acid), which is about 2–4% of total calories. MCT oil is added to some formulas. The oligomeric and monomeric diets were formulated to require minimal digestion by the gastrointestinal tract, with little necessity for bile and



pancreatic secretions, and minimal “work” by the enterocyte in terms of brush-border enzyme activity or re-esterification. Hence, these diets have been commercially promoted as ideal for patients with decreased bile output (cholestasis), pancreatic insufficiency and short bowel. However, there is little evidence that these diets are superior to polymeric diets. Furthermore, since the diet is “predigested,” osmolality is high. Finally, the high cost of these diets (often five to 10 times that of polymeric diets) rarely justifies their use.

Most of these formulas provide enough protein, calories, water, electrolytes, minerals, vitamins and trace elements in 2 L/day or less for most “nonstressed” patients. In other words, these diets are “complete.” Excess requirements may exist in patients with multiple injuries, major infections or burns.

As with polymeric formulas, specialized amino acid solutions have been made for use in special circumstances – for example, liver disease, renal disease and “stress,” such as trauma and sepsis. For liver disease, these solutions are composed mostly or exclusively of branched-chain amino acids, whereas for renal disease the solutions are predominantly essential amino acids. In general, these solutions are expensive and their efficacy is controversial.

There has been considerable interest in “immunonutrition” which refers to formulas which have been enriched with nutrients purported to alter immunity. Such nutrients include amino acids such as arginine and glutamine, fish oil (omega-3 fatty acids), antioxidants and nucleotides. Systematic reviews of immunonutrition have been reported in intensive care and surgical patients but the role of these specialized products remains controversial.

7.4.1.3 Complications

Complications of enteral feeding may be divided into aspiration, mechanical, gastrointestinal and metabolic. In general, enteral feeding is well tolerated, and provided the complications are known, preventive and/or corrective measures may be undertaken to minimize patient risk.

Aspiration of the infused formula, with development of pneumonia, is a potentially lethal complication of tube feeding. Proper positioning of the tube requires radiographic verification. Risk factors for aspiration include patients on a ventilator and those with gastroesophageal reflux, poor or absent gag reflex, and impaired mentation. To minimize aspiration, it is suggested that patients, when possible, be fed with the head of the bed elevated 20–30°. Gastric contents should initially be checked by aspirating the tube every four to six hours and if the residual volume is > 150 mL, the infusion should be temporarily stopped. Unfortunately, the small nasoenteric tubes in current use often collapse when aspirated, so small returns do not guarantee that the stomach is not becoming distended with fluid. Hence, examination for epigastric distention and succussion splash should be done. If there is any concern, an upright (if possible) plain film to assess gastric size may be useful. It has also been suggested that the feeding tube be placed into the small bowel well beyond the pylorus to minimize aspiration in those at risk, though studies have failed to confirm this.

The following mechanical problems in patients with nasoenteric tubes include problems in the upper respiratory tract and esophagitis with development of esophageal ulceration, stenosis and even tracheoesophageal fistula. Upper respiratory problems include pharyngeal irritation, nasal erosions and necrosis, sinusitis and otitis media. These mechanical problems can be largely avoided by the use of soft, small-bore



nasoenteric tubes.

Gastrointestinal problems related to nasoenteric feeding are common, occurring in 20–30% of patients. The most frequent complaints are nausea, vomiting, abdominal distention and altered bowel habit. Symptoms may be minimized by feeding at a slow rate with dilute solutions, but these symptoms may be just as common as with full-rate, full-strength solutions. Alternatively, a different enteral solution may be tried. If a lactose-containing solution is being used (generally not recommended for tube feeding), changing to a lactose-free solution is indicated. For constipation, fiber-containing solutions may be tried, although they are often unhelpful. Fiber, however, is a potential energy source for the colon, as previously discussed, and may therefore be important for maintenance of the colonic mucosa. At the present time, fiber-containing solutions are not routinely used.

Metabolic complications include overhydration, dehydration, hyperglycemia (including hyperosmolar nonketotic coma) and electrolyte disturbances. Electrolyte problems include hyponatremia, hyper- and hypokalemia, hyper- and hypophosphatemia and hypomagnesemia. In healthy, reasonably nourished individuals with normal cardiac, liver and renal function, these problems are not common. It is recommended that appropriate blood tests be done at intervals over the first few weeks to check for these potential problems.

7.4.2 Total Parenteral Nutrition

Total parenteral nutrition (TPN) involves intravenous administration of all known essential nutrients. This form of therapy is as effective as oral or enteral intake in terms of growth and maintaining body nitrogen. Indications include inability to eat for a minimum of seven to 10 days with a nonfunctional gut. Total parenteral nutrition is also used for “bowel rest,” especially in Crohn disease, intestinal fistulas and pancreatitis, even if adequate absorption is possible. Several studies suggest, however, that bowel rest is not helpful in Crohn disease. Furthermore, other studies have shown that elemental diets can be used instead of TPN, except when bowel obstruction is present. In general, if the gut is functional, enteral feeding is preferred since it is safer, cheaper and more physiologic.

7.4.2.1 Solutions

Amino acids “Protein” is supplied as synthetic crystalline, L-amino acid solutions; these are commercially available in 5-20% concentrations. Specialized amino acid solutions for liver and kidney disease have been discontinued in many jurisdictions.

Fat The predominant source of fat in parenteral nutrition has been soybean oil, which has a high concentration of linoleic acid, an omega-6 essential fatty acid in humans as a precursor to arachadonic acid. It has been estimated that 2-4% of total calories should be provided to avoid essential fatty acid deficiency. There has been concern that providing fat solely as a soybean emulsion may not be ideal, which has led to the development of alternative sources of oils for parenteral infusion. Both olive oil and fish oil are available commercially in many parts of the world, alone or as part of a mixture. Parenteral lipid emulsions are available mostly as 20% or 30% (weight/volume) concentrations.

Carbohydrate Glucose is the preferred carbohydrate for intravenous use. Glucose is widely available in concentrations from 5–70%. The osmolality of these solutions may be markedly hyperosmolar up to about 2,500 mOsmol/L.

Nonprotein energy source Once the initial 100 g of glucose is provided for use in the



brain, renal medulla and red blood cells, glucose and fat are equally effective in preserving body nitrogen after an equilibration period of four to five days. Glucose is very inexpensive as an energy source, but requires insulin for uptake into cells, and hyperglycemia can be a problem when large amounts of glucose are utilized. The high osmolality of glucose solutions means that only dilute solutions can be used in peripheral veins, and if glucose is used as a major energy source, a large central vein is necessary to prevent thrombosis. Furthermore, glucose has a respiratory quotient (R.Q. = CO_2 produced/ O_2 consumed) of 1.0, meaning that large amounts of carbon dioxide may be produced. Finally, glucose infusion leads to catecholamine release and increased metabolic rate, further increasing carbon dioxide production. These changes may be deleterious for patients being weaned from ventilators, or with borderline respiratory function.

Lipid solutions offer the benefit of being iso-osmolar, containing essential fatty acids and having a lower respiratory quotient of 0.7, with less carbon dioxide production. Drawbacks include somewhat higher cost compared to glucose, and poor tolerance in patients with hyperlipidemia.

Combined solutions

While parenteral nutrition solutions are available as separate amino acid, lipid and glucose components, there has been increased use of solutions which have been mixed commercially ("premixed"), either as a "2 in 1" (amino acid/glucose with lipid provided separately) or as a "3 in 1" (amino acid/glucose/lipid) mixture.

7.4.2.2 Routes of delivery

Central The most flexible way to deliver total parenteral nutrition is through a large central vein, usually the superior vena cava, usually via the subclavian vein or a peripheral vein, the latter by using a peripherally inserted peripheral catheter (PICC). With the large flow through the superior vena cava, solution osmolality is not of great concern, and thrombosis of this vessel is uncommon.

Peripheral The high osmolality of parenteral nutrition solutions and the widespread availability limit the indications for parenteral nutrition provided by a peripheral (non-central) catheter. However, parenteral nutrition may be appropriate when central venous catheterization is not possible, advisable or feasible and the duration of parenteral nutrition is expected to be short term (preferably not longer than 2 weeks). Since the parenteral nutrition solutions must be of relatively low osmolality (≤ 900 mosm/L), the patient must be able to tolerate large (> 2 L) volumes. Midline (7.5-20 cm) 22 or 23 gauge catheters made from polyurethane or silicone may last up to 2 weeks and are preferred over short (< 7.5 cm) catheters. There are commercially available premixed solutions available for peripheral parenteral nutrition.

7.4.2.3 Complications

Complications of total parenteral nutrition may be divided into local and systemic. Local problems relate to the catheter site, and in the case of central lines involve all the complications of central catheters, including inadvertent arterial catheterization with bleeding, pneumothorax, hemothorax and inadvertent infusion of solutions into the pleural cavity. Air embolism may occur at the time of insertion or any time thereafter with a central line. Catheter embolization may occur, and as mentioned, thrombosis has been



reported, particularly with the use of stiff catheters. It is essential that catheter placement be done by persons with considerable experience to minimize these complications.

Systemic complications include sepsis, metabolic problems and bone disease. Bacteremia or fungemia occurs in 3–7% of patients given total parenteral nutrition, and this appears to arise predominantly from the hub where the catheter joins the intravenous tubing. Catheters are always inserted in a strictly aseptic manner, with personnel fully gowned and gloved. Metabolic problems include hyperglycemia, which can be treated by reducing the amount of glucose given in the solutions, hypertriglyceridemia when excess calories and/or excess lipid are given, and alterations in electrolytes. In particular, total parenteral nutrition causes anabolism with increased intracellular water, so that potassium and phosphate are driven into cells, leading to possible hypokalemia and hypophosphatemia. These complications are very uncommon if adequate amounts of these electrolytes are provided and careful monitoring is performed (daily values for at least 3 days). Liver disease remains a frustrating complication of total parenteral nutrition, but in most cases the changes are restricted to enzyme elevations. In general, mild elevations in AST and alkaline phosphatase occur in the second week, with occasional elevations in bilirubin occurring later. Liver biopsy may show mild cholestasis. Some of these changes may be due to overfeeding or by providing lipid in excess of 1 g/kg; this can be treated by reducing total calories and by ensuring excess lipid is not given. Providing a lipid solution high in omega-3 fatty acids (fish oil) may result in improvement in liver tests, with the best data in the paediatric patient. Rarely, long-term TPN (extending over years) may result in cirrhosis without a well-defined cause.

7.4.3 Home Enteral and Parenteral Nutrition

7.4.3.1 Home enteral nutrition

Enteral nutrition may be provided on a long-term basis at home using any of the standard enteral formulas. While highly motivated individuals may do this using nasogastric tubes placed nightly with nocturnal feedings, most patients will need a gastrostomy or jejunostomy tube for long-term feeding. Intermittent bloodwork and physician follow-up visits, similar to home parenteral nutrition, will need to be done to ensure that the formula is appropriate and that the nutritional goals are being met. The patient or caregiver must be adequately versed in the management of the gastrostomy and jejunostomy tubes as well as in the potential complications of enteral feeding using such tubes. Intermittent replacement of these tubes is generally on an as-needed basis although some nutrition programs provide replacement on a predefined timetable, for example every 12 to 18 months.

7.4.3.2 Home parenteral nutrition

Home parenteral nutrition is used in patients who require long-term parenteral nutrition but who do not need hospital admission for any other medical reason. These patients have gut failure due to short bowel syndrome (e.g., Crohn disease, ischemic bowel disease), severe motility disturbances (scleroderma, idiopathic pseudo-obstruction), hyperemesis gravidarum and other miscellaneous problems.

Home parenteral nutrition patients and/or their caregivers need to undergo appropriate training in aseptic techniques as well as training in management of catheter and pump care. This training may be done in a hospital setting or in an outpatient setting depending on the underlying condition of the patient. Regular bloodwork and follow-up



visits with the physician, home care nurse and dietitian are essential.

Long-term complications of home parenteral nutrition include the usual complications of parenteral nutrition. However, line sepsis, venous thrombosis and liver disease represent profound challenges in the long-term setting. Metabolic bone disease is also common in patients receiving home parenteral nutrition, but is likely due to the underlying conditions which require home parenteral nutrition (e.g., Crohn disease with previous corticosteroid use) rather than due to the parenteral nutrition itself.

7.5. Nutrition Support in Specific Conditions

7.5.1 The Malnourished Patient

The malnourished patient represents a special challenge in nutrition. Malnourished patients have energy requirements which are 10% to 20% below predicted by the Harris-Benedict equation, as discussed above. Furthermore, such patients are at particular risk for “refeeding syndrome,” consisting of a variety of problems occurring when nutrition is initiated. Fluid retention with marked edema and even congestive heart failure may occur. As the intracellular compartment is regenerated with refeeding, there may be shifts of extracellular substances into the cell including phosphorous, potassium and magnesium. These shifts are facilitated by insulin which is released in response to glucose given as part of the nutrition. It is very important to provide adequate amounts of phosphorous, potassium and magnesium. Other problems include glucose intolerance and thiamine deficiency.

With the above problems in mind, the malnourished patient who is being re-fed requires careful clinical monitoring of fluid status and daily measurement of serum phosphorous, potassium, magnesium and glucose until normal, stable levels are obtained. Vitamins, especially thiamine, should be administered at the onset of nutritional repletion and continued for several days.

7.5.2 Crohn disease

Crohn disease represents a special situation for nutrition due to potential problems with strictures, short bowel and sepsis. Parenteral nutrition plays a role as adjunct therapy in Crohn's patients who are obstructed or have short bowel syndrome. There is clearly a role for enteral nutrition in the paediatric population, where this modality provides for linear growth in growth-retarded patients. It should be noted that monomeric (elemental) diets have not been shown to be more effective than polymeric diets when these formulas have been compared.

7.4.4 Pancreatitis

Pancreatitis offers a unique challenge in nutrition. First, infusion of nutrients into the duodenum stimulates pancreatic secretion, which may be theoretically harmful in patients with pancreatitis. Second, patients with pancreatitis frequently have vomiting and ileus as a manifestation of their condition. Finally, the pancreas secretes both exocrine and endocrine products important in nutrition, namely pancreatic enzymes and insulin. Despite these considerations, the preferred method of providing nutrition in acute pancreatitis is elemental jejunal feeding which has been found to be safer than parenteral nutrition with fewer septic complications. Uncommonly, parenteral nutrition may be necessary if enteral feeding is not tolerated.





PAEDIATRICS

Chapter 21: General Approach to Paediatric Gastroenterology and Hepatology

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1. Abdominal Pain

1.1 Overview

Abdominal pain is one of the most common complaints among children seeking medical attention. Its prevalence varies among the studies, but is around 8-20% of all school-age children.

Children may suffer of abdominal pain only or experience abdominal pain together with other gastrointestinal and extra-gastrointestinal symptoms. Children may present acutely or sub-acutely demanding immediate medical attention or they may present with a history of continuous or intermittent episodes of abdominal pain over a prolonged period of time. Further, the experience and expression of abdominal pain may vary greatly among children of different ages or socioeconomic backgrounds. Abdominal pain lasting more than 2 months is defined as chronic abdominal pain.

The work-up of abdominal pain requires a thorough clinical evaluation and a holistic approach including investigations for intra- and extra-abdominal etiologies as well as non-organic causes of pain.

1.2 Approach

The experience and the expression of abdominal pain in children are different compared to adolescents or adults. Abdominal pain in infants and toddlers may present as irritability, crying or food refusal. Apart from the pain, the presence of other accompanying symptoms such as vomiting, diarrhea, bloating or failure to thrive will often prompt more targeted clinical investigations in these very young children. Toddlers and school-age children can report abdominal pain, but when asked about the frequency, duration and localization of the pain, the answers are inconsistent. For this age group, it has to be kept in mind that children often localize pain to the abdominal area, even if its' origin is different, such as the lungs (e.g. pneumonia) or the pelvis (urogenital tract)

The adolescent patient is capable of giving a more detailed description of pain; however, psychosocial factors or mental disorders, such as anxiety or depression may strongly impact not only the experience of the pain, but also description of it in the medical interview. Self-reported severity and acuity of the abdominal pain alone do not often help determining whether a child has a condition that requires immediate medical or surgical attention in order to prevent organ damage or not. Children and adolescents with constipation may present to the Emergency Department with equally severe abdominal pain, as children and adolescents with e.g. acute appendicitis.

A detailed medical history should focus on patient and parental reports: what triggers the pain, how severe is it (for example on a scale from 1-10 with 1 being no pain and 10 being the worst possible pain), what other signs and symptoms are present (e.g. fever, vomiting, diarrhea), what happens to the pain with eating and/or bowel motions, what measures alleviate the pain and what makes it worse. Care should be also taken to evaluate whether there is a past medical or family history of migraines and anxiety, if there are any current social stressors or any recent changes in the school or the family. A thorough physical exam will then help to establish a working diagnosis and will determine the urgency of the diagnostic work-up.

An overall distressed clinical appearance, the presence of alarm symptoms (see below) and significant alterations in vital signs warrants looking for an underlying organic disease and should always prompt further diagnostic testing.



Red flags: Alarm symptoms are, but are not limited to, involuntary weight loss, deceleration of linear growth, gastrointestinal blood loss, significant vomiting (in terms of volume or frequency), any bilious vomiting, chronic diarrhea, persistent right upper or right lower quadrant pain, unexplained fever and family history of inflammatory bowel disease or celiac disease (Table 1).

Table 1. Red flags symptoms

-
- Involuntary weight loss
 - Impaired growth
 - Gastrointestinal Blood loss
 - Significant vomiting or bilious vomiting
 - Chronic severe diarrhea
 - Perianal disease
 - Persistent right upper or right lower quadrant pain
 - Dysphagia, Heartburn
 - Unexplained Fever
 - Iron deficient anemia
 - Night waking (relative since night waking is also observed in FGID)
 - Family History for inflammatory bowel or Celiac disease, Peptic ulcer disease or MALT Lymphoma
-

Gastrointestinal diseases presenting with acute abdominal pain that require acute medical or surgical intervention are listed in Table 2. In these cases further diagnostic information using laboratory and imaging methods if readily available may help the triaging process, but if done in a peripheral hospital or community office, should not delay treatment.

Abdominal pain that is continuous or intermittent for 2 months or longer is considered chronic. In most children the origin of the abdominal pain is benign and the diagnosis of a functional gastrointestinal disorder (FGID) can be established. However, structural, metabolic, inflammatory, infectious and neoplastic disorders need to be considered and ruled out. The extent of the diagnostic work-up depends on the presence of alarm symptoms as described above, and may otherwise follow a stepwise approach.

In the absence of any specific medical history or symptoms that direct further investigations, the diagnostic work up of chronic abdominal pain includes blood work and possibly abdominal imaging. Blood work should include blood cell counts, erythrocyte indices, inflammation markers, albumin, glucose, amylase, lipase, liver parameters and celiac serology. Abdominal ultrasound is a cost-effective, non-invasive imaging technique



that can assist in ruling-out disease processes such as cholelithiasis, pancreatitis, mesenteric lymphadenitis, etc.. A urinalysis is necessary to exclude renal involvement, such as urinary tract infection. Further testing for the evaluation of gastrointestinal diseases includes: upper gastrointestinal X-rays with small bowel follow-through, upper endoscopy and colonoscopy, or MR enterography.

Table 2. Differential diagnosis of abdominal pain in children, not neonates

Acute		
Obstructive	Intestinal malrotation Volvulus Intestinal herniation Intussusception Intestinal duplication cysts Congenital adhesions Foreign bodies Choledocholithiasis	Ultrasound/CT Upper Gi series
Inflammatory	Appendicitis Pancreatitis Cholangitis/Cholecystitis	Ultrasound/CT Blood work
Other	Ovarian rupture/torsion Testicular Torsion Obstructive Uropathy Pyelonephritis Pneumonia	Ultrasound/CT
Chronic		
Inflammatory	Crohn's Disease Ulcerative Colitis Celiac disease Food allergies	Blood work Upper endoscopy/ Colonoscopy MR enterography
Maldigestion	Lactose intolerance Fructose intolerance Small intestinal bacterial overgrowth	Upper endoscopy Breath test or trial of elimination
Other	Peptic ulcer disease Gastritis Mediterranean Fever Superior Mesenteric Artery (SMA) syndrome	Upper endoscopy Genetic Upper Gi series

For the approach in neonates presenting with irritability and pain assumed to be of abdominal origin the reader is directed to specific literature in Neonatology.



1.3 Management

Managing children presenting with chronic abdominal pain can be challenging, primarily because it is often difficult to establish a diagnosis and secondarily because chronic pain is associated with increased patient and parental anxiety to miss a serious disease.

Dietary restrictions can be trialed in patients for whom food sensitivities/allergies are suspected (lactose or fructose intolerance, cow's milk protein allergy) to see whether certain food groups affect the pain. These trials should be performed only for a limited time (2-3 weeks) and while maintaining nutritional balance in the diet that is consumed. If the symptoms do not change with these dietary restrictive measures, normal diet should be resumed.

The treatment of the organic causes of abdominal pain is disease specific, some of which are described in later chapters.

Nevertheless, most patients presenting with chronic abdominal pain are diagnosed with functional abdominal pain. The ROME III criteria published in 2006 define functional gastrointestinal disorders (FGID) in infants, children and adolescents. There are four categories involving abdominal pain: Functional dyspepsia, Abdominal Migraine, Irritable Bowel Syndrome, Childhood functional pain (Table 3). These descriptive definitions, as well as the absence of any organic findings, will help establish a diagnosis of FGID, and provide some re-assurance towards the concerned family that no further testing is necessary. Negative findings of various investigations should be communicated clearly to the patients and their families to facilitate a process of understanding that not a medical drug or intervention, but a long-term approach involving psychotherapy and cognitive behavioral therapy is needed to treat the pain. While establishing the diagnosis of FGID allows the cessation of extensive investigations, it is important to ask the patients and their families to report any new symptoms that may be indicative of other organic conditions.

Table 3. Functional gastrointestinal disorders associated with abdominal pain

Classification	Diagnostic criteria		
Functional Dyspepsia	1. Persistent/recurrent pain/discomfort in the upper abdomen 2. No relief by defecation, no association with change in stool frequency or form	Criteria full filled at least once a week for last 2 months	No evidence of an inflammatory, anatomic, metabolic or neoplastic process
Irritable bowel syndrome	Abdominal discomfort or pain associated with: 1.improved with defecation or 2. onset with change in frequency of stool or 3. onset with change in form of stool at least 25% of the time	Criteria full filled at least once a week for last 2 months	No evidence of an inflammatory, anatomic, metabolic or neoplastic process



Classification	Diagnostic criteria		
Abdominal migraine	1. Paroxysmal episodes of intense, acute periumbilical pain that lasts ≥ 1 hour 2. Intervening periods of usual health lasting weeks to months 3. Pain interferes with normal activities 4. Pain is associated with ≥ 2 of the following: a. Anorexia, b. Nausea c. Vomiting, d. Headache e. Photophobia, f. Pallor	Criteria full filled at least 2x for the last 12 months	No evidence of an inflammatory, anatomic, metabolic or neoplastic process
Functional abdominal pain	1. Episodic or continuous abdominal pain 2. Insufficient criteria for other FGIDs	Criteria full filled at least once a week for last 2 months	No evidence of inflammatory, anatomic, metabolic or neoplastic processes

2. Vomiting

2.1 Overview

Vomiting is a very frequent, non-specific symptom in children. Vomiting may be indicative for a gastrointestinal pathology but may also be a secondary symptom of any other medical condition including uropathies, systemic diseases or increased intracerebral hypertension.

2.2 Approach

Similar to the approach to a child with abdominal pain, a carefully taken medical history will help determining whether vomiting is part of a systemic illness or the main indicator for a specific gastrointestinal pathology. The medical history should focus on the onset and duration of the vomiting (acute or chronic), diurnal variation in its presentation (e.g. does it occur at night?), its nature (e.g. bloody, bilious), association to eating and change in bowel movements, and concomitant symptoms.

Red flags: Acute onset of bilious vomiting is a sign of paralytic or obstructive intestinal ileus requiring emergent diagnostic work-up to identify surgical causes that need immediate intervention. Vomiting of fresh blood (hematemesis) can be secondary to any mucosal oral, nasal, pharyngeal or esophageal lesions (including variceal bleeding). The source and amount of bleeding determine the need for emergent work-up. A child presenting with coffee-ground emesis needs emergent evaluation and treatment of a



possible underlying bleeding gastroduodenal ulcer. It is important to note that food flavouring may stain the vomit green or red and confuse the clinical picture; parents should be asked regarding recent food intake.

Obstructive causes: Vomiting may be a symptom of intestinal malrotation, gastric outlet and/or duodenal obstruction that need further investigations with abdominal ultrasound, upper GI series and upper endoscopy. Gastroparesis, primary or secondary post-infectious, can also result in chronic vomiting. Gastroparesis can be diagnosed with gastric emptying studies of a radioactive traced meal or fluid.

Non-obstructive causes: Vomiting most often presents as part of a viral or bacterial gastritis or gastroenteritis. In these instances the onset is acute, usually accompanied by nausea, diarrhea, fever and malaise. Viral gastrointestinal infections are self-limited and no further diagnostic evaluation is needed; however when symptoms are prolonged, stool studies (culture for bacteria, electron microscopy for viruses and specific ova and parasite investigations) are helpful to identify the disease-causing pathogen. Acute infection with *Helicobacter pylori* may also present with vomiting, and can be diagnosed by obtaining tissue biopsies from the stomach during an esophagoduodenogastroscopy.

Further vomiting and epigastric pain is a classical clinical presentation of acute pancreatitis. Thus, if blood work is initiated to control electrolyte status and infectious parameter, serum amylase and lipase should be included. Also children with acute hepatitis can present with vomiting. Approaches to pancreatitis and hepatitis are described in subsequent chapters.

Other causes: Eosinophilic gastroenteritis, Celiac disease, Crohn's disease may affect the gastric and/or duodenal mucosal integrity and, hence, lead to vomiting. To investigate these conditions a targeted work-up including blood work and upper endoscopy as described in later chapters is indicated.

Vomiting can be the result of acute or chronic drug use; it is often seen in children/adolescents with chronic cannabis use. In older children and adolescents vomiting may be the lead organic symptom of an underlying eating disorder, such as bulimia. Similar to the approach for functional gastrointestinal disorder, a thorough diagnostic work-up is necessary to convince the families of the absence of any organic disease.

Lastly, it should be pointed out that vomiting is a very non-specific symptom and may accompany other, non-gastrointestinal disease, such as sepsis, meningitis, urinary tract infection, obstructive uropathy, inborn error of metabolism, diabetic ketoacidosis and intracranial hypertension or mass lesion, etc.

Gastroesophageal reflux: Parents may refer to symptoms secondary to gastroesophageal reflux (GER), vomiting. These reflux episodes are usually related to feeding, but may occur throughout the day and also the night when the child is in supine position. Most infants <12-15 months of age show physiological reflux symptoms with some vomiting after feeding, but appear otherwise well and show normal weight and height gain. These children do not require treatment. However, in some infants' gastroesophageal reflux affects health and well-being; this condition is called GER disease (GERD). These infants can be irritable due to reflux/vomiting episodes after feeding and in severe cases they may fail to thrive due to food refusal and/or frank feeding aversion. Older children and adolescents with GERD often report vomiting rather than heartburn. Thus, GERD should be considered when evaluating children with recurrent vomiting.



The diagnosis of GERD is made clinically on the basis of the medical history and physical examination. Imaging techniques such as upper GI series are not required to establish this diagnosis and should not be used routinely. Gastroesophageal pH assessment is not necessary for the diagnosis of GERD. It is occasionally used to clarify the role of GERD in symptoms such as irritability, coughing and chest pain of infants and children with neurological, respiratory or other chronic conditions. It is also sometimes used to assess the efficacy of anti-acid treatment.

Mostly, but not exclusively in infants, there is significant clinical overlap between GERD and cow's milk protein allergy; the latter is also frequently associated with vomiting. In suspected cases changing the formula may often be beneficial to differentiate vomiting due to cow's milk protein intolerance from other causes of GERD. Partial or extensively hydrolyzed or amino acid based formulas can be trialed for 2-4 weeks. During these feeding trials close monitoring is warranted to assess cessation of vomiting, changes in weight and/or appearance of new symptoms that may suggest a more complex systemic condition.

Functional gastrointestinal disorders with vomiting: Children reporting vomiting episodes that follow a particular pattern may suffer from cyclic vomiting syndrome. This functional gastrointestinal disorder can be diagnosed in children of various ages. The pattern includes vomiting attacks that may last for a couple of days. During these attacks the affected child may exhibit high frequent vomiting, may experience severe malaise with or without headaches or abdominal pain. Often these episodes are preceded by a sensory aura, similar to what is described with migraines, and are followed by a phase of exhaustion and recovery. Periods of good health in between these episodes hint to a diagnosis of cyclic vomiting. Nevertheless, before making a diagnosis of this FGID, organic causes need to be rule out.

Similarly, rumination syndrome is a FGID that presents with painless and effortless regurgitation of food, re-swallowing and/or spitting within minutes after starting a meal. Also in these cases organic causes need to be ruled out before to make a diagnosis.

2.3 Management

The fact that vomiting may be secondary to various causes limits the ability to make universal recommendations regarding the diagnostic work-up. Blood work including electrolytes, blood gas, urea nitrogen and/or hepatic, renal and pancreatic parameters, as well as infectious markers is required for any child presenting with prolonged or severe vomiting episodes or for infants presenting with vomiting and weight loss. A celiac serology may be considered as well. Initial imaging to evaluate for gastrointestinal causes may include abdominal ultrasound and Upper GI series. Upper endoscopy may be used as well if the aforementioned work-up is negative.

Emergency situations: Children presenting with bilious and bloody emesis require emergent care including assessment for acute surgical causes and/or gastroduodenal ulcer bleeding. In these cases a clinical exam should be accompanied by blood work to assess the degree of blood loss, dehydration and electrolyte dysbalances as well as cross sectional imaging, or in the later case by upper endoscopy. Acute onset of upper gastrointestinal bleeding should trigger immediate treatment with continuous intravenous proton-pump inhibitor infusion.

Obstructive and Non-obstructive causes: Malrotation, gastric or duodenal webs and duplications require referral to a Paediatric Surgeon. Gastrointestinal infections are in



most cases self-limiting, and for the otherwise healthy child don't require specific anti infectious treatment. In these instances, the main treatment aim is to initiate and monitor sufficient hydration. Studies have suggested using single doses of ondansetron (0.2 mg/kg oral; parenteral 0.15 mg/kg; maximum 4 mg) to prevent hospital admission and iv-hydration.

Managing GERD: For infants <12 months with GERD a change to a prone or lateral sleeping position is no longer recommended due to the increased risk of sudden infant death syndrome (SIDS). However, children may profit from a more upright sleeping position (about 30 degrees incline). The adolescent child may identify certain triggers (mainly food triggers) helping to reduce GER episodes to a minimum by avoiding these. Children for whom a clinical diagnosis of GERD is made can be treated with H₂-blockers or Proton-Pump Inhibitors (PPI) (Table 4). GER should not be treated with medications.

Table 4. Proton Pump inhibitors

Generic drug name	Paediatric dosing	Dose limits
Omeprazole	0.5-1.5 mg/kg/dose PO once daily	
CYP2C19 inducer and inhibitor	Erosive esophagitis: 1 month-2 years: 1-3 mg/kg/day PO qd or div bid >2 years: 0.7-2.5 mg/kg/day PO qd or div bid	Dose limit: 3.5 mg/kg/day, or 80 mg/day, whichever is less
Lansoprazole	<10 kg: 7.5 mg PO qd 10-30 kg: 15 mg PO qd ≥30 kg: 30 mg PO qd	Dose limit: 1.6 mg/kg/day or 30 mg/day, whichever is less
CYP2C19, CYP3A4 inducer Orally-disintegrating tablets available		
Esomeprazole	Non-erosive reflux disease (>1 month) <5 kg: 5 mg PO daily ≥5 kg: 10 mg PO daily 12-17 years: 20 mg PO daily Erosive esophagitis (>1 month) <5 kg: 5 mg PO daily 5-20 kg: 10 mg PO daily ≥20 kg: 20 mg PO daily 12-17 years: 20-40 mg PO daily	Dose limit: 40 mg/day
CYP2C19 inducer Granules for oral suspension available		
RABEprazole	<i>U.S. labeling:</i> Children ≥12 years: 20 mg qd for ≤8 weeks	
CYP2C19, CYP3A4 inducer, but less enzymatically metabolized		



Caution: Long-term use may cause atrophic gastritis or osteoporosis-induced fracture,s as well as increases the risk for gastrointestinal and pulmonary infections.

H₂-blockers have a rapid onset of action, but are characterized by tachyphylaxis (loose efficacy over time). Thus for longer-term treatment, PPI are more adequate. The North American, as well as European Society for Paediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN and ESPGHAN) recommended using the smallest effective dose, as well as once a day dosing. However, for some patients dose optimization to the upper range as well as b.i.d. dosing may help treat breakthrough symptoms. Older children and adolescent who present with symptoms suggesting GERD, an empiric trial with PPI can be initiated. It is nevertheless important to keep in mind, that symptom cessation may also be due to a placebo effect in cases of functional dyspepsia.

Though prokinetics are widely prescribed in Paediatrics, these drugs have a very unfavorable safety profile. The NASPGHAN and ESPGHAN do not recommend routine use of prokinetics for GERD.

If symptoms do not respond to treatment, further work-up is recommended. That includes upper endoscopy to look for esophageal or gastric inflammation, secondary for e.g. to eosinophilic gastroenteritis or *Helicobacter pylori* infection.

Functional gastrointestinal disorder with vomiting: Managing cyclic vomiting is challenging and requires effective communication with the family and the child. Often a thorough work-up is necessary to not only rule out organic causes but to also allow families accept the diagnosis and participate in cognitive behavioral counseling. In some instances social or physical stressors can be identified that trigger the vomiting attacks. Identification of these triggers and counseling of relief strategies may help limiting the symptoms. Management of CVS is divided in acute and chronic therapy. The family and child should be given practical advice on how to deal with the symptoms. The management in the acute setting include use of antiemetic medications early on (e.g. repeat doses of ondansetron and/or sumatriptan). PPI and acetaminophen can be given when there is concomitant abdominal pain. The family is to be instructed that while food intake can be stopped during the acute events, adequate fluids should be provided. Once the high frequent vomiting has started, sedation with mild doses of benzodiazepine at home, or iv-doses in a hospital setting, have been successful to cease the attack. Families often seek medical attention in the Emergency room during the acute attacks, and management is facilitated when a document that includes diagnosis and treatment instruction is available for the physician-on call. In cases of frequent CVS attacks, chronic preventative treatment with tricycle antidepressants, such as amitriptyline can be considered.

3. Diarrhea

3.1 Overview

Acute diarrhea is the most common indication for hospitalization in children < 5 years of age. It is defined as 4 or more watery stools a day and is considered acute if it lasts for less than 2 weeks and chronic or protracted if it continues longer than that.



3.2 Approach to the child with acute diarrhea

Toddlers' diarrhea and infections are the primary causes of acute diarrhea. The former occurs from excessive consumption of juice that surpasses the absorptive capacity of the intestinal mucosa leading to osmotic diarrhea. The latter is usually secondary to viruses, such as Rotavirus, Norwalk and Torovirus. Bacterial pathogens are identified less frequently and include *Escherichia coli*, *Campylobacter jejuni*, *Salmonella typhi*, *Shigella dysenterica* and *Yersinia enterocolitica*. The most common parasites are *Giardia* and *Cryptosporidium*. Besides gastrointestinal infections, other causes of acute diarrhea include other infections (e.g. urinary tract infections), medication side effects (e.g. antibiotics), surgical complications (e.g. partial intestinal obstruction, appendicitis), metabolic disorders.

The medical history helps to establish the acute duration of the diarrhea, as well as onset and the presence of any concomitant symptoms, such as fever, vomiting and/or abdominal pain. Identifying sick contacts may help to confirm an infectious etiology. The physical exam should be focused on assessing hydration. Changes in weight have been used for that purpose; however, more recent data challenge the accuracy of this tool. Assessment of skin turgor, capillary refill time, alertness and respiratory pattern can help determine the presence and severity of dehydration.

Management of the child with acute diarrhea

Generally infectious diarrhea is self-limited and does not require specific treatment, except in instances of prolonged infection with bacterial pathogens and parasites. The management of acute diarrhea is aimed at treating secondary complications, such as dehydration, as well as addressing the underlying condition. Mild dehydration is managed with adequate, oral fluid resuscitation. In cases of moderate (>5% of weight loss) to severe dehydration (>9% of weight loss) a more aggressive approach is warranted including blood work and careful re-hydration, occasionally in the hospital setting. Rapid electrolyte (e.g. Na) shifts should be avoided. The reader is directed to the general paediatric literature (see references) to manage re-hydration therapy in children.

Stool cultures are indicated when the diarrhea is prolonged (7-10 days), high frequent or voluminous or bloody in order to identify a pathogen and determine the necessity for and the type of treatment. Probiotics may help to shorten the duration of diarrheal symptoms in the uncomplicated acute gastroenteritis. Early feeding and continuation of breastfeeding is recommended. There is no evidence to follow 'bland' diets in the setting of diarrhea.

Acute diarrhea in the immune compromised child necessitates immediate work-up to search for the causative pathogen. These patients are at risk for life-threatening opportunistic infections and often require targeted antibiotic or antiviral treatment.

Restriction of juice consumption is required to manage toddlers' diarrhea.

3.3 Approach to the child with chronic diarrhea

Prolonged or protracted diarrhea may present very early with onset in the neonatal period or later in childhood or adolescence (see Table 5 for differential diagnoses). Diarrhea and failure to thrive may signify malabsorption or maldigestion, as seen in patients with celiac disease or inflammatory bowel disease. Steatorrhea needs to be discriminated as a symptom of fat maldigestion or absorption seen in patients with



pancreatic insufficiency, which may be primary (e.g. cystic fibrosis) or secondary (e.g. enterokinase deficiency secondary to duodenal inflammation).

Table 5. Differential diagnosis of chronic diarrhea

Neonatal diarrhea		
Structural defects		Severe
- Microvillous inclusion disease		Malabsorption
- Tufting enteropathies		Often TPN dependent
Channel defects	Mutations in	Watery diarrhea
- congenital chloride losing enteropathy	SLC26A3	Metabolic alkalosis
- congenital sodium losing enteropathy	unknown	Increased chloride, sodium or bile in stool
- Sodium-glucose transporter defect	SLC5A1	
- Ileal bile acid receptor defect		
Acrodermatitis enteropathica	Zinc deficiency, seen e.g. in Cystic Fibrosis	Clinical improvement upon Zinc substitution
Diarrhea in infancy and childhood		
Toddler's diarrhea	Relative Disaccharidase deficiency due to overconsumption of juices and fruits	Normal growth Symptom relief with elimination
Postinfectious gastroenteropathies	Gastrointestinal symptoms triggered by an infection of the GI tract	Self-limiting
Lactose or Fructose intolerance	Lactase or Disaccharidase deficiency	Normal growth Symptoms relief with elimination
Food allergies (e.g. cow's milk protein allergy)	Allergic inflammatory response to Cow's milk protein	Symptom relief with complete CMP elimination
Celiac disease	Inflammatory response to Gluten	Cured with complete Gluten elimination
Autoimmune enteropathy	Mutation in FOXP3 gene	Anti enterocyte antibodies
- immune dysregulation polyendocrinopathy, enteropathy syndrome (IPEX)		CD3-T cell infiltrate in intestinal mucosa



Diarrhea in infancy and childhood

Protein-losing enteropathy	Primary or secondary due to intestinal lymphangiectasis, autoimmune enteropathies or congenital glycosylation defect	positive α -antitrypsin clearance with α -antitrypsin being determined in serum and a 24h stool collection
Steatorrhea	Pancreas insufficiency, relative or absolute, bile acid deficiency	72hr fat measurements in stool
Hirschsprung's disease		Rectal biopsies
Intestinal Pseudoobstruction	Diarrhea caused by Small bowel bacterial overgrowth (SBO)	Symptom improvement following SBO treatment
Irritable bowel syndrome	FGID	Absence of organic causes

There is overlap in the presentation age between all 3 age categories of many of the listed diarrheal causes.

Children and adolescents may develop chronic diarrheal symptoms following an episode of acute gastroenteritis. This phenomenon is called postinfectious enteropathy and is secondary to impaired integrity of the intestinal mucosa due to the primary infection. Recovery may take up to several months in some individuals. Further, similar to the observations made in adults, predisposed children or adolescents may develop irritable bowel syndrome (IBS) following an episode of acute gastrointestinal infection. Alternatively, their diarrhea may be secondary to IBS without the presence of an identifiable infectious trigger. Table 6 lists the ROME III criteria for IBS. The absence of red flag symptoms such as poor growth, fever, vomiting, bloody diarrhea, perianal disease, suggest a functional gastrointestinal disorder. That is further supported by the lack of laboratory abnormalities, such as electrolyte imbalances, raised inflammatory markers (e.g. ESR, CRP) and iron deficiency anemia, as well as a negative celiac screen (normal tissue transglutaminase/endomysial antibodies in the setting of normal total IgA). However, the diagnostic work-up may require more extensive investigations to reassure the family and the physician that there is no organic etiology for the symptoms.

In general, in patients with chronic diarrhea a stepwise diagnostic work-up helps to avoid unnecessary investigations. Initial blood work should include electrolytes, venous blood gas, inflammatory markers, blood cell counts, iron status, as well as albumin. This can be followed by blood work to assess fat-soluble vitamins, such as vitamin A and E, zinc (through alkaline phosphatase levels) and celiac serology in children on gluten-containing diet. Stool should be sent for bacterial cultures (and PCR for *Clostridium difficile* toxin), viral and parasite analysis even in the setting of protracted diarrhea to



exclude infectious etiologies. Following exclusion of infectious agents protracted diarrhea should always raise concerns regarding chronic inflammatory changes of the intestine.

Table 6. Functional gastrointestinal disorder associated with diarrhea

Classification	Diagnostic criteria		
Irritable Bowel syndrome	1. Abdominal discomfort or pain associated with <i>2 or more</i> of the following at least 25% of the time: a. Improved with defecation b. Onset associated with a change in frequency of stool c. Onset associated with a change in form (appearance) of stool.	Criteria full filled at least once a week for last 2 months	No evidence of an inflammatory, anatomic, metabolic or neoplastic process

Distinguishing between osmotic and secretory diarrhea may help to direct further tests. This is done by stopping all oral intake; if the symptoms cease it is osmotic diarrhea but if they continue it is secretory. This trial should be done in hospital where iv-fluids are available.

Further, watery stool can be analyzed for electrolyte and osmolality, and can also be tested for reducing substances to search for carbohydrate malabsorption. Fat malabsorption is best assessed with a 72h-stool collection accompanied by a strict diet diary to allow calculation the fat absorptive coefficient. Fast qualitative orientation of fecal fat excretion can be achieved by performing a Sudan red stain on a stool smear sample and look for fat globules using a normal light microscope. The pancreas status can be evaluated by determining the fecal elastase concentration in a spot stool sample.

Esophagogastroduodenoscopy, colonoscopy and/or magnetic resonance enterography (to image the small bowel), is often necessary to confirm diagnosis for celiac disease, to establish a diagnosis of lactase and disaccharidase deficiency (with determination of the enzyme activity on fresh frozen tissue samples), to establish or rule out inflammatory bowel disease as well as diagnose diseases that cause structural defects at the intestinal brush border membrane.



3.4 Management of the child with chronic diarrhea

In infants and children in whom intolerance to CMP is suspected, a change in formula and/or CMP elimination from the diet of the breast-feeding mother can be trialed to see if the symptoms resolve. In children with suspicion for specific food intolerances, diets that eliminate the causative food allergen need to be established. This needs to be done very carefully and under continuous professional monitoring of the nutritional status the child.

Children who suffer of diseases causing structural defects at the level of the intestinal mucosa or chronic intestinal inflammation need to be followed by Paediatric Gastroenterologists or ideally, in a specialized centre.

Children and adolescents, who meet criteria of a functional gastrointestinal disorder, require re-assurance in regard to the absence of any organic causes. Several studies in adults have shown some efficacy for partial serotonin agonists, non-absorbable antibiotics, chloride channel activators and probiotics. However, in Paediatrics data are not sufficient to support specific medical treatments. In children there is some suggestion that cognitive behavioral therapy and gut-directed hypnotherapy are effective in the treatment of children with irritable bowel syndrome.

4 Constipation

4.1 Overview

Constipation is a frequent complaint that represents about 25% of the Paediatric Gastroenterologist referrals. Often constipation is a chronic issue associated with significant parental and/or patient anxiety. Hence its management demands sensitive and clear guidance from health providers.

4.2 Approach

Constipation is defined as reduced frequency of bowel movements, occasionally associated with the painful passage of large stool volumes or hard stools and even fecal retention. Encopresis (soiling of underwear with loose fecal material without realizing it) is often associated with severe constipation. Most often constipation is non-organic, functional. The role of genes, nervous system dysregulation and muscular dysfunction in the pathogenesis of functional constipation has yet to be explored (Table 7). The treatment approach, however, is the same despite variable presentation of functional constipation.



Table 7. Functional gastrointestinal disorder associated with constipation

Classification	Diagnostic criteria		
Functional constipation	Must include 2 or more of the following: 1. Two or fewer defecations in the toilet per week 2. At least 1 episode of fecal incontinence per week 3. History of retentive posturing or excessive volitional stool retention 4. History of painful or hard bowel movements 5. Presence of a large fecal mass in the rectum 6. History of large diameter stools that may obstruct the toilet	Criteria full filled at least once a week for last 2 months in a child with a developmental age of at least 4 years with insufficient criteria for diagnosis of IBS	no evidence of an inflammatory, anatomic, metabolic or neoplastic process

Organic causes of constipation need to be screened for to allow early implementation of constipation management strategies rather than prolong diagnostic testing.

Key questions in history taking include meconium passage within the first 48 hours of life, the ability to defecate as neonate/toddler, as well as the success of toilet training. Details about the frequency and consistency of the stool, the presence of soiling or encopresis, as well as the presence of blood in stool need to be obtained. Often children with long standing constipation have anorexia; some develop nausea and others complain of abdominal pain and/or distension. Red flags potentially indicating other causes of constipation include failure to thrive, fever, vomiting and/or presence of perianal disease, as well as urinary incontinence. It is important to note, however, that urinary incontinence with or without bladder dysfunction and/or vesico-urethral reflux disease can be seen in patients secondary to extensive fecal impaction.

Infants and children may develop constipation upon introduction of cow's milk. These associations may be indicative of cow's milk protein allergy/intolerance. Cases of cow's milk protein intolerances have been described presenting with equally severe constipation compared to patients with Hirschsprung's disease. Similarly, constipation following gluten introduction may hint for an underlying celiac disease.

Further, in the older child onset of constipation is often associated with toilet training, life-altering events, and/or other psychosocial stressors. Often the child has experienced hard painful rectal eliminations and has adopted withholding strategies avoiding defecation. Key questions to identify withholding behaviors include whether the child is witnessed squeezing their buttocks, sitting in room corners and rocking back and forth.



Anal fissure may develop from the passage of hard stools and usually present as streaks of bright red blood on the stool or as blood seen on the toilet paper. Absence of red flags and identification of fissures on perianal inspection supports the diagnosis of functional constipation and enables the physician to provide patient re-assurance. Table 8 summarizes the differential diagnosis for rectal discharge of bright red blood, which need to be addressed if the bleeding persists despite adequate treatment of constipation or in cases of voluminous blood loss.

On physical examination fecal matter is frequently palpable, usually at the left abdominal quadrants. Perianal inspection should always be performed to identify fissures, signs of trauma, fistulas and abscesses. Haemorrhoids are extremely infrequent in childhood (outside of portal hypertension) and, hence, detection of lesions reminiscent of haemorrhoids should raise concerns regarding inflammatory bowel disease (inflamed skin tags may have a similar appearance) or immune deficiencies (e.g. severe perianal disease is often identified in patients with chronic granulomatous disease). Digital rectal examination is helpful in investigating Hirschsprung's disease (tight sphincter and explosive stool discharge upon insertion of a finger); however, only experienced physicians should perform it. Lastly, a close look should be given at the child's back. Skin changes overlying the base of the spine, such as dimples, hyperpigmented patches with or without tufts of hair, or a fatty growth may indicate the presence of spina bifida occulta and/or tethered cord, which can cause fecal and urinary incontinence.

Blood work is not necessary in most of the cases and should only be performed in children for whom the medical history and/or examination raise suspicion of an underlying organic etiology to exclude celiac disease and hypothyroidism, and also chronic inflammation.

In term neonates, problems with meconium passage are indicative of conditions such as cystic fibrosis, Hirschsprung's disease, as well as anorectal malformations. Physical examination as well as imaging using rectal contrast enemas and histopathological evaluation of rectal tissue biopsies will support establishing or excluding a diagnosis of the two later diseases. In some instances magnetresonance imaging of the spine to look for malformation of the central nervous system, e.g. tethered cord may conclude the diagnostic work up.

Table 8. Differential diagnosis of rectal bloody discharge

Diseases	Clinical presentation	Investigation
Meckel diverticulum	Often painless bloody discharge in absence of stool	Meckel scanning using technetium-99m pertechnetate scintiscan
Juvenile polyp	Painless bloody discharge	Colonoscopy



Diseases	Clinical presentation	Investigation
Polypsis syndromes - Familial adenomatous polypsis - Juvenile polypsis syndrome (hamartomatous polypsis)	Painless bloody discharge often extracolonic manifestations Skin and buccal pigmentation in Peutz-Jeghers Syndrome	Upper endoscopy and Colonoscopy
Proctitis/ distal colitis	Painful bloody discharge, often mixed with stool, patients experience urgency, possible presence of other markers of IBD	Colonoscopy
Single rectal ulcer	Painful bloody discharge, often mixed with stool,	Colonoscopy
Vascular malformations	Painless bloody discharge	Colonoscopy
Trauma/Abuse	Medical history	Physical exam

4.3 Management

In cases in which the dietary elimination of cow's milk protein (CMP) results in symptom relief, a CMP free diet should be continued until the age of 15-24 months, at which point re-introduction can be tried. Patients on dairy-free diets need to be assessed and counseled regarding optimal vitamin D and calcium intakes.

Maintenance of a regular bowel routine is important to prevent re-accumulation of stool and re-establish normal fecal load sensing. This can be achieved with regular use of a laxative. According to current data, polyethylene glycol is safe and effective in achieving treatment success and recommended by The North American Society for Paediatric Gastroenterology, Hepatology and Nutrition. Also mineral oil is effective and safe but its unpalatable taste may be a barrier. In addition, its use is not recommended in children with gastroesophageal reflux and/or at risk of aspiration due to concerns of chemical pneumonitis. It is important to note that a recent meta-analysis found the overall quality of the studies assessing various treatment options for paediatric constipation to be poor (due to lack of placebo controlled trial, lack of blinding and heterogeneity in the study designs); clinical management is currently guided by various paediatric guidelines, such as the aforementioned. Novel medications are currently being studied in randomized controlled trials the results of which are eagerly anticipated.

Bowel clean-outs may be necessary which in the younger child should be done in a hospital setting. These clean-outs are achieved with oral intake of polyethylene glycol solutions. Since often the amount needed for sufficient clean-out is not consumed orally, infusion of a polyethylene solution via nasogastric tube in a hospital setting is occasionally used.

Management of functional constipation and adherence to a treatment plan is quite challenging. A good working relationship between the family and the caregivers is the key



to success. The first step in the management includes educating the family on the causes of constipation (low fiber diets, limited fluid intake or excessive milk intake etc.), optimal defecation techniques (e.g. sitting on the toilet for 5 minutes 20 minutes after each meal to take advantage of the gastrocolic reflex, even when the urge to defecate is absent; use of a foot stool to assist with the generation of adequate abdominal pressure in smaller children), as well as the mechanism of action of various medications. Discussions with the family should address limiting the negative psychosocial effects of soiling and encopresis and overcome the guilt and/or shame the child may be experiencing. Re-assurance about the absence of any organic abnormality and the extremely low likelihood of cancer will help to set the scene for a more behavioral based approach to constipation.

The outcome of patients with Hirschsprung's has improved with the introduction of less invasive laparoscopic and transanal pull-through techniques. However, despite the success of these techniques, symptoms such as soiling, encopresis and persistent constipation can still be a problem post-operatively. These require medical attention and management. Nevertheless, long-term studies show that most adult patients are able to resume full social function.

5 The Cholestatic Infant

5.1 Overview

Neonatal jaundice due to elevation of unconjugated bilirubin is physiologic in the majority of cases in infants. In contrast, the elevation of conjugated hyperbilirubinemia is always pathological, and requires further investigation. As a general rule, infants whose jaundice does not resolve by two weeks of age, or recurs within weeks to months postnatal, may have a severe underlying illness that requires prompt intervention. With conjugated hyperbilirubinemia ($>34 \mu\text{mol/L}$ [$>2 \text{ mg/dL}$] or $>15\%$ of the total bilirubin concentration), cholestasis is frequently present. Cholestasis is defined as the impairment in flow of bile acids, bilirubin, cholesterol and drug or metabolic breakdown products normally excreted via the biliary system. Approximately one in every 2,500 infants develops cholestatic jaundice. The most common cause of infantile cholestasis is biliary atresia (25-30%), while other causes are much less frequent (intrahepatic cholestasis syndromes, such as Alagille syndrome: 20%, alpha-1-antitrypsin deficiency: 7-10%, infection: 3-8%, metabolic/endocrine: 2-7%). In approximately 15%, no specific cause can be identified (idiopathic neonatal hepatitis).

Biliary atresia is discussed in detail in a later chapter.

5.2 Approach to the Cholestatic Infant

Infants with cholestatic jaundice either present within the first few weeks of life, or later within a few months of life. The timing of presentation, as well as associated symptoms, depends on the underlying diagnosis (Table 9). Although liver disease can be the cause of this presentation, infants should also be assessed for extrahepatic manifestations such as cardiac murmurs, renal involvement and neurologic signs, such as hypotonia, that could direct further investigations. There is a wide spectrum of diagnoses associated with conjugated hyperbilirubinemia. Thus, a systematic diagnostic approach is strongly recommended to provide targeted treatment in a timely manner to a young infant, as well as to minimize unnecessary phlebotomy.



Table 9. Differential diagnosis of the cholestatic infant**Obstructive jaundice**

Choledochal cyst
 Congenital Hepatic Fibrosis / Caroli's Disease
 Gallstones or biliary sludge
 Inspissated bile
 Neonatal sclerosing cholangitis

Hepatocellular injury

Bacterial infection
 Urinary tract infection
 Sepsis
 Idiopathic neonatal hepatitis
 Listeriosis
 Syphilis
 Toxoplasmosis
 Tuberculosis
 Viral infection
 Adenovirus
 Cytomegalovirus
 Ebstein barr virus
 Coxsackie virus
 Echovirus
 Hepatitis B
 Herpes virus
 HIV
 Parvovirus B19
 Rubella

Genetic/metabolic disorders

Cystic fibrosis
 Alagille Syndrome
 Alpha-1-antitrypsin deficiency
 Bile acid synthetic defects
 Galactosemia
 Niemann-Pick disease
 Progressive familial intrahepatic cholestasis
 Tyrosinemia
 Urea cycle Disorders

Endocrine

Hypothyroidism
 Panhypopituitarism

Toxic/secondary

Parenteral nutrition-associated cholestasis
 Perinatal asphyxia / shock

Vascular disorders

Budd-Chiari syndrome

Hematologic disorders

Hemophagocytic Lymphohistiocytosis (Primary versus Secondary)



The well term infant who presents with persistent neonatal jaundice past two weeks of age, or the preterm infant past three weeks of age, requires a thorough pregnancy, birth and family history assessment, as well as a fractionated bilirubin measurement. While breast milk jaundice can cause a persistence of unconjugated hyperbilirubinemia in the second or third week of life, further investigations are required if the conjugated or direct bilirubin is elevated. A jaundiced infant with alarming symptoms such as lethargy, poor feeding, temperature instability, seizures, etc, should be investigated immediately, with a fractionated bilirubin measurement, regardless of the age at presentation.

In order to provide essential therapeutic management, the most time-sensitive diagnoses include: sepsis, galactosemia, tyrosinemia, biliary atresia, and hypothyroidism, with or without panhypopituitarism. A septic infant can present in the first week of life, or later, with temperature and hemodynamic instability, and may display rashes consistent with a viral infection. Those with metabolic disorders, such as galactosemia, panhypopituitarism, amino acid metabolic defects, and glycogen storage diseases, may present as acutely unwell with hypoglycaemia, hyperammonemia, or metabolic acidosis. Patients with biliary atresia are typically well children with persistent jaundice past two weeks of age.

Once conjugated hyperbilirubinemia has been identified, initial hepatobiliary assessments include liver biochemistry (alanine aminotransferase [ALT], aspartate aminotransferase [AST], gamma-glutamyl transferase [GGT], alkaline phosphatase [ALP], albumin, and international normalized ratio [INR], Table 10). Metabolic illnesses that can cause a conjugated hyperbilirubinemia must be excluded quickly as early intervention can be life saving. The preliminary metabolic work-up should include examination of urine for reducing substances (galactosemia), succinylacetone (tyrosinemia), urine amino acids, and urine organic acids, as well as serum amino acids and serum alpha-1-antitrypsin levels (alpha-1-antitrypsin deficiency). Panhypopituitarism, including hypothyroidism and adrenal insufficiency, can cause conjugated hyperbilirubinemia. The diagnosis of hypopituitarism, with abnormal free T4 [fT4], thyroid-stimulating hormone [TSH], and cortisol levels, can obviate the need for invasive hepatic investigations such as a liver biopsy. Testing for infectious etiologies should include a urine culture, blood culture, and virology studies for so-called *TORCH* infections (a panel of intrauterine and perinatal infections, e.g. viral PCR and serologies as in Table 2). Ophthalmological assessment in these patients may reveal cataracts, chorioretinitis, or other characteristic findings that may be helpful for diagnosis. An abdominal ultrasound with doppler assessment is also necessary in all cases to evaluate for any structural abnormalities.

Infants who present < 5-6 weeks of life may be investigated with a hepatobiliary iminodiacetic acid (HIDA) scan to rule out biliary atresia. After treatment with phenobarbital for 5 days to encourage choleresis, appropriate excretion of the tracer into the intestine confirms a patent biliary system. However, the HIDA scan may be omitted in infants who present $\geq$ 5-6 weeks of life, as this could delay the diagnosis and treatment of biliary atresia. Subsequent investigations are performed systematically to effectively assess the differential diagnosis of conjugated hyperbilirubinemia of the infant (Table 10).



Table 10. List of Initial Diagnostic Investigations for the Cholestatic Infant

-
- Blood testing
 - Hepatology
 - Unconjugated bilirubin, conjugated bilirubin, delta bilirubin (or direct bilirubin)
 - ALT, AST, GGT, ALP
 - Albumin, glucose, INR
 - Metabolics / Genetics
 - Alpha-1-antitrypsin deficiency
 - Red cell galactose-1-phosphate uridyl transferase
 - Serum amino acids
 - Consider lactate, pyruvate, urine ketones with an episode of hypoglycaemia
 - Endocrine
 - Serum TSH, fT4, cortisol
 - Infectious diseases
 - Blood culture, *TORCH* screen (including: HSV PCR, CMV PCR, hepatitis B surface antigen, hepatitis C virus antibody, HIV serology, toxoplasmosis serology, rubella serology, VDRL)
 - Hematology
 - CBC
 - Urine testing
 - Urine reducing substances
 - Urine organic acids, urine succinylacetone
 - Urine culture
 - Sweat testing
 - Sweat chloride
 - Imaging
 - Liver ultrasound + Doppler assessment
 - Consider HIDA scan
 - Consider percutaneous or intraoperative cholangiogram
 - Histopathology
 - Consider liver biopsy
-

Abbreviations: alanine aminotransferase [ALT], aspartate aminotransferase [AST], gamma-glutamyl transferase [GGT], alkaline phosphatase [ALP], albumin, international normalized ratio [INR], hepatobiliary iminodiacetic acid [HIDA], free T4 [fT4], thyroid-stimulating hormone [TSH] herpes simplex virus [HSV], cytomegalovirus [CMV], polymerase chain reaction [PCR], Venereal Disease Research Laboratory [VDRL], complete blood count [CBC]



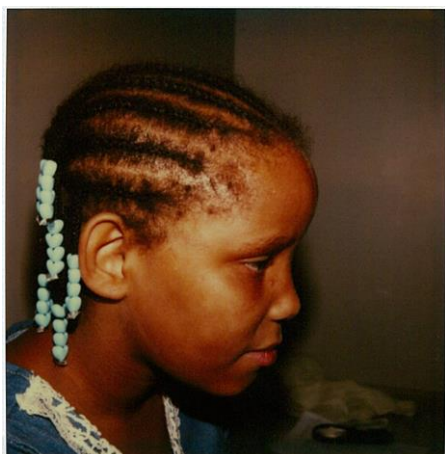
In the majority of cases of conjugated hyperbilirubinemia, a percutaneous liver biopsy is strongly recommended. Histology can be essential in differentiating hepatobiliary diseases in a timely manner, including biliary atresia, congenital hepatic fibrosis, neonatal sclerosing cholangitis, and alpha-1-antitrypsin deficiency.

Extrahepatic manifestations are common in Alagille syndrome and less often in biliary atresia (refer to the chapter on biliary atresia). The combination of a cholestatic infant, abnormal facies and a cardiac murmur on physical examination should encourage the physician to investigate for Alagille syndrome (Figure 1). An echocardiography could reveal pulmonic stenosis (or another cardiac abnormality), a skeletal survey could demonstrate butterfly vertebrae, and an ophthalmology consult with slit lamp examination could identify the presence of posterior embryotoxon.

Finally, since cystic fibrosis can present with cholestatic liver disease in absence of other symptoms, a sweat chloride study should be performed. This is especially true in an infant with a history of failure to thrive or meconium ileus.

Figure 1. Picture of a child with Alagille Syndrome

Characteristic facies include features of frontal bossing, deep-set eyes, hypertelorism, a bulbous nose tip with a saddle or straight nasal bridge, and a pointed chin. Xanthomas are also common in this group and can be pronounced on the palmar creases, digital extensor surfaces, the popliteal fossa, the ears, the nape of the neck, the inguinal creases, and the buttocks.





5.3 Management

Initial management of cholestatic infants should include an assessment of the child's overall general condition. Additionally, the acute presentation of an unwell infant may initially require resuscitative measures as well as targeted treatments for liver failure. Contrarily, the management of a well cholestatic infant will be directed at their underlying diagnosis as well as supportive management with nutrition, and anti-pruritic therapies.

Patients with sepsis may suffer from hemodynamic instability requiring intravenous hydration and antibiotics. Cholestatic infants presenting with liver failure, should prompt an evaluation for coagulopathy. In this case, the administration of parenteral vitamin K (phytonadione) is important to maximize the liver's ability to synthesize coagulation factors. However, in cases with active bleeding, coagulation repletion with fresh frozen plasma may be required. Furthermore, the disposition of this infant must be evaluated as they might require transfer to a tertiary care institution with paediatric intensive care facilities as well as consultation with a paediatric hepatologist or metabolic geneticist.

Cholestatic infants frequently require aggressive dietary modifications to support nutritional rehabilitation. Supplementation with medium chain triglycerides (MCT) allow for improved fat and calorie absorption, as MCT do not require bile acids for digestion. However, care must be taken to ensure that the child is receiving adequate long chain triglycerides to avoid an essential fatty acid deficiency. Commonly, infants are also started on a protein-hydrolysed formula as these commonly contain high percentages of MCT oil. Fat-soluble vitamin levels are routinely measured and are frequently supplemented, as their absorption is impaired in cholestasis (Table 11). In the fasting infant, intravenous fluids should include 10% dextrose with 0.45% normal saline to avoid hypoglycaemia and to minimize the accumulation of ascites.

Table 11. Recommendations for Fat-Soluble Vitamin Supplementation in the Cholestatic Infant

Vitamin D (cholecalciferol):	1,200 – 12,000 IU/day PO
Vitamin K (phytonadione):	2.5 – 5.0 mg/day PO
Vitamin E (α-tocopherol):	25 – 100 IU/kilogram/day PO
Vitamin A (retinol):	5,000 – 25,000 international units [IU]/day PO



Pharmacological and surgical therapies will differ depending on the underlying diagnosis. In certain situations, such as biliary atresia or intestinal failure-associated liver disease, some paediatric hepatologists encourage choleresis with the use of ursodeoxycholic acid. Furthermore, cholestatic patients frequently complain of significant pruritus. In these situations, apart from, antihistamines, serotonin 5-HT₃ receptor antagonists (ondansetron), cholestyramine, rifampin, naloxone, and partial biliary diversion may provide some relief.

See table 12 for the overall approach to and management of cholestatic jaundice.

Table 12. Summary of Investigations and Management of the Cholestatic Infant

-
1. Recognition of pathologic jaundice with conjugated hyperbilirubinemia measurement (especially with persistent jaundice after two weeks of age)
 2. Urgent investigations, including serum, urine and imaging, to evaluate for different causes of conjugated hyperbilirubinemia
 - Emphasis on timely investigations to rule out biliary atresia, to expedite surgical correction, as well as metabolic diagnoses that require urgent dietary changes
 3. Therapeutic management is specific to the underlying diagnosis
 4. Supportive management in most patient includes:
 - An assessment of general well-being and acuity; consider urgent transfer to a paediatric tertiary care centre
 - Correction of elevated INR with vitamin K, and acute bleeding with fresh frozen plasma
 - Assessment of weight gain, and nutrient deficiency; consider dietary fortification/supplementation or changes of formula
 - Management of pruritus
-





Chapter 22: Eosinophilic Esophagitis

C. Sokollik



Eosinophil esophagitis (EoE) is an antigen- induced cell-mediated disorder with isolated eosinophilic infiltration of the esophageal mucosa responsive to treatment with dietary removal of allergens and topical corticosteroids.

1. Overview

In children, the prevalence of EoE is estimated to be approximately 1 in 10 000. EoE has a male predominance (66- 78% are male). Atopy with sensitization to environmental and especially food allergens (cow's milk, eggs, fish, wheat, soy) is common (53%). A genetic disposition is suggested due to a positive family history for EoE in 7% of the patients, and genome-wide association studies have identified susceptibility loci in the eotaxin-3 and thymic stromal lymphopoietin genes.

EoE shows strong allergic components with a Th2-type inflammatory response. A selective expansion of eosinophils is induced by IL-5 producing T-cells in the esophageal mucosa. Additionally, the tissue recruitment factor eotaxin-3 is over expressed in esophageal endothelial cells in patients with EoE. However, the role of thymic stromal lymphopoietin overexpression and the causative events are still not completely elucidated.

2. Clinical Presentation

A case: A 15 year old male patient presents acutely with food impaction after having had dinner outside home. He complained about dysphagia for the last 6 months with changes in his eating habits (avoiding of meat, extensive chewing, change to soft food diet, washing food down with liquids). Additionally, he is known to suffer from seasonal rhino conjunctivitis.

Presenting symptoms of children with EoE vary with age. Infants may show irritability and unspecific feeding problems, school children may complain about abdominal pain and vomiting, and adolescents mainly present with heartburn, classically with dysphagia or food impaction. The physical examination is typically normal, and the patient appears in overall healthy condition.

3. Differential Diagnosis and Investigations

There is no blood test confirming the diagnosis. Blood eosinophils are elevated in half, and serum IgE levels are raised in over three thirds of the patients with EoE.

Typical, but non-specific esophageal findings on endoscopy are furrowing, trachealization and whitish exudates (Figure 1). These exudates are distinctive from candida colonization, because they are small, regular- shaped and can't be washed away, and represent eosinophilic microabscesses. The patchy involvement requires more than one biopsy for histological examination, ideally biopsies from each of distal, mid and proximal esophagus. In children it is also recommended to obtain duodenal and gastric biopsies due to the variety of symptoms and overlap with other diseases. An increased number of esophageal eosinophils may be found in patients with gastro- esophageal reflux, inflammatory bowel disease, achalasia, celiac disease, graft versus host disease, vasculitis or drug hypersensitivity. The minimum threshold of 15 eosinophils per high power field is required to support the diagnosis of EoE.



Food-specific serum IgE and skin prick testing for immediate type food hypersensitivity as well as patch testing to detect delayed-type food hypersensitivity reactions are used to identify antigen triggers and to guide therapeutic elimination diets. However, the trigger is not always identifiable with these tests. Despite milk being the most common food allergen in children with EoE, skin prick testing for milk has a low sensitivity and specificity (26.6% and 87.8%, respectively).

4. Management

The main columns of treatment are dietary, immunosuppressive and interventional therapy (see Table 1). The empiric 6-food elimination diet which excludes the most common allergens in children and topical steroids are first line treatment options with a high rate of clinical and histological improvement (> 80% and > 85%, respectively). Elimination of Cow's milk alone may prove to be sufficient in a number of patients. Cromolyn sodium and Leukotriene receptor antagonists showed no therapeutic affect and are not recommended.

Proton pump inhibitors may prove beneficial as treatment for associated GERD and represent the treatment of choice for 'PPI-responsive esophageal eosinophilia' which may be classified as a subtype of GERD or EoE characterized by a clinical and histopathological response to PPI monotherapy.

5. Prognosis

Complete resolution of EoE is uncommon and food allergies may persist lifelong. Retrospective data suggest that children diagnosed with EoE still have symptoms as adults. There is no parameter available to predict individual outcome. It needs to be determined if the chronic inflammation of the esophageal mucosa is associated with an increased risk of the development of pre- malignancies or malignancies.

Table 1: Management of Eosinophilic Esophagitis

Dietary therapy	Implications	Limitations
Dietary restriction based on allergy testing or elimination of the most common food allergens	- should be considered in all children - 6-food elimination diet [SFED] excludes milk, egg, wheat, soy, peanut/tree nuts, and seafood (fish/shellfish)	- no standardized protocol for reintroduction of eliminated food available - adherence issues - adequate vitamin and micronutrient supply must be warranted - if necessary with supplements (e.g. Calcium)
Amino acid – based formula	- high success rate (88-95%) - used as induction therapy, followed by an elimination diet for maintenance	- no standardized protocol for reintroduction of normal diet - compliance issues due to low palatability



Immunosuppressive therapy

Corticosteroids	- induction and maintenance therapy - puffed and swallowed fluticasone (children 88-440ug twice to four times daily) - topical administration of oral budesonide (children <10y 1mg daily, >10y 2mg twice daily for 8 weeks followed by 1mg and 2 mg respectively for another 8 weeks) which can be mixed in Splenda to make a viscous solution - systemic only in severe cases (1-2mg/kg/day)	- reoccurrence of disease if discontinued - local fungal infections with topical application - long term side effects of steroid therapy (bone mineralization, growths, adrenal suppression)
Monoclonal Antibodies	- anti - IL-5 targets on factor of underlying pathomechanism and was able to reduce esophageal eosinophilic inflammation - future agents may act against IL-13 or eotaxin	- in development; risk and benefits to be determined

Interventional therapy

Esophageal dilatation	- to release high-grade esophageal strictures	- complications like esophageal perforation (0.8%), chest pain (5%) - concomitant therapy, does not address underlying pathomechanism



The image shows the macroscopic view of an esophagus during upper endoscopy. The esophagus demonstrates furrowing, diminished vasculature and a net-like mucosal pattern as expression of an altered esophageal mucosa.

Figure 1: Endoscopic picture of Eosinophilic Esophagitis



Chapter 23: Peptic Ulcer disease

C. Sokollik



1. Overview

Peptic ulcers are deep mucosal lesions of the gastric or duodenal wall and classically attributed to *Helicobacter pylori* (*H pylori*) infection. However, in recent years there has been a rise in non- *H pylori* - associated peptic ulcers in children in developed countries. Also in children an important differential diagnosis is the use of nonsteroidal anti-inflammatory drugs (NSAIDs). In general, treatment with proton pump inhibitors is effective in addition to eradication of *H pylori* in positive cases. The frequency of peptic ulcer disease in *H pylori* positive European paediatric patients undergoing upper endoscopy for various reasons is approximately 7%. A retrospective database analysis found an incidence of 0.5 to 0.9/100,000 of peptic ulcer bleeding among the US paediatric population. A disruption of the balance between acid secretion and the bicarbonate-mucus barrier is considered to be the underlying pathomechanism. Exposure of the gastric and duodenal mucosa to pepsin and hydrochloric acid results in gastritis and ulcerations.

2. Clinical Presentation

A case: A 13 year old female patient presents with recurrent epigastric abdominal pain and a first episode of hematemesis. She complains that over the last two months the pain woke her also up at night. For headaches she takes ibuprofen every other week.

Epigastric abdominal pain and discomfort are the most common symptoms. However, studies can not demonstrate a clear association of abdominal pain and *H pylori* infection, and therefore abdominal pain itself is not an indication to test for *H pylori* infection. In contrast, hematemesis, melena and weight stagnation are red flags for the presence of peptic ulcers. Other signs include exacerbation of the pain after meals or nocturnal awakening, vomiting, early satiety and iron deficiency anemia. The main complications of peptic ulcers are bleeding, perforation and gastric outlet obstruction.

3. Differential Diagnosis and Investigations

Differential diagnoses for endoscopically demonstrated gastric and duodenal ulcers include *H pylori* infection, Celiac disease, Crohn's disease, Zollinger- Ellison syndrome, eosinophilic gastroenteritis, medication (especially non – steroidal anti- inflammatory drugs) and stress ulcers in critical ill patients. The history should therefore focus on recent (self-) medication, atopic predispositions, further symptoms like diarrhoea and a positive family history of celiac disease, IBD or multiple endocrine neoplasias type I (MEN I).

Upper endoscopy is the investigation of choice to prove the existence of a peptic ulcer. For the initial diagnosis of *H pylori* infection, new guidelines suggest a positive histopathology plus a positive rapid urease test or a positive culture is required. Stool antigen and ¹³C urea breath test are used to determine the eradication of *H pylori* after treatment. (Figure 1)



4. Management

If an underlying cause is evident, specific treatments need to be initiated. An *H pylori* related peptic ulcer is an indication for anti- *H pylori* therapy to reduce the risk of recurrence (Table 1). Antibiotic resistance (clarithromycin, metronidazole) is becoming an increasing challenge, resulting in a decline of eradication rates. Primary cultures with sensitivity testing may guide the choice of antibiotics as resistance rates are locally distinct. Sequential therapy aims at reducing the bacterial load and protecting against clarithromycin resistance by pre- treatment with amoxicillin followed by a course of clarithromycin + metronidazole. Newer experience favors sequential therapy in regards to eradication rates. Eradication should be monitored 4 to 8 weeks following therapy with a urea breath test or stool antigen. Idiopathic peptic disease shows good response rates to treatment with PPI alone.

5. Prognosis

Adult studies indicate that treatment of *H pylori* related peptic ulcers reduces the relapse rate. Paediatric data are not available yet. However, it is also assumed that in children eradication of *H pylori* prevents recurrence.

Table 1: Eradication therapy of *H pylori* infection (adapted according to Ref 1)

First line therapy 1) triple therapy for 7 -14 days a) PPI + amoxicillin + imidazole b) PPI + amoxicillin + clarithromycin c) Bismuth salts + amoxicillin + imidazole 2) sequential PPI + amoxicillin for 5 days, followed by PPI + clarithromycin + metronidazole Second line therapy increase of dose and/or duration of therapy, adding antibiotics, change antibiotics, adding bismuth 1) quadruple therapy PPI + metronidazole + amoxicillin + bismuth 2) triple therapy PPI + levofloxacin + amoxicillin Dosing PPI (Proton pump inhibitor): 1-2 mg/kg/d Bismuth salts: 8 mg/kg/d Amoxicillin: 50 mg/kg/d (max 2 g/d) Metronidazole: 20 mg/kg/d (max 1 g/d) Clarithromycin: 20 mg/kg/d (max 1 g/d)





Chapter 24: Celiac Disease

C. Sokollik



Celiac disease (CD) is a T-cell mediated tissue-specific autoimmune disease that develops in genetically predisposed individuals after exposure to gluten. The only available therapy is a lifelong strict gluten free diet.

1. Overview

The prevalence of childhood celiac disease ranges from 1:100 in United Kingdom to 1:67 in Finland including patients with silent and potential CD (Table 1). The incidence in North American children is predicted to be approximately 1:104.

Gluten is found in wheat, barley and rye. The proposed pathomechanism states that tissue transglutaminase (tTG), the auto- antigen in CD, deamidates dietary gluten peptides which are then presented by macrophages and dendritic cells via disease-associated human leukocyte antigen (HLA-DQ2/8) molecules to gluten specific CD4+ T-helper cells. The activation of these T-helper cells contributes to mucosal inflammation and injury, which lead to the typical but not pathognomonic distortions of the small bowel mucosa as well as to the intestinal and extraintestinal symptoms.

2. Clinical Presentation

A case: A previously very active and happy 1 year old boy presents with decreased appetite and failure to thrive. He appears pale. His blood work shows iron deficient anemia. His mother was diagnosed with celiac disease five years ago.

Classical symptoms of CD are diarrhea with and without steatorrhea, constipation, vomiting, chronic abdominal pain, abdominal distension, weight loss and failure to thrive. However, increasingly children present with minor gastrointestinal or only with extraintestinal manifestations. Iron deficiency anemia, fatigue, arthritis, delayed puberty, infertility, transaminasemia, dental enamel defects or mood swings are often the leading symptoms, and should raise suspicion of CD.

Diseases with an increased prevalence of CD are type 1 diabetes mellitus (3-12%), autoimmune thyroiditis, dermatitis herpetiformis, autoimmune alopecia, autoimmune liver disease (12-13%), Down syndrome (5.5%), Turner syndrome (6.5%), William syndrome (9.5%) and selective immunoglobulin A deficiency (2-8%). First degree relatives of CD patients have a prevalence of 10-20% and serological screening for CD should therefore be offered to these persons.

3. Differential Diagnosis and Investigations

The diagnosis of CD rests on four pillars – suggestive symptoms, specific antibodies, genetic predisposition and histological findings on duodenal biopsies (see Table 1).

Nearly all patients with CD have positive anti tissue transglutaminase (tTG) and anti endomysium (EMA) IgA antibodies, which combined have a sensitivity and positive predictive value of nearly 100%. The measurement of total IgA is important to identify patients with IgA deficiency where the determination of IgG antibodies (anti deamidated



gliadin peptide (DGP) IgG, anti tTG IgG and anti EMA IgG) provides a diagnostic alternative, yet with an inferior specificity and sensitivity. HLA-DQ2/ DQ8 testing is positive in > 97% of patients with CD, however; 30%-35% of the general population express HLA-DQ2 or DQ8 of which only 2-5% develop celiac disease.

Table 1: Subtypes of Celiac Disease

Subtypes of CD	Clinical symptoms or signs of CD	CD specific antibodies	Genetic predisposition to CD (HLA DQ2/8)	CD specific biopsy findings
Classical	Yes	Positive	Positive	Existing
Silent	No	Positive	Positive	Existing
Latent	No	Positive	Positive	Lacking, but previously existing
Potential	Yes/No	Positive	Positive	Lacking

The NASPGHAN consensus guideline requires an intestinal biopsy in all cases of suspected CD in order to confirm the diagnosis. During upper endoscopy ≥ 4 duodenal biopsies are required taken from the second part of the duodenum, and due to the patchiness of lesions duodenal bulb biopsies are recommended to improve the diagnostic yield. Histological hallmarks are villus atrophy, crypt hyperplasia and increased intraepithelial lymphocyte (IEL) density. There severity is classified according to Marsh.

Depending on the symptom complex, the differential diagnoses of villous atrophy include infectious diarrhea (e.g. Giardiasis, viral gastroenteritis), autoimmune enteropathy and food protein hypersensitivities (cow's milk, eggs, chicken, etc).

4. Management

At the moment, the only treatment for CD is a strict gluten- free diet. Wheat, barley, rye and triticale contain gluten. Oats is tolerated by CD patients. However; oats can be contaminated with gluten during growing and processing, and is therefore not recommended.

In practice, it is sometimes reintroduced if the child has responded well to the gluten free diet. Rice, potatoes, soy, corn and buckwheat flours are gluten free, also are legumes, millet and nuts. Gluten- free products are often low in some vitamins (e.g. vitamin B, vitamin D), micronutrients (e.g. calcium, iron, zinc, and magnesium) and fiber. Therefore the involvement of a dietitian is recommended to guide the patient during the implementation of a gluten free diet. Adherence to a strict gluten- free diet is challenging, and practical as well as feasible treatment alternatives are desired. Modified flours with lower immunogenicity, inhibitors of tTG activity or gluten binders are therapeutic strategies in development, which may in time permit the patients to be more liberal in their intake of gluten.



5. Prognosis

The gluten- free diet usually results in symptomatic improvement in a couple of weeks with normalization of CD specific antibodies within 12 months. Thereafter, repeat antibody testing is used for compliance control. Compliance is certainly an issue in children, particularly when they develop more independence from their families. Regular visits to the Paediatric Gastroenterologist or family doctor should be used to re-enforce the importance of dietary adherence and should address dietary challenges and identify situations of potential cross contamination.

Untreated celiac disease is associated with osteopenia. Some literature disputes whether untreated patients are at increased risk for developing enteropathy- associated T-cell lymphoma and other malignancies of the gastrointestinal tract. Patients with Celiac disease that is refractory to treatment seem to be at risk to develop these kinds of intestinal lymphomas.



Chapter 25: Inflammatory bowel disease

A. Elkadri and A. Muise



1. Overview

Inflammatory Bowel Disease (IBD) is a family of auto-inflammatory disorders includes Ulcerative Colitis (UC) and Crohns Disease (CD). It is characterized by a dysregulated immune response causing inflammation in the gastrointestinal tract. The current theory on what causes IBD includes a combination of genetic, environmental, luminal microbial and immunological factors. In general, the belief is that the systems in place to control inflammation induced by either a component of our bacterial flora or an external pathogenic agent fail,, leading to an uncontrolled inflammatory response with subsequent tissue damage. As a result, patients develop a chronic, frequently relapsing disorder of the gastrointestinal tract with systemic manifestations.

The incidence of IBD is increasing around the world. In particular, paediatric patients presenting less than 10 years of age are the fastest growing group. The reasons for this phenomenon are currently unknown.

2. Clinical Presentation

A Case: 14-year-old male presents with a 6-month history of crampy and periumbilical abdominal pain located in the right lower quadrant. He has had 3 to 5 loose, bloody mucoid stools per day. These bowel movements are usually painless, but take up a significant portion of his day as he is on the toilet constantly.

A careful medical history usually reveals that the disease has had an impact on the activities of daily living. Patients may have missed school, experienced excessive fatigue, or skipped meals due to excessive nausea or pain. A common presenting complaint is a change in the stooling pattern, with the development of nocturnal stools being a indicator of significant bowel pathology. Additionally, paediatric patients with IBD, and mainly CD, present with poor growth and weight gain, thought to result from appetite suppression secondary to the circulating inflammatory cytokines. Finger clubbing is another clinical manifestation seen in IBD (mainly CD).

When asking about abdominal pain, the timing, location, radiation, and relationship to stooling is important to help in directing further workup. Severe right lower quadrant pain suggests ileocecal pathology and the possibility of development of a phlegmon or abscess. CD patients often complain of periumbilical or vague abdominal pain that may or may not be associated with eating or stooling. Patients with UC are more likely to describe tenesmus, a feeling of incomplete bowel evacuation associated with a painful cramping spasm of the colon. Finally, asking about pain upon sitting down or upon passage of stool should raise suspicion for a perianal fistula or abscess.

Fever, growth delay, pyoderma gangrenosum, perianal pain and severe laboratory abnormalities warrant immediate medical attention. In CD, a low-grade fever is more common, whereas fever in UC raises a concern for toxic megacolon, a severe inflammation of the colon associated with ileus, abdominal dilatation, perforation, sepsis and even mortality. Abdominal abscesses or strictures may develop in CD patients, with



the majority of these occurring in the terminal ileum and/or distal small bowel. A high index of suspicion and early imaging with ultrasound or MRI is key to diagnosing strictures and abscesses.

A physical exam should also include a thorough assessment of the perianal area to identify fistulae and abscesses. Growth and pubertal delay should be screened for as patients who develop IBD during childhood are at an increased risk for a lower overall adult height, as well as the development of osteoporosis. Other points to note on physical exam include oral findings of aphthous ulcers, lip swelling, and/or buccal or gingival inflammation. Joint manifestations may either involve large joints (axial, knees, hips) or small joints (fingers, toes and ankles). Patients infrequently can present with erythema nodosum, pyoderma gangrenosum, psoriasis, primary sclerosing cholangitis, uveitis or iritis.

3. Differential Diagnosis and Investigations

Patients presenting with symptoms suggestive of IBD require a workup to rule out infectious etiologies such as *Clostridium difficile*, rotavirus, *Salmonella*, *Campylobacter*, *Shigella* and *E. coli*. As the time for recovery from an acute infection ranges widely between patients (up to 6 weeks at times), early referral of a patient with what is ultimately an infectious gastroenteritis exposes them to needless investigations. Patients with functional gastroenterological disorders, a diagnosis of exclusion, may often present with symptoms identical to IBD, though are usually lacking signs of systemic chronic illness such as clubbing, weight loss and generalized cachexia. Important points to note are: (1) that bloody diarrhea is NOT normal and warrants a basic level of investigation (CBC, albumin, stool culture, and acute phase reactants), (2) that anal fissures do not explain mucous in stools and (3) a finding of a skin tag in a paediatric patient is not explained by hemorrhoids, as it is highly unlikely that children develop hemorrhoids.

Investigations for the diagnosis of IBD utilize multiple modalities, mainly centering on endoscopic and histo-pathological evidence of inflammation and its systemic effects. Initial investigations include stool cultures for infectious etiologies, as well as screening blood work to look for manifestations of IBD. Table 1 lists the main differential diagnosis.

Table 1. Differential diagnosis of Inflammatory Bowel disease

Differential diagnosis	Main differences	Diagnostic testing	Comments
Infectious gastroenteritis	• Lack of chronicity, usually under one month, • Self limiting • Exposure or sick contacts	• Stool for culture, ova and parasites, electron microscopy and assay for <i>C. difficile</i> cytotoxin	• The acute presentation is almost indistinguishable from acute IBD (except for chronic symptoms)



Differential diagnosis	Main differences	Diagnostic testing	Comments
Juvenile polyp	• Lack of systemic symptoms • Intermittent bleeding with mucous • May have prolapse of the polyp	• Colonoscopy	• Multiple polyps (>5) are associated with SMAD4 or PTEN defects and an increased risk of cancer
Eosinophilic Gastroenteritis	• Diffuse infiltration of the intestinal epithelium with eosinophils	• Endoscopy with biopsies showing >10-15 eosinophils per high powered field	• May or may not be associated with peripheral eosinophilia
Chronic Granulomatous Disease (CGD)	X-linked and autosomal recessive disease of recurrent infections. 48% of CGD patients have colitis.	• Neutrophil Oxidative Burst Index (NOBI) • Genetic testing of CYBB, CYBA, NCF1, NCF2 genes	• Pigmented macrophages noted on biopsies
Rare causes of colitis	• Hyper IgE: Associated with skin rashes and elevated IgE secondary to recurrent Staph skin infections • IL10/IL10R defects: Treatment non-responsive severe perianal disease with recurrent folliculitis and joint disease • Wiskott-Aldrich Syndrome (WAS): X-linked recessive eczema, thrombocytopenia and immunodeficiency associated with bloody diarrhea	• Hyper IgE: Elevated IgE with eosinophilia • IL10/IL10R: Genetic testing WAS: Low immunoglobulins and genetic testing for WASp gene	• Hyper IgE: Antibiotics and good skin care • IL10/IL10R: Bone marrow transplantation • WAS: NSAIDs, splenectomy, and in severe cases, bone marrow transplantation



Blood work should include a complete blood count (screening for anemia or infection), soluble transferrin receptor b (elevated in iron deficiency), acute phase reactants (erythrocyte sedimentation rate, C-reactive protein, alpha-1-acid galactosidase protein), transaminases (screening for PSC), albumin, and serological markers of autoimmunity (celiac serology, Janti-saccharomyces cerevisiae antibody (ASCA), atypical perinuclear anti-neutrophil cytoplasmic antibody (atypical p-ANCA), anti-Outer membrane protein C (anti-OmpC) and anti-flagellin) and thyroid disease (free T4 and TSH). The levels for 25-hydroxy-vitamin D and vitamin B12 should be drawn, as they are sometimes low in IBD. Fecal calprotectin, a stable marker of inflammation is a useful tool in differentiating functional disorders from IBD, as it is elevated in the presence of intestinal inflammation. In anticipation of possible future treatment with an immunosuppressant, an initial work-up may also include an evaluate of the immunization status of varicella and hepatitis b, immune status of EBV and CMV, as well as to examine for signs of latent or overt tuberculosis.

Patients should undergo esophagogastroduodenal endoscopy and lower endoscopy as a portion of patients may have gastritis with minimal symptomatology. The aim of the colonoscopy is to macroscopically describe the extent and the degree of the colonic inflammation, to judge the extent and continuity of disease, and to visualize the terminal ileum to assess the presence and extent of ileal inflammation.

A special emphasis is placed on the histopathological evaluation of tissue specimen. The findings in UC are limited to the mucosa (except in toxic megacolon) and pathologists look for signs of chronic inflammation such as crypt distortion. Crypt abscesses with infiltration of polymorphic neutrophils are also commonly described. The hallmarks of CD are signs for transmural inflammation and the identification of non-caseating granulomas.

As for radiological studies, small bowel follow through may be utilized to assess small bowel involvement. Due to the high exposure to ionizing radiation, this exam is being replaced by careful ultrasonographic examination of the small bowel and terminal ileum. Recently, tertiary care institutions are utilizing magnetic resonance enterography, which allows for a thorough examination of the small bowel and mesentery without the use of ionizing radiation.

4. Management

Depending upon the diagnosis, severity, localization and extent of inflammation, treatment varies greatly.

IBD therapy consists of two major components: a) induction, directed at decreasing the level of inflammation and achieving remission, and b) maintenance, directed at modulating the immune system in a way to prevent inflammation and maintain remission. There are a various treatment options (Table 2) that can be offered to patients with IBD, but all have side effects that should be taken in to consideration when selecting therapy. When counseling patients, it is important to remember that the diagnosis of IBD is a lifetime diagnosis, and that patients will likely experience a relapse during their lifetime. Further, patients presenting at a younger age (under 10 years old) are more likely to have an aggressive disease course, and may benefit from an accelerated treatment strategy. In the discussion of therapeutic options with the family, the responsible IBD physician needs to carefully balance benefit and potential risk resulting from drug induced side effects on



one hand, and long term sequelae of undertreated inflammation on the other, to derive to the best individualized treatment plan.

Table 2: Treatment option in Inflammatory Bowel disease

Treatment	Most Effective Use	Side Effects	Route
Exclusive Enteral therapy	- CD: Induction therapy, especially patients with pronounced weight loss and/or small bowel disease. Maintenance therapy possible, though difficult to maintain - UC: No role	Bloating, diarrhea, abdominal pain, intolerance of therapy	Enteral (oral vs. nasogastric)
Corticosteroids	- CD: induction therapy, especially with extensive disease - UC: induction therapy	- Adrenal suppression, cushingoid facies, acne, avascular necrosis of the hip, sleep disturbance, agitation - Long term use causes growth disturbance and osteoporosis	Oral or intravenous
Sulfasalazine	- Sulfapyridine bonded with a disulphide bond to 5-ASA (the active drug in IBD) - CD: Mainly used in maintenance therapy for mild to moderate colonic CD. - UC: Used as induction and maintenance therapy	- Contraindicated in G6PD and Sulfa allergy - DRESS syndrome - Intolerance characterized by headache, nausea, emesis - Transient reversible decreased sperm count 5-ASA intolerance characterized by watery diarrhea	Oral (in pill or suspension)
Aminosalicylates	- Multiple forms with differing mechanisms of release - CD: may be helpful in mainly colonic disease. Not used in maintenance regularly - UC: Useful in induction and maintenance therapy	- Contraindicated in ASA allergy 5-ASA intolerance characterized by watery diarrhea - Interstitial nephritis (rare) - Pancreatitis (rare)	Oral in pill form



Treatment	Most Effective Use	Side Effects	Route
Methotrexate	• CD: Useful in maintenance therapy • UC: No clear evidence for efficacy	• Contraindicated in liver disease and pregnancy • Hepatotoxicity • Nausea • Bone marrow suppression	Subcutaneous injection or oral
Azathioprine or 6-Mercaptopurine	• Useful in maintaining remission in both UC and CD. • Not used in induction therapy	• Contraindicated in patients with TPMT deficiency • Pancreatitis • Bone marrow suppression • Hepato-splenic T-cell lymphoma	Oral (pill and suspension)
Anti-TNF	• CD and UC: Useful in induction and remission	• Reactivation of latent infections such as Tuberculosis, Hepatitis B and Varicella • Anaphylaxis	Infliximab: IV Adalimumab: subcutaneous
Surgery	• CD: Useful for fibrotic strictures and perianal disease • UC: If diagnosis is sure, curative	• Recurrence in CD is common, most likely at site of surgery • If UC diagnosis incorrect, recurrence in small bowel	

5. Prognosis

As IBD is a lifelong disease, discussion of a patient's prognosis depends on various factors including the age of onset, the extent of disease, the rapidity of disease development, and other factors not easily quantified such as genetics and environmental exposures. Individual response to therapy also determines whether a patient will continue to have ongoing inflammation, and subsequently require surgical intervention due to the development of irreversible mucosal damage or not. Most of the outcome data have been derived in adult cohorts and not in children. Further, the current generation of therapies is thought to change the long term prognosis of disease, thereby making previous studies on the prognosis and long term risk difficult to interpret.

In CD, cumulative damage from unchecked long-term inflammation results in irreversible fibrosis, which ultimately requires surgical correction. In adults 50% of CD patients were found in one study to develop intestinal complications over 20 years of disease.



In UC however, the concern is that the patient may not respond to therapy in the initial or subsequent flares, or that they may not be able to discontinue steroid therapy, ultimately requiring colectomy. Patients diagnosed younger than 6 years old are at an increased lifetime risk for surgery, noted in one population to be 71% vs. 55% for the older age at diagnosis group. In UC, colectomy risks 10 years after diagnosis ranges from 20-30% in patients with mild disease to 40% in patients with extensive disease.

Long term complications in IBD include an increased lifetime risk of developing colonic dysplasia and colorectal cancer. Originally, adult meta-analyses estimated the risk of colon cancer in UC to be 2% at 10 years of disease and as high as 18% at 30 years of disease. CD risk of cancer was found to be 3% at 10 years of disease, and 8% at 30 years of disease. Recent studies have shown the risk to be lower, but it remains elevated with increased duration of disease and increased activity over time. For this reason, patients with disease duration of 8 years are taken for a re-evaluation endoscopy. Those with poor compliance or uncontrolled disease should be considered for earlier surveillance endoscopy.

Life expectancy is slightly reduced for CD patients, whereas mortality rates are unaltered in patients with UC. Patients with IBD are at increased risk for developing depression or anxiety disorders and should be screened accordingly.



Chapter 26: Cow's Milk Protein Allergy

C. Sokollik



Allergic or immunologic reactions to food allergens involving the gastrointestinal tract can be classified into IgE-mediated, non-IgE mediated (cell-mediated) or mixed immune reactions. Urticaria, angioedema, acute rhinitis or asthma and anaphylaxis are common features of acute IgE- mediated reactions. Eosinophil gastrointestinal disorders and atopic dermatitis are presentations of mixed reactions. Dietary protein enterocolitis and Celiac disease are examples of delayed- onset cell-mediated reactions.

Cow's milk protein allergy (CMPA) combines IgE and non- IgE mediated immune mechanisms. The majority of patients outgrow CMPA by the age of three years. Cow's milk protein elimination is the treatment of choice.

1 Overview

The population-based estimate of CMPA is 0.6% - 0.9%, using skin prick test, food specific IgE or food challenges. The prevalence of CMPA in childhood ranges between 2% and 3%, representing the main food allergy in infants and children younger than three years of age. Exclusively breast feed infants can be sensitized via dairy proteins in breast milk.

1.1 Clinical Presentation

A case: A 4 week old girl on cow's milk based formula presented with recurrent vomiting soon after feeding and new onset of intermittent bloody streaks in her stool. Two weeks after switch to an extensively hydrolyzed formula her symptoms had resolved.

There is no singular clinical sign or symptom specific for CMPA. Infants may present with vomiting, regurgitation, food refusal, diarrhea or constipation, rectal bleeding, failure to thrive and abdominal colic are possible presentations. Food protein induced enterocolitis syndrome (FPIES) is a rare severe non- IgE mediated manifestation of CMPA in infants presenting with profuse vomiting, dehydration and metabolic acidosis. In older children CMPA symptoms include gastro-esophageal reflux, dyspepsia, diarrhea, constipation and abdominal pain. Atopic eczema is a common extraintestinal comorbidity.

2 Differential Diagnosis and Investigations

Specific serum immunoglobulin and skin prick test, which measures IgE bound to mast cells, are used to diagnose food allergy. However, these two tests show low concordance, and may not reflect the clinical picture. Both test are for specific IgE, and therefore do not detect non IgE- mediated CMPA. Also, positive specific serum IgE indicates sensitization and not necessarily clinical allergy. The double blind placebo – controlled oral food challenge is superior to both, and is considered to be the gold standard for the diagnosis of food allergy in infants. In most clinical settings, an open challenge is more practicable as a diagnostic test, with a cow's milk free diet for 2-4 weeks followed by a re-introduction of cow's milk protein. This protocol may also



distinguish between gastro- esophageal reflux (GER) as an independent entity or a manifestation of CMPA in infants. A switch to extensively hydrolyzed formula with resolution of symptoms and the reintroduction of cow's milk protein with symptom reoccurrence may suggest an underlying CMPA. However, extensively hydrolyzed formula increases the rate of gastric emptying and may acutely treat the delayed gastric emptying as a pathomechanism of GER.

In cases with a history of anaphylaxis or high serum IgE levels, an inpatient challenge performed under medical supervision is advisable.

FPIES may be misdiagnosed as viral gastroenteritis due to similar clinical features. Suspicion of FPIES comes from the onset of symptoms one to four weeks after introduction of cow's milk protein and repetitive emesis 1-3 hours after ingestion leading to lethargy, dehydration with abdominal distension. In older patients, functional gastrointestinal disorders or lactose intolerance should be considered.

3 Management

Cow's milk free diet is a sufficient therapy in most cases. However, nutritional consultation should be undertaken to secure adequate intake of micronutrients such as calcium and vitamin D. Goat's and sheep's milk have high cross-reactivity and should be avoided in infants with cow's milk allergy.

In non- breast feed infants, extensively hydrolyzed formula is the first choice of diet therapy, as 17% of the patients have a cross reactivity to soy. Recent guidelines state that soy based formulas may be considered in infants beyond the age of six months if extensively hydrolyzed formula is rejected due to its bitter taste. In the breast fed infant, the elimination of dairy in the mother's diet can be tried. Infants with only mild symptoms of CMPA (non-IgE mediated) and adequate weight gain should be continued on breast feeding. Only in infants with severe symptoms are amino acid based formulas preferably used.

To avoid an unnecessarily restrictive diet, and since tolerance develops over time in the majority of the patients, a re-challenge with cow's milk protein should be performed after three to twelve months of dietary therapy (not before the age of 1 year) depending on the initial severity of the symptoms and the IgE testing. Patients with negative IgE seem to develop tolerance at a younger age. After a severe immediate IgE mediated reaction, the patient should be on an elimination diet for 12 to 18 months before re-challenging.

4 Prognosis

Ninety percent of infants with CMPA outgrow their sensitivity by the third year of life. However, infants with IgE- mediated CMPA have a higher risk to retain their sensitivity, and may develop sensitivities to other foods. In this group, reaction to less than 10ml of milk, symptoms in the first month of life, and larger wheal size on skin prick test are associated with an increased risk for persistence of CMPA. Independent risk factors for the persistence of CMPA are immediate allergic symptoms, coexisting asthma and other food allergies.





Chapter 27: Autoimmune Hepatitis

P.L. Valentino and B.M. Kamath



1. Overview

Autoimmune hepatitis (AIH) is an inflammatory condition of the liver, which can cause progressive fibrosis and cirrhosis. Consequently, AIH is one of the top five indications for liver transplantation in adolescents. In a London, England tertiary paediatric liver center this disease has a prevalence of 1.2%. The etiology of AIH is unknown; theories include environmental triggers, immune system dysregulation, as well as a genetic predisposition². AIH subclasses include type 1 and type 2, depending on the type of serum autoimmune antibodies. Most commonly, patients with type 1 disease are positive for anti-smooth muscle antibody (SMA), while those with type 2 show positivity for anti-liver/kidney microsome type 1 antibody (LKM-1). Type 2 disease has a much higher prevalence in children compared to adults (38% vs. 4% respectively); however, type 1 disease remains the most common type of AIH in all age groups.

2. Clinical Presentation

A case: A 15-year-old girl presents to the emergency department with a 5-day history of progressively increasing jaundice, scleral icterus, fatigue, malaise, and intermittent fevers. On examination, she has tender hepatomegaly.

Patients with AIH can present insidiously with symptoms of jaundice, scleral icterus, abdominal pain, nausea, malaise, fatigue and arthralgias. However, symptomatology can range from extremely mild to severe disease with acute liver failure. On physical examination, patients with AIH commonly have hepatomegaly and splenomegaly. Infrequently, patients can display signs of portal hypertension at AIH presentation with ascites, spider nevi and esophageal variceal bleeding. The King's College Hospital group in London, England reported a median age at presentation of 10.5 years for paediatric type 1 AIH and 7.4 years for paediatric type 2 AIH. In general, this disease has a strong female preponderance regardless of AIH type (75% of all paediatric AIH). AIH is associated with other autoimmune diseases. Patients with AIH type 1 may have either a personal or a family history of thyroiditis, diabetes mellitus, ulcerative colitis, nephrotic syndrome, Behçet's disease, and urticaria pigmentosa. AIH type 2 is associated with Addison's disease, thyroiditis, hypoparathyroidism, and vitiligo.

3. Differential Diagnosis and Investigations

The acute presentation of AIH includes non-specific signs and symptoms, and preliminary investigations, including abnormal liver biochemistry (alanine aminotransferase [ALT], aspartate aminotransferase [AST], or bilirubin), can be unhelpful in directing the clinician towards a specific diagnosis (Table 1). The initial assessment should include a screen for the major causes of acute hepatitis, including serum ceruloplasmin, 24-hour urine copper, serum alpha-1 antitrypsin, viral hepatitis serologies, immunoglobulin G, and autoimmune antibodies. Further testing can be directed by information obtained on history, such as a urine toxicology screen to assess for a drug hepatotoxicity in an adolescent with acute liver failure. An ultrasound with doppler should always be obtained to assess for signs of biliary duct abnormalities or evidence of portal hypertension.



Table 1. Differential Diagnosis of Autoimmune Hepatitis**Obstructive jaundice**

Choledochal cyst
 Gallstones or biliary sludge
 Primary sclerosing cholangitis***
 Secondary sclerosing cholangitis
 Cystic fibrosis

Hepatocellular injury

Viral infection
 Hepatitis A, B, C, D, E***
 HIV
 Alcoholic hepatitis
 Non-alcoholic fatty liver disease***
 Non-alcoholic steatohepatitis***
 Medications and toxins (*amanita phalloides*) ***

Genetic/metabolic disorders

Alpha 1-antitrypsin deficiency
 Wilson Disease***
 Celiac Disease***
 Hemochromatosis

Vascular Abnormalities

Budd-Chiari Syndrome
 Portal vein thrombosis

Non-Hepatic Causes to Consider

Acute Rhabdomyolysis
 Hypothyroidism

*Diagnoses marked with *** are common or important diseases for investigation.*

The diagnosis of AIH involves an overall assessment of multiple investigations. Although, a liver biopsy is extremely helpful in contributing to the final diagnosis, there is no one specific diagnostic gold standard for AIH. The international AIH group (IAIHG) has created and validated a scoring tool in order to assist clinicians in establishing a diagnosis. This scoring tool includes the following: elevated ALT or AST (compared to ALP), elevated immunoglobulin G (IgG), elevated anti-nuclear antibody (ANA), or SMA, or LKM-1, negative viral hepatitis markers, negative drug history, low alcohol intake, contributory findings on liver histology, seropositivity for HLA DR3 or DR4, and appropriate response to therapy. Liver histology findings at diagnosis include interface hepatitis, plasma cell infiltration, lobular inflammation, bridging necrosis or fibrosis, and occasionally cirrhosis (Figure 1). Though this index was developed with data from a mostly adult population, a retrospective study by Ebbson et al found the tool to be accurate in diagnosing AIH in their cohort of children. Despite this, the IAIHG scoring tool is not routinely used in paediatrics.

Diagnosing paediatric AIH can be quite challenging as IgG levels, as well as autoantibody titres, can be relatively low or even normal. The paediatric section within the American Association for the Study of Liver Disease (AASLD) AIH guideline recognizes this common finding in paediatric AIH and describes ANA and SMA titres of 1:20 as well



as LKM-1 titres of 1:10 as clinically relevant in children. In patients with normal titres, the diagnosis of AIH is based on exclusion of other illnesses, as well as the presence of compatible histology findings. Another challenge in paediatric AIH includes an overlap syndrome known as autoimmune sclerosing cholangitis (ASC). In ASC, features of both AIH and primary sclerosing cholangitis (PSC) co-exist. Liver histology demonstrates additional findings consistent with PSC, such as peri-cholangitis, or “onion skinning” fibrosis (Figure 2). Furthermore, cholangiography, including magnetic resonance cholangiopancreatography (MRCP), can demonstrate medium to large duct strictures as well as saccular dilatations. All paediatric AIH patients followed at the King’s College Hospital in London, England, between 1984 and 1997, were investigated with cholangiography, and 49% were found to have concurrent ASC. This is quite different from an adult cohort where only 8% had ASC.

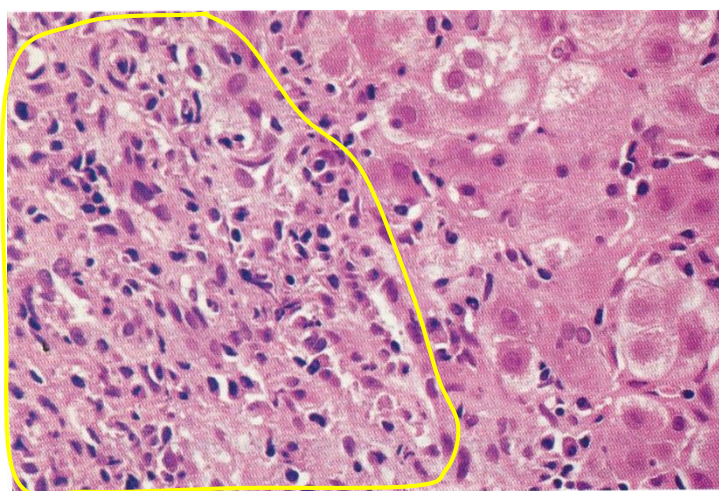


Figure 1: Slide of histopathology of autoimmune hepatitis

The image shows the histopathology, a) H&E stain and b) Masson trichrom stain, of a liver biopsy from a patient with a diagnosis of primary sclerosing cholangitis. The images demonstrate the hallmarks of this disease with periductal inflammation and fibrosis, the “onion ring” sign.

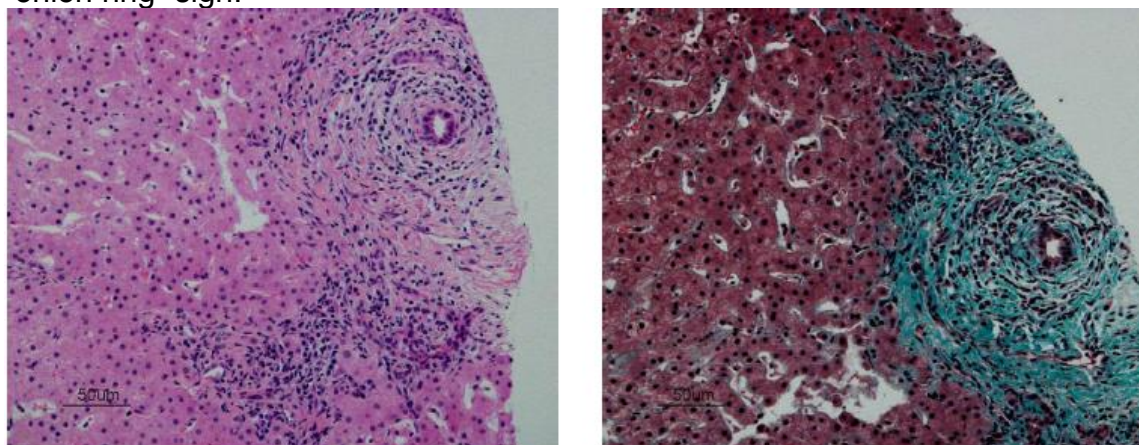


Figure 2: Slide of histopathology of primary sclerosing cholangitis



4. Management

Prompt initiation of treatment in paediatric AIH can prevent an aggressive progression to cirrhosis and end stage liver disease. The first line treatment includes corticosteroid administration at 1-2mg/kg/day (to a maximum of 60mg/day). Most patients respond to oral administration of prednisone or prednisolone, although in patients presenting acutely and with signs of liver failure, intravenous methylprednisolone may be a more appropriate option. Immunosuppressant medications are routinely continued for a minimum of approximately 2-3 years to prevent relapses in disease. In order to allow the patient to wean down to lower doses of steroids (2.5 – 5 mg daily) and minimize the risk of adverse effects (e.g. hypertension, psychological effects, sleep impairment, growth impairment, poor bone health/osteopenia, etc.), a second medication, azathioprine (AZA, 1-2mg/kg/day), is typically recommended. The timing for commencing AZA varies according to expert opinion. It is important to use caution when using azathioprine in the presence of significant jaundice, or advanced liver disease, due to the hepatotoxic effects of this medication. The AASLD guidelines recommend treatment with the combination of prednisone and azathioprine in children to diminish the liver inflammation, allow for healing and regeneration, and minimize corticosteroid side effects (Table 2).

Table 2: Management of Autoimmune Hepatitis

Induction of remission:

Corticosteroids (PO prednisone or prednisolone) – 1-2mg/kg/day (maximum 60mg/day)

- Consider intravenous methylprednisolone in the child with signs of liver failure
- Treat at high dose for 2-3 weeks
- Wean over 6-8 weeks by 0.1-0.2mg/kg/dose on a weekly to bi-weekly basis

Maintenance of remission:

Corticosteroids (PO prednisone or prednisolone) – 0.1-0.2mg/kg/day or 5mg daily

Azathioprine (AZA) – 1-2mg/kg/day

- AZA treatment can be added at diagnosis or once the liver biochemistry has shown modest improvement

Monitoring:

- Monitor liver biochemistry (ALT, AST, GGT, ALP, conjugated bilirubin, albumin, INR) on a weekly basis initially.
- Once biochemistry has normalized and AZA dose is stabilized, can monitor liver biochemistry monthly for 2-3 months, and then every 3 months.
- Monitor CBC on a weekly basis to assess for leukopenia (neutropenia or lymphopenia) with addition of AZA, or with dose changes

End-Point:

- Continue immunosuppressant medications for a minimum of ~2-3 years
 - Avoid discontinuation of medication if patient is pubertal due to high risk of relapses
 - Goal to achieve a minimum of 18-24 months of normal liver biochemistry as well as a normal repeat liver biopsy prior to medication discontinuation.
-



Treatment response is monitored by closely following the liver biochemistry (weekly initially) to ensure normalization over the following months. With improvement in liver biochemistry the corticosteroid doses can be reduced, whereas any elevations in liver biochemistry should result in intensifying the treatment. Patients should also be monitored for toxicities associated with AZA such as cytopenias. Furthermore, patients should be informed about the risk of pancreatitis and skin cancer so that they may take action with the development of corresponding symptoms, as well as undertake appropriate prevention strategies. Other medications of benefit in AIH include budesonide and mycophenolate mofetil (MMF). These therapies can be used according to patient preference or with a history of intolerances to the standard medication regimen.

After treatment with the above-mentioned therapeutic strategy for 2-3 years, discontinuation of the medications can be considered. Prior to discontinuation, the AASLD guidelines recommend the confirmation of a “biochemical remission,” with normal liver biochemistry, normal serum IgG, and negative to low autoimmune antibody titres (<1:20) for 12 months. Also, a liver biopsy should be repeated to confirm the absence of hepatic inflammation². While off medications, the patients are required to obtain frequent laboratory investigations, as the first indication of a relapse is frequently sub-clinical with mild elevations in liver biochemistry. In the event of a relapse, the standard regimen of corticosteroids and azathioprine can be restarted. It is important to inform the patient and their family that relapses are frequent (50-85%), and that recurrent relapses (>2 relapses) are associated with poor outcomes. Furthermore, relapse rates are even higher during puberty, and changes to the regimen are ill-advised until the completion of puberty.

5. Prognosis

In 50% of children with AIH, cirrhosis is present at diagnosis. Despite this finding, the majority of children respond extremely well to standard treatment regimens. While it may require several months for complete normalization of liver biochemistry, 80% of patients will experience a significant improvement within six weeks. Relapses, described as elevations of liver biochemistry with or without signs of hepatitis, occur in 40% of patients while on therapy. These deteriorations can be treated with temporary increases in corticosteroids and maximization of azathioprine doses. Despite adequate therapy, patients may nonetheless progress to end stage liver disease requiring liver transplantation (LT), with the development of ascites, esophageal variceal hemorrhage, or hepatic encephalopathy. The King's College experience in London, England described 5/47 (11%) patients requiring LT, while the adult literature describes a 4-6% LT rate. Unfortunately, recurrences in the liver grafts have also been described in approximately 30% of patients with LT for AIH. In this situation, the addition of steroids ± azathioprine to standard post-transplant immunosuppression regimens long-term is required.



Chapter 28: Viral Hepatitis

C. O' Connor and S.C. Ling



1. Hepatitis A

1.1. Overview

Hepatitis A infection is caused by a non-enveloped, single serotype RNA virus. The World Health Organization estimates that there are 1.4 million cases of acute hepatitis A infection globally each year. The highest rates of hepatitis A infection occur in the developing world and are associated with poor sanitary conditions.

In highly endemic areas, up to 90% of children have been infected with the virus before 10 years of age. In Canada, the annual incidence of hepatitis A infection is 1.5-2.5 cases per 100,000 in younger children and less than 2% of unvaccinated children are sero-positive by 10 years of age. The incidence has declined since the hepatitis A vaccine was introduced in 1996.

Hepatitis A is transmitted via the fecal-oral route by direct person-to-person contact, by contamination of food or water, or by contact with contaminated objects. Up to 50% of reported Canadian cases occur during or after travel to endemic parts of the world. Community outbreaks of hepatitis A infection occur uncommonly, are most often linked to infected food handlers, and have also been reported amongst First Nations communities. The incubation period for hepatitis A infection is usually 14 – 28 days but may be as long as 50 days. Patients are typically infectious for two weeks before the onset of symptoms until one week after symptoms appear.

1.2. Clinical presentation

A case: A fifteen year old boy presents with a three day history of nausea and vomiting, followed by one day of fatigue and jaundice. He returned from a vacation to visit family in South America 2 weeks ago. Blood work shows a conjugated bilirubin of 50 $\mu\text{mol/L}$, ALT of 457 U/L, AST of 387 U/L, an INR of 0.9 and a positive IgM anti-HAV antibody.

In as many as 90 % of children under six years of age, hepatitis A infection may be asymptomatic or associated with mild non-specific symptoms such as fever, poor appetite or fatigue; jaundice occurs in only 10% of patients in this age group. Older children may present with anorexia, nausea, fatigue, fever; jaundice occurs in up to 70% of cases in this age group. Rare cases of acute liver failure are reported due to hepatitis A, but this virus does not cause chronic infection.

1.3. Differential diagnosis and investigations

In a child presenting with these symptoms, liver biochemistry and coagulation tests (direct and indirect bilirubin, ALT, AST, GGT, albumin, INR) will usually show a significant hepatitis (elevated ALT and AST) with normal liver function maintained (normal INR and albumin).

Serologic testing should be ordered. IgM antibody to hepatitis A is indicative of acute infection and is usually detected by the time symptoms are present, 1 to 2 weeks after infection with the virus, and persists for up to 14 weeks. IgG antibody to hepatitis A is



indicative of past infection or acquired immunity via immunization. If acquired following infection, the IgG antibody usually confers lifelong immunity to future hepatitis A virus infection.

The differential diagnosis of acute jaundice in a child includes virus infections, biliary obstruction, autoimmune hepatitis, Wilson disease and other metabolic disorders. Although rare, acute liver failure must always be ruled out by urgent evaluation of the INR. Other signs of liver failure, like the drowsiness or confusion associated with hepatic encephalopathy, are often absent in children.

1.4. Management

There is no specific treatment for hepatitis A infection. Management of symptoms is aimed at ensuring comfort and adequate hydration and nutrition during illness. Patients with evidence of liver failure including either hepatic encephalopathy or coagulopathy should be urgently assessed by a liver specialist. Hepatitis A is a reportable disease and any newly identified cases should be brought to the attention of local Public Health authorities.

1.4.1. Primary prevention:

Hepatitis A vaccine is at least 85 to 90 % effective in preventing hepatitis A infection when given prior to exposure. Children over one year of age may receive the hepatitis A vaccine. Hepatitis A vaccine should be routinely given to persons planning travel to endemic regions. Vaccine is also recommended for men who have sex with men, illicit drug users, and residents of specific institutions like correctional facilities and those for developmentally challenged individuals. Patients with chronic liver disease should also be vaccinated to avoid the potential for decompensation of liver function during hepatitis A infection in this patient group.

Human immune globulin injected intramuscularly can provide hepatitis A protection when administered prior to exposure to the hepatitis A virus or during its incubation period. Its effectiveness in preventing hepatitis A infection is estimated to be up to 79%. Immune globulin should be considered in infants less than 1 year of age, immunocompromised individuals and people for whom hepatitis A vaccine is contraindicated. The efficacy of hepatitis A immunization strategies in immunocompromised children is likely to be reduced, but has not been accurately quantified.

1.4.2. Secondary prevention:

Household and close contacts of individuals known to have acute hepatitis A infection should be immunized immediately, because immunization within one week of exposure to hepatitis A may be effective in preventing infection in up to 79% of contacts.

1.5. Prognosis

The severity of acute hepatitis A infection ranges from the usual mild symptoms lasting from days to two weeks, to rare cases of severely disabling disease lasting for several months (more commonly in adults). A small minority (3-15%) may have a relapsing episode of hepatitis with prominent cholestatic features, usually within 3 weeks of the first episode. Mortality associated with hepatitis A infection is 0.1 – 0.3%, with the highest risk amongst patients with pre-existing morbidity including chronic liver disease.



2. Hepatitis B

2.1. Overview

Hepatitis B infection is caused by an enveloped virus containing both double-stranded and single-stranded DNA. The World Health Organization estimates that more than 2 billion people have evidence of past or present hepatitis B infection and that 350 million people are chronically infected with hepatitis B worldwide. Endemic regions, where prevalence of chronic infection is greater than 2% of the population, include Asia, Africa, South and Central America, Eastern Europe, the Middle East and some South Pacific countries. Globally, complications of hepatitis B infection are the cause of about 1 million deaths each year.

Chronic hepatitis B infection prevalence data is not collected in Canada but is estimated to be up to 6% in immigrant populations from endemic regions and 4% in Aboriginal populations. The incidence of reported acute hepatitis B infection is now extremely low in children, likely due to universal immunization programs and maternal hepatitis B screening.

The most common mode of transmission of hepatitis B to children is the vertical route from mother to infant during pregnancy. Hepatitis B virus may also be transmitted via parenteral or mucosal contact with infected body fluids, including through sexual contact and health care-associated infection from blood or blood product transfusions. Canadian Blood Services implemented screening for hepatitis B surface antigen (HBsAg) in the 1970's and added a secondary screening test (antibody to hepatitis B core antigen, anti-HBc) in 2005, so transfusion acquired hepatitis B is highly unlikely to occur in Canada.

2.2. Clinical presentation

A case: A 9 year old girl, who has been adopted from outside Canada, presents for her annual checkup. The girl is well with no symptoms and a normal physical examination. Blood work shows a conjugated bilirubin of 0 $\mu\text{mol/L}$, an ALT of 47 U/L, AST of 38 U/L, positive HBsAg, negative anti-HBs, positive HBeAg, negative anti-HBe and a HBV DNA of 4.52×10^7 iu/ml.

Hepatitis B is most commonly diagnosed during the chronic phase of infection, as an incidental finding when liver biochemistry is tested for another reason, or following screening of a child born to a mother with hepatitis B infection. Infants who acquire hepatitis B from their mothers during pregnancy or at birth are usually asymptomatic. Symptomatic presentation of acute hepatitis B infection in a child is now very rare in Canada. Non-specific clinical symptoms such as fatigue, malaise, loss of appetite, mild fever and vomiting may occur either at the time of an acute infection, or during a flare in the hepatitis activity in someone with chronic infection (see below); a small proportion of patients may develop jaundice. The risk of developing chronic hepatitis B infection after acute infection is about 90% in infants, up to 50% in children aged 1 to 5 years and 5-10% in adolescents. Once chronic hepatitis B infection has been established, spontaneous clearance of the virus is rare (approximately 0.5% of carriers annually).



Fulminant hepatitis B with massive necrosis of liver tissue is very rare in childhood in North America. Patients with fulminant hepatitis B may present with signs of liver failure including jaundice, hepatic encephalopathy and coagulopathy.

2.3. Differential diagnosis and investigations

Hepatitis B infection and details of the phase of infection are identified by serologic tests in conjunction with liver biochemistry (Table 1). Chronic hepatitis B infection is defined by the presence of HBsAg on two separate blood tests at least 6 months apart. Acute infection is suggested by the presence of IgM antibody against hepatitis B core antigen.

Table 1. Common patterns of hepatitis B serology in children

HBsAg	Negative	Not infected, immune to hepatitis B
Anti-HBs	Positive	
HBsAg	Negative	Not infected, not immune to hepatitis B
Anti-HBs	Negative	
HBsAg	Positive	Active infection with hepatitis B (acute = < 6 months from exposure and/or positive anti-HBc IgM, chronic = > 6 months from exposure)
Anti-HBs	Negative	If ALT is normal = “immune tolerant” phase of infection
HBeAg	Positive	If ALT is high = eAg positive hepatitis, with possible impending seroconversion or need to consider treatment
Anti-HBe	Negative	
HBV DNA	High*	
HBsAg	Positive	Hepatitis B “chronic carrier” phase
Anti-HBs	Negative	
HBeAg	Negative	
Anti-HBe	Positive	
HBV DNA	Low*	

**Hepatitis B DNA is defined as high if present at >20,000 IU/ml (>10⁵ copies/ml), and low if <2,000 IU/ml (<10⁴ copies/ml)*



Most children with chronic hepatitis B infection have no or minimal liver inflammation and are said to be “immune tolerant” to the virus. In this phase, children are positive for HBsAg and HBeAg, have a high hepatitis B viral load and have normal liver enzymes. Up to 50% of children will undergo HBeAg seroconversion in childhood as evidenced by the development of anti-HBe, the loss of HBeAg and a significant drop in hepatitis B viral load. Seroconversion is often preceded by immune recognition of the virus resulting in a flare of acute hepatitis (ALT and AST > 2 times the upper limit of normal). This is usually asymptomatic, but may be associated with malaise and lethargy. The majority of children who undergo HBeAg seroconversion (>95%) enter the chronic carrier phase of infection and remain positive for HBsAg.

2.4. Management

Hepatitis B is a reportable disease and any newly identified cases should be reported to local Public Health authorities.

2.4.1. Primary prevention:

Hepatitis B vaccination is effective in 95% or more of children and young adults in preventing hepatitis B infection. In Canada, a universal school age-based immunization program was implemented in the 1990's, with some Provinces and Territories also offering a universal infant immunization program. Hepatitis B immunization should be offered to children at high risk, including those living with infected individuals, from endemic regions or communities, immunocompromised individuals and anyone engaging in high risk behaviours.

2.4.2. Secondary prevention (post-exposure):

For infants born to hepatitis B positive mothers, hepatitis B immune globulin (HBIG) should be given immediately after birth and the first dose of hepatitis B vaccine should be given within 12 hours of birth. In other cases of exposure to hepatitis B, hepatitis B immune globulin (HBIG) should be given as soon as possible within 7 days followed by hepatitis B vaccine. The efficacy of HBIG is significantly reduced after 48 hours post-exposure.

2.4.3. Acute hepatitis B infection

Supportive care and management of symptoms like fever and dehydration caused by poor intake or vomiting should be provided in addition to the above secondary prevention measures. Patients with impaired liver function including conjugated hyperbilirubinemia, hypoalbuminemia or coagulopathy should be urgently assessed by a liver specialist.

2.4.4. Chronic hepatitis B infection

Children with chronic hepatitis B may benefit from being followed by a paediatric liver specialist for ongoing monitoring and age-appropriate teaching. Teaching for the child and family includes information about immunizing household contacts, minimizing risk of transmission, avoiding high risk behaviours, and promoting a healthy lifestyle to prevent other causes of liver damage.



Children in the immune tolerant or chronic carrier phases of infection should have serum liver enzymes monitored every 6 months and hepatitis B serology annually in order to identify hepatitis flares that may require treatment. Screening abdominal ultrasound is recommended at least every 2 years to help identify those rare children who may progress to cirrhosis or hepatocellular carcinoma.

In children with persistently elevated ALT (greater than 1.5-2 times the upper limit of normal) and no evidence of developing anti-HBe antibody after 6 months, treatment should be considered. A liver biopsy may be warranted to help clarify the need for treatment.

There is no cure for chronic hepatitis B infection. Current therapy aims to achieve a reduction in the degree of hepatitis, a reduction in viral load, loss of HBe antigen and seroconversion to anti-HBe antibody positivity. Available therapies that are licensed for use in children in Canada include interferon, lamivudine, and entecavir (from the age of 16 years). Due to the potential for viral resistance to lamivudine, the mainstay of therapy for children with hepatitis B continues to be subcutaneous injections of interferon for 24 weeks. The goals of therapy described above are successfully achieved in approximately 33-50% of children treated with interferon for a hepatitis flare whilst HBe antigen positive. Due to the significant side effects of interferon, hepatitis B treatment should be undertaken by those experienced in its use in children.

Other oral medications used for hepatitis B treatment in adults, which act directly to decrease hepatitis B viral replication, are not currently licensed for use in children in Canada.

2.5. Prognosis

Most children with hepatitis B do not develop symptoms or complications associated with liver disease during their childhood. However, rare cases of cirrhosis and hepatocellular carcinoma have been reported in children. Children and families affected by hepatitis B should be educated about the much higher risks of hepatitis B when they grow up to be adults, and the consequent need for continued careful medical monitoring and possible future therapy. As children approach adulthood, factors that may increase the risk of development of cirrhosis and carcinoma include male sex, other causes of liver injury (such as alcohol abuse or fatty liver disease secondary to obesity), and a positive family history of hepatocellular carcinoma.

3. Hepatitis C

3.1. Overview

Hepatitis C infection is caused by a blood borne, RNA virus that leads to inflammation and scarring of the liver over time. The World Health Organization estimates that 3% of the global population is infected with the hepatitis C virus, with country specific prevalence ranging from less than 1% to 15%. In Canadian adults, the most common mode of transmission is intravenous drug use. In adults, 75-85% of those who are exposed to the hepatitis C virus will become chronically infected. As hepatitis C infection may be asymptomatic, an estimated 21% of infected Canadians are unaware of their hepatitis C infection.

Infants most commonly acquire the virus via maternal transmission from an infected mother. The rate of mother to child infection is low, approximately 6%, but



increases to nearer 25% if the mother is co-infected with HIV. Spontaneous clearance of the virus occurs in 25 – 40 % of infants infected via maternal transmission of the virus, usually before 18 months of age, although occasionally later up to 7 years of age.

Universal screening of blood products for hepatitis C was implemented in Canada in 1992 and it is thus extremely unlikely for children in this country to become infected via blood transfusion or blood product use. However, many countries remain unable to reliably screen 100% of their donor blood supply. Therefore children from endemic nations in the developing world may still be at risk of transfusion-acquired hepatitis C infection or infection during other health-care related exposures, such as via improperly sterilized syringes and medical equipment.

The overall prevalence of chronic hepatitis C infection in Canada is estimated at 0.8%. The reported rate of hepatitis C infection in Canadian children is 2.3 cases per 100 000 population in children under 15 years of age and 18.5 case per 100 000 in youth between the ages of 15 and 19 years. The highest prevalence of hepatitis C infection in individuals less than 19 years of age occurs in street youth.

3.2. Clinical presentation

A case: An 18 month old boy, whose mother is known to be chronically infected with hepatitis C, presents for hepatitis C screening. The boy is well, with normal physical examination and normal developmental assessment. Blood work shows a conjugated bilirubin of 0 $\mu\text{mol/L}$, an ALT of 62 U/L, an AST of 48 U/L, positive anti- HCV, and an HCV RNA 1.48×10^5 iu/ml.

Hepatitis C infection in children is generally asymptomatic and is usually diagnosed coincidentally when liver enzymes are tested for another reason, or when a high-risk child is screened. In children infected after infancy, a history of general malaise and fatigue may coincide with the time of infection; rarely an episode of jaundice will be reported.

3.3. Differential diagnosis and investigations

Children born to mothers known to be infected with the hepatitis C virus should be screened at 18 months of age. Older children with elevated liver enzymes should be screened for the hepatitis C virus, especially when maternal infection status is unknown, when medical procedures or immunizations have occurred outside of Canada, or when high-risk behaviours such as intravenous drug abuse may have occurred.

The serum IgG antibody to hepatitis C virus (anti-HCV) has a high specificity and sensitivity (approximately 98% and 97%, respectively) in identifying individuals over 18 months of age who are chronically infected with the hepatitis C virus. In infants born to hepatitis C infected mothers, positive anti-HCV results may reflect passively acquired maternal antibodies and are therefore not useful in determining infective status. In older individuals, IgG anti-HCV testing may remain negative for one to three months after exposure to the hepatitis C virus and should be repeated if initial testing was performed earlier.



Tests for hepatitis C RNA (HCV RNA) may become positive in as little as two to four weeks after hepatitis C exposure. In children born to hepatitis C positive mothers, HCV RNA is an insensitive marker of chronic infection before 6 months of age, because viremia may fluctuate. Consequently, testing of infants should ideally be delayed until 18 months of age to confirm or exclude infection. Chronic HCV infection is confirmed by two positive tests, six months apart.

Serologic testing should be performed in conjunction with liver function tests (direct and indirect bilirubin, albumin, INR) and liver transaminases (ALT, AST, GGT).

3.4. Management

Hepatitis C is a reportable disease and any newly identified cases should be reported to local Public Health authorities. Education for the family and child includes discussion about the risk of transmission to other household contacts, avoidance of high risk behaviours, maintenance of a healthy lifestyle, long term prognosis and the need for ongoing monitoring.

Annual blood work and biannual ultrasound imaging is recommended for children with chronic hepatitis C infection, who often have persistent mild elevation of ALT and AST (less than 2 times the upper limit of normal). Fibroscan® and blood-test indices for fibrosis measurement are currently only for experimental use in children.

Treatment may be indicated for certain children with evidence of progressive fibrosis due to hepatitis C, or children with a high likelihood of successful viral eradication. For example, treatment is much more successful for children infected with HCV genotype 3 (approximately 80-90% success) than for children with HCV genotype 1 (approximately 50% success). However, the most effective combination therapy (pegylated interferon and ribavirin) is not currently licensed for use in children in Canada. Referral to a specialized paediatric liver clinic is therefore advisable, where treatment options can be discussed, including involvement in clinical trials of the new generation of direct-acting antiviral medications.

3.5. Prognosis

Chronic hepatitis C infection in childhood is a progressive liver disease with 1 -2 % of those infected developing cirrhosis in childhood. Up to 20% of patients with chronic infection will develop liver cirrhosis within the first 20 – 30 years of infection. Chronic liver failure occurs in 2 – 5 % of adult patients per year. Hepatitis C related hepatocellular carcinoma occurs at a rate of 1 – 4 % per year in adults with cirrhosis. Hepatitis C remains the leading indication for liver transplantation among adults in Canada.

It seems likely that recent advances in treatment for hepatitis C will ultimately enable effective therapy for most children such that these risks of cirrhosis and hepatocellular carcinoma will be significantly reduced.





Chapter 29: Gallstone disease

T. Gonska



1. Overview

Gallstone disease is a diagnosis that needs to be considered in children and adolescents presenting with acute abdominal pain. Its incidence is on the rise in paediatric patients with about 2% for gallstones and 1.5% for biliary sludge, as determined by abdominal ultrasound in paediatric patients presenting with abdominal pain.

Bile is composed of bilirubin, bile acids, phospholipids and cholesterol. Their relative concentration determines the solubility of the bile. Changes in the abundance of one of these components, alteration of the so called nucleation factors involved in hepatobiliary transport processes, as well as dysmotility of the gallbladder increase the lithogenicity of the bile with the risk of stone formation; these may be cholesterol, pigment or mixed gallstones. While cholelithiasis describes stone formation in the gallbladder, choledocholithiasis refers to gall stones within the common bile duct. Stones or sludge within the bile duct may disrupt the bile flow leading to severe, acute, colicky abdominal pain. This obstruction may cause further complications, such as acute cholestasis or biliary pancreatitis. The presence of sludge or stones together with the altered flow properties of the bile can in turn cause inflammation and secondary infections, such as cholecystitis or ascending cholangitis.

2. Clinical Presentation

A case: 14 year old girl presenting with acute onset of abdominal pain, no vomiting and no jaundice. On exam she is overweight and is tender in the upper abdominal area. Blood work shows a conjugated bilirubin of 15 $\mu\text{mol/L}$, $\gamma\text{-GT}$ of 215 U/L, AST of 533 U/L, ALT of 644 U/L, Amylase of 40 U/L and lipase of 30 U/L.

Cholelithiasis or gallbladder sludge can occur in children of all ages. Often the diagnosis is made accidentally in an asymptomatic child that undergoes abdominal imaging for other reasons. Nevertheless, children and adolescents may present with acute onset of severe, frequently colicky abdominal pain secondary to acute ductal obstruction or biliary pancreatitis. When evaluating a paediatric patient with abdominal pain, one has to remember that the presentation of pain varies across different age groups ranging from irritability and feeding avoidance seen in very young infants, to a more generalized complaint of abdominal pain and nausea in toddlers and school-age children, and a more distinct localized pain sensation in adolescent patients. In this regard right upper quadrant tenderness, as well as positive Murphy sign (inspiratory arrest due to pain upon deep palpation below the liver margin), may or may not be appreciated on the physical exam. In some instances patients may be jaundiced or complain about nausea and vomiting. The presence of fever or a history of prolonged illness should prompt immediate work-up and management for cholecystitis and/or cholangitis.



3. Differential Diagnosis and Investigations

The initial work-up focuses on establishing a diagnosis for cholelithiasis and on assessing the extent of the gallbladder disease specifically investigating for possible choledocholithiasis, cholecystitis and/or cholangitis. The differential diagnosis for acute upper abdominal pain is listed in Table 1.

Table 1: Differential diagnosis of upper abdominal pain

Pathophysiology	Etiologies	Work-up
Gallbladder disease	Choledocholithiasis Biliary pancreatitis Cholecystitis Cholangitis	Blood work Ultrasound, MRCP ERCP
Biliary duct obstruction	Choledochal cysts Pancreatobiliary duct anomalies Intrahepatic ductal plugging (seen in Cystic Fibrosis) Extrinsic compression due to peritoneal or retroperitoneal tumor	Ultrasound, MRCP Ultrasound, MRCP MRCP Ultrasound, MRCP
Hepatic pain	Vascular: Venous occlusive disease (seen in patients undergoing bone marrow transplant), Budd-Chiari, capillary ischemic events (seen as crisis in patients with sickle cell disease) Focal hepatic lesion, tumor, vascular malformation Hepatitis	Concomitant disease, exam, ultrasound, MRCP Ultrasound, MRCP, α -fetoprotein Blood work, serology
Acute Pancreatitis	Infectious, hereditary, metabolic, drug induced, idiopathic	Blood work, ultrasound, MRCP
Peptic ulcer disease	Helicobacter pylori, no H. pylori	Upper endoscopy and immune histochemistry
Abdominal vascular events	Superior Mesenteric Artery syndrome	Barium enterography Contrast CT
Dyspepsia	Functional gastrointestinal disorder	Clinical and r/o organic disease



Blood work should include cholestatic parameters (conjugated and unconjugated bilirubin, alkaline phosphatase, γ -glutamyltransferase), liver enzymes (ALT, AST), liver function tests (INR, PTT, albumin), pancreatic enzyme (amylase, lipase), CBC and inflammation markers (C-reactive protein, ESR).

The presence of stones or biliary duct obstruction needs to be investigated using abdominal imaging. Ultrasound as a first non-invasive imaging modality has a reported sensitivity of about 80% to identify ductal obstruction without necessarily identifying the obstructive cause itself (50% sensitivity). However, ultrasound may demonstrate stones in the gallbladder, which in the presence of intra-or extra hepatic bile duct dilatation may raise suspicion for choledocholithiasis. Abdominal CT is slightly more sensitive in identifying bile duct stones but radiation exposure limits its use. MR based cholangiopancreatography (MRCP) is the most sensitive modality for the identification of bile or pancreatic ductal obstruction and inflammation, as is endoscopic retrograde cholangio-pancreatography (ERCP), which, in addition, offers means for immediate therapeutic interventions. In the presence of clinical symptoms, elevated cholestatic markers and documented ductal dilatation on ultrasound, ERCP may be used as first diagnostic and interventional modality even if ductal stones have not been documented on ultrasound. In children with other co-morbidities and low evidence of ductal obstruction, MRCP is a better option to establish a diagnosis of choledocholithiasis. Nevertheless, general anesthesia is required for the use of MRCP in young children and infants.

In all children presenting with acute symptoms and cholelithiasis, but particularly in those with concomitant fever, apathy or lethargy, special attention should be directed to identify laboratory indicators of cholecystitis or cholangitis, such as increased inflammatory markers, increase white blood cell count or imaging describing thickened or irregular shaped gall bladder or ductal wall. Blood cultures should be taken immediately to support targeted antibiotic therapy.

To prevent recurrence, patients need to be assessed for co-morbidities that have been associated with an increased risk for gallbladder disease. These include obesity, use of oral contraceptives, haemolytic disease (sickle cell disease, spherocytosis, thalassemia major, glucose-6-dehydrogenase deficiency), hepatobiliary disease, cystic fibrosis, abnormalities in cholesterol metabolism (ABCB4 gene mutation) or co-inheritance of Gilbert syndrome (UGT1A1 mutation) and trisomy 21. In addition, cholelithiasis has been associated with systemic infection, antibiotic use, ileal disease in infants and children, whereas bile sludge has been described in association with systemic disease and/or antibiotic use and total parenteral nutrition in infants.

4. Management

In the acute setting, initial management is focused on relieving the ductal obstruction. Patients need careful monitoring, iv-fluid infusion and pain management in a hospital setting. While in some instances stones may pass spontaneously, often ERCP is the intervention of choice to successfully locate and remove the obstructive stone. Lithotripsy is widely discussed in the literature, but it is not a treatment option in Paediatrics. Consequent cholecystectomy in the symptom-free interval to avoid recurrence is recommended and demands early discussion with the family and referral to a General/Paediatric Surgeon. Suspicion of cholecystitis or cholangitis should prompt the initiation of broad-spectrum iv-antibiotic therapy, e.g. ampicillin and cefotaxime, or



ampicillin, gentamicin and metronidazole followed by targeted antibiotic therapy as per the results of the blood cultures a few days later. Lastly, risk factors for cholelithiasis need to be identified and addressed. Since obesity is increasingly associated to gallstone disease, dietary counseling for reduction of dietary fat, as well as weight loss, are recommended.

5. Prognosis

The outcome of gallstone disease and bile duct obstruction in Paediatrics is generally good, but depends on the expertise of the centre. ERCP complication rates are highly centre-specific and general comparative outcome data are missing. Frequent recurrence of cholelithiasis with complications and particularly following the first event of biliary pancreatitis warrants early cholecystectomy. This is primarily performed laparoscopically.





Chapter 30: Pancreatitis

T. Gonska



1. Overview

Over the last decade the incidence of acute pancreatitis in children has increased to around 13 per 100,000 children. Pancreatic injury triggers disruption of the fine balance between highly reactive (proteolytic and lipolytic) pancreatic enzymes (e.g. trypsinogen) and inhibitory elements (serine protease inhibitor SPINK) and in turn causes premature activation of pancreatic enzymes, inflammation and thus pancreatitis. Imbalance between these activating and inhibitory mechanisms is probably not the sole cause of pancreatitis, as other pathways that trigger pancreatic inflammation have been recently identified.

In contrast to adults alcohol and gallstone disease are not the main causing factors of pancreatitis in children, and in most of the cases the cause of acute pancreatitis remains undetermined.

2. Clinical Presentation

A case: 13-year-old girl presenting with acute onset of severe abdominal pain and vomiting. She reports that she had similar abdominal pain episodes before, but not as severe. On exam her upper abdominal area is tender, Amylase is 1500 U/L, Lipase is 3000 U/L, liver parameters are normal.

Children of all ages can present with acute pancreatitis. Symptoms of epigastric pain radiating to the back may not be appreciated in children and often the symptoms may be quite heterogenous leading to under diagnosis of pancreatitis. Irritability, general abdominal pain, nausea, vomiting and feeding avoidance may all be signs of acute pancreatitis. Children may present with fever, but often are afebrile. Thus, it is important to include pancreatitis in the differential diagnosis of acute abdominal pain in paediatric patients. In most instances the clinical course is less severe in children compared to that seen in adults. However, in some cases acute pancreatitis is accompanied by a systemic inflammatory response syndrome, which often requires admission to the intensive care unit. Further, one third of all pancreatitis cases in children are associated with systemic illness.

3. Differential Diagnosis and Investigations

The diagnosis of acute pancreatitis is established in the presence of abdominal pain and increased amylase and lipase ($> 3 \times$ upper limit of normal) or imaging findings consistent with acute pancreatitis. **Caveat:** Amylase and lipase may be low in infants and young children despite the presence of pancreatitis due to the delayed expression of these enzymes in the development. In these cases imaging may assist in establishing the diagnosis of pancreatitis.

Most common etiologies include systemic disease, trauma, medications and biliary disease. Careful exploration of the medical history should focus on drugs and alcohol in adolescents, gallbladder diseases, metabolic syndromes or family history of pancreatitis or cystic fibrosis (Table 1). The initial blood work ideally includes blood cell counts with hematocrit to assess the hydration status, electrolytes (especially calcium), albumin, inflammatory markers, hepatic (AST, ALT) and cholestatic markers (γ -GT, conjugated



bilirubin) and triglyceride levels. Elevated liver and cholestatic parameters as well as serum amylase and lipase are a sign of biliary duct obstruction. Abdominal ultrasound should be made available immediately to rule-out gallstone disease, which would require specific targeted imaging and intervention. Further, ultrasound imaging allows early identification of possible pancreatitis-associated complications (Table 2).

Table 1: Etiologies of acute pancreatitis

• Systemic disease • Trauma • Infection • Drugs, e.g. - valproate - azathioprine - sulfasalazine - asparaginase	• Biliary disease • Hypertriglyceridemia • Hypercalcemia • Metabolic disease
metronidazole	
acetaminophen	

Table 2: Etiologies of acute recurrent or chronic pancreatitis

Acute recurrent/chronic pancreatitis	
Diagnosis	Suggested w/u
CFTR dysfunction	Sweat chloride test
Cystic Fibrosis / CFTR-related disorder	CFTR gene analysis 1) panel of most common mutations 2) sequencing
Hereditary Pancreatitis Mutation* in PRSS1	1. family history 2. gene analysis
SPINK1	
CTRC	
CaSR	
Autoimmune pancreatitis	subacute IgG4 (often not positive in children) Imaging (ultrasound, MRCP, ERCP) Other diseases (PSC, PBC, UC, Sjoergen, Sialadenitis)
Fibrosing pancreatitis (There is not yet sufficient evidence to show that the is the same disease as autoimmune pancreatitis)	Subacute Imaging (ultrasound, MRCP, ERCP) Characteristic: presentation with obstructive jaundice)



Acute recurrent/chronic pancreatitis

Pancreatobiliary duct anomalies	Imaging studies (ultrasound, MRCP, ERCP)
Pancreas divisum	
Pancreas annulare	
Duplication cysts of duodenum	Imaging studies (ultrasound, MRCP, enteroclysis)
Tropical pancreatitis	Regional (tropical countries), association with malnutrition, imaging: intraductal calculi

**PRSS1 - Cationic trypsinogen gene, SPINK1 Serine protease inhibitor Kazal-type 1, CTRC -chymotrypsin C, CaSR - Calcium sensing receptor*

Most patients will only experience one bout of pancreatitis, and often the exact etiology remains uncertain. Patients presenting with two or more bouts of acute recurrent pancreatitis meet the diagnostic criteria of recurrent acute pancreatitis while signs of chronicity on imaging studies establish the diagnosis of chronic pancreatitis. Active and vigorous investigations for an underlying etiology are required in these patients to provide specific medical counselling. Cystic fibrosis, CFTR-related syndrome, hereditary pancreatitis, pancreatobiliary duct anomalies and other conditions should be in the differential diagnosis. In patients with acute recurrent or chronic pancreatitis more extensive imaging, as well as genetic testing is justified. MR cholangiopancreatography (MRCP) is the imaging of choice for the evaluation of ductal anomalies such as pancreas divisum, as it has a general diagnostic accuracy of 90%.

4. Management

Generally acute pancreatitis follows a much milder clinical course in children compared to adults. Nevertheless, in the acute event the patient is ideally monitored in a hospital setting with pancreatic rest by putting the child NPO, adequate volume expansion with intravenous fluids to maintain cardiovascular stability following paediatric guidelines of fluid substitution and pain management, often with opioids. In patients with medication-induced pancreatitis medication should be discontinued and/or changed to other alternative agents. If the pancreatitis episode has not resolved within 2-3 days or the patient is systemically ill, enteral feeding should be started using nasogastric or nasojejunal tube feeding. Though paediatric data are missing, adult studies suggest improved clinical outcomes with enteral compared to parenteral nutrition, particularly in patients requiring intensive care. Clinical symptoms should dictate decisions about re-initiation of oral feeding and length of hospital stay; serum amylase and lipase levels correlate poorly with the severity of inflammation.



There are numerous complications of the acute pancreatitis, each of which needs to be managed (Table 3).

Table 3: Complication of Acute Pancreatitis

Local	Systemic
• Acute fluid collection • Pseudocyst • Necrotizing pancreatitis • Pancreatic abscess • Cholangitis/Cholecystitis • Portal vein/splenic vein thrombosis • Ileus	• Diaphragmatic fistulisation • Pleural effusion • Systemic inflammatory response syndrome • Peritonitis • Disseminated intravascular coagulopathy • Panniculitis

In patients with acute recurrent or chronic pancreatitis risk factors need to be addressed and patients should be followed in a specialized centre. Often the etiology is complex and multifactorial. There is currently no evidence that low-fat diet prevents pancreatitis attacks. However, in some patients, pancreatic enzyme supplementation and inhibition of gastric acid production may help to reduce the frequency of attacks. This is thought to work by interfering with the stimulation of pancreatic secretion mediated by food sensing of the intestine.

5. Prognosis

In general, acute pancreatitis in paediatrics is a self-limiting disease with a very good outcome. Some patients, however, develop pancreatitis –associated complications. The most common are a pancreatic pseudocysts, which in the presence of clinical symptoms, requires endoscopic or surgical drainage. For patients with acute recurrent or chronic pancreatitis the outcome is variable with some patients having few and manageable pancreatitis episodes whereas others suffer from chronic abdominal pain. Early involvement of pain management teams in the care of these patients is recommended. After years of chronic inflammation the pancreatic parenchyma may become replaced by fibrous-fatty tissue with subsequent pancreatic insufficiency.





Chapter 31: Cystic Fibrosis

T. Gonska



1. Overview

Cystic Fibrosis (CF) is still the most common life-limiting, autosomal-recessive disease among Caucasian children. However, the incidence is decreasing to currently about 1: 3500, since the introduction of nationwide newborn screening programs and the availability of prenatal carrier testing. Though CF disease is mainly found in whites, CF diagnoses have been established in patients from different ethnic backgrounds (Caribbean, African, East Asian, First Nations).

CF is caused by mutations in the *Cystic Fibrosis Transmembrane Conductor* (CFTR) gene, which encodes a cAMP-dependent chloride channel on the apical membrane of epithelial cells. Loss of CFTR function results in impaired transepithelial ion and fluid transport and thus changes of the fluid milieu on top of epithelial surfaces (altered pH and hydration status). This in turn leads to recurrent infections, inflammation and eventual organ failure. All epithelial organs are affected, and patients with CF may develop chronic and progressive lung disease, pancreatic disease (pancreatitis or pancreatic insufficiency), gastrointestinal disease (e.g. meconium ileus, distal intestinal obstruction syndrome), hepatobiliary disease, salt loss syndrome, obstructive azoospermia and infertility.

2. Clinical Presentation

A case: 2-year-old boy presents with failure to thrive, some abdominal pain, frequent and large bowel movements. He had some upper respiratory tract infections, but no signs of prolonged cough or pneumonia.

From a gastrointestinal point of view, CF should be considered in any patients presenting with failure to thrive or malnutrition due to maldigestion/malabsorption, steatorrhea, liver disease (most CF patients have mild hepatic involvement with small ALT/AST elevation that does not require special treatment, but some patients present with advanced hepatic cirrhosis and progressive liver disease requiring liver transplant and pancreatitis (see previous chapter).

Special clinical presentations in infancy that warrant CF work-up are: 1) hypoalbuminemia, haemolytic anemia and/or acrodermatitis enteropathica (zinc deficiency), 2) meconium ileus, 3) cholestatic liver disease/acute liver failure.

2.1 Newborn screening for CF

Most provinces in Canada have implemented newborn screening (NBS) programs for CF (in 2012: Ontario, British Columbia, Alberta, Saskatchewan, Yukon). This screening test is based on measurements of serum immune reactive trypsinogen (IRT) levels from heel prick blood samples and is a first tier test. This is followed by a second tier test in cases in which IRT levels exceed a pre-determined cut-off (usually the 95-99th percentile). Many provinces have chosen to screen for the most common CFTR mutation as second tier test. If the screen is positive, the family is contacted to present to a CF centre for a confirmatory sweat chloride testing (gold standard diagnostic test). CF NBS is highly sensitive (>95%). However, this does not mean that a child with negative NBS



result can't have CF: 1) There are still patients born after NBS introduction, who have not yet sought medical attention, 2) Mislabelling of samples may result in erroneous reporting, 3) Some CF newborns may have false negative IRT and/or even falsely low sweat chloride concentration, 4) CFTR genetic screen may fail to identify less common CFTR mutation. Patients presenting with clinical symptoms suggestive of CF (Table 1) therefore need to undergo diagnostic testing regardless of their newborn screening result.

Table 1: Clinical symptoms suggestive of Cystic Fibrosis

Respiratory	Gastrointestinal	Others
Chronic sinopulmonary disease	Failure to thrive due to maldigestion	Chronic metabolic alkalosis
Chronic cough or sputum production	Acute recurrent or chronic pancreatitis	Salt loss syndrome
Persistent chest x-ray abnormalities	Meconium ileus in infancy or later Distal intestinal obstruction	Acrodermatitis enteropathica
Airway obstruction	Hypoalbuminemia in infancy	Complication secondary to fat soluble vitamin deficiencies
Nasal polyps	Liver disease: Prolonged neonatal jaundice Focal biliary or multilobular cirrhosis	Obstructive azoospermia
Digital clubbing	Rectal prolapse	

2.2 CF as a disease spectrum

Over the last decades, a large variability in phenotypic and genotypic manifestation of CF disease has been appreciated. This has broadened the view of CF as a disease with a variable spectrum of clinical manifestations, which are associated with different levels of CFTR dysfunction and specific CFTR mutations. CF patients presenting with pancreatic insufficiency early in childhood are at the one end of this spectrum. These patients carry severe CFTR mutations and are at risk of developing specific disease complications (Table 2). CF patients who have maintained a pancreatic sufficient status beyond 10 years of age usually carry milder CFTR mutations that allow for some degree of residual CFTR function. These patients usually experience a milder disease course, though they still are at risk of developing severe progressive lung disease. Pancreatic sufficient CF patients have a 20% risk of developing acute recurrent or chronic



pancreatitis. The last group in this disease spectrum consists of patients with a CFTR-related disorder. These are patients presenting with clinical symptoms in one CF-affected organ, e.g. acute recurrent pancreatitis, and CFTR dysfunction on diagnostic testing (e.g. borderline sweat test), but who do not meet the strict diagnostic criteria for CF (Table 3). Since it is currently not known whether these patients are at increased risk of developing progressive disease, management similar to that for CF patients is recommended.

Table 2: Gastrointestinal organ disease complication

Complication	Incidence	Comment
Pancreatic insufficiency	~80% of all CF patients	Occurs within 1-2 years of life
Meconium ileus	~20% of pancreatic insufficient patients	all immediate perinatal complication CF
Distal intestinal obstruction syndrome	~10% of pancreatic insufficient patients	all incidence data from cohort studies, occurs mainly in teenagers and adult patients CF
Severe CF related liver disease	~7% of pancreatic insufficient patients	all risk of requiring liver transplant CF
CF-related diabetes	~25% of pancreatic insufficient patients	all Insulin dependent, need to be screened for CF



Table 3: Consensus Criteria of establishing a CF diagnosis

CF diagnosis	CFTR –related disease	Query CF*
Clinical signs or symptoms for CF, or positive NBS and/or a sibling with CF	Clinical signs and symptoms in CF-affected organ	Positive screened NBS
AND Sweat Chloride Test > 60mmol/L and/or 2 CF-causing (!) CFTR mutation and/or positive nasal potential difference test (done only in CF centres with expertise)	AND Sweat Chloride Test 40-60 mmol/L if > 6 months of age and/or 2 CFTR mutation of which one can be CF causing and/or borderline nasal potential difference test (done only in CF centres with expertise)	AND Sweat Chloride Test 30-60 mmol/L if < 6 months of age and/or 2 CFTR mutation, one of which can be CF causing

*Canadian CF caregivers refrain from labeling these infants with the diagnosis of a CFTR-related metabolic syndrome or CRMS as recently introduced at CF centres in the US.

3. Differential Diagnosis and Investigations

3.1 CF diagnostic tests

The sweat chloride test by quantitative pilocarpine iontophoresis with consequent determination of the sweat chloride concentration is the first diagnostic test for establishing or ruling out a diagnosis of CF. Due to large differences in sweat test performance among various laboratories, patients should be referred to accredited CF centres for sweat testing.

Molecular analysis to search for *CFTR* gene mutation is usually done in two steps: firstly to investigate for the presence of one of the most common 39 *CFTR* mutations within a given population, and secondly to complete molecular analysis using *CFTR* gene sequencing in cases of increased clinical suspicion. Around 70% of all CF patients are homozygous for *F508del*, while most of the other *CFTR* mutations (>1800 currently) occur at much lower frequency. Many of these have not yet been proven to be disease-causing mutations, and hence, their identification alone does not help to confirm or exclude the diagnosis of CF. Adjunctive test to assess for CFTR function at the level of the nasal mucosa (nasal potential difference measurements) or colonic mucosa (intestinal potential difference measurements) are available in some CF centres but are not used routinely in clinical practice.

Note, a diagnosis of CF or a CFTR-related disorder is increasingly established in adolescent and adult patients; these persons have usually not been previously diagnosed due to milder symptomatology or because CF had not yet been considered as a differential diagnosis.

3.2 Pancreatic function test

Assessment of the pancreatic function is important to further investigate the cause of failure to thrive or malnutrition in patients. This information also helps evaluating the



underlying CF phenotype (pancreatic sufficient or insufficient). Most of the CF patients are pancreatic insufficient (~80%) by 1-2 years of age. Pancreatic function can easily be determined via fecal elastase measurement in a stool spot sample. Elastase is a pancreatic enzyme that does not get degraded during intestinal passage. A fecal elastase concentration $>200 \mu\text{g/g}$ stool is within range for normal pancreatic function, $100\text{--}200 \mu\text{g/g}$ stool is borderline and $<100 \mu\text{g/g}$ stool is indicative of pancreatic insufficiency. Serum trypsin or fat-soluble vitamin levels (vitamin A, D and E or INR for vitamin K) can also be used as indicators of pancreatic sufficiency or insufficiency.

4. Management

Patients with a diagnosis of CF should ideally be followed in a specialized CF centre. A multi-disciplinary team approach that addresses respiratory, gastrointestinal, nutritional, endocrinological and psychosocial problems has been proven to lead to best outcomes. Ideally, all CF patients have immediate access to their support team and to experts within and outside this team in case of special needs. Though non-CF physician should not make therapeutic decision, the outside physicians, who are the child or family main caregivers may nevertheless be involved in some aspects of the acute or chronic care of these patients.

Briefly, the main columns of CF therapy aim 1) to achieve optimal nutrition, 2) to maintain lung health and 3) to identify and treat disease complications. Thus, CF patients are commonly treated with provision of high energy diets to overcome energy losses secondary to maldigestion and to meet the increased energy requirement secondary to chronic lung inflammation, pancreatic enzyme supplementation to enhance digestion, supplementation of fat soluble vitamins to correct for deficiencies, laxatives to treat intestinal obstruction and constipation, physiotherapy and inhalation therapies to optimize mucociliary clearance and occasionally antibiotic regimens to treat secondary infections, which primarily affect the respiratory system.

Keeping this medical and therapeutic cocktail in mind, the non-CF physician is invited to support patient compliance and to discuss any acute change in treatment with the responsible CF centre. In the event of chronic lung or liver failure, organ transplantation has become an increasingly accepted option with encouraging levels of success.

5. Prognosis

CF is a life limiting disease. However, early and aggressive nutritional interventions, as well as improved therapies targeting organ-specific complications have increased the median survival into mid adulthood. Careful organized transition from a paediatric to an adult CF centre has ensured continuous care of these patients into adulthood. Over the last decade, worldwide efforts have been directed to develop drugs targeting the basic molecular defect of this condition. In fact the first generation of this type of drugs is currently being tested in phase 3 trials. In 2012, the FDA approved Ivacaftor, a drug that improves CFTR function in patients with G551D mutations (3% of all CF patients). This has sparked a lot of hope and motivation for further drug development for patients carrying other mutations as well. Since 100% restoration of CFTR function is unlikely, a change in phenotype rather than complete symptom resolution is expected.



Chapter 32: Biliary Atresia

P.L. Valentino, and B.M. Kamath



1. Overview

Biliary atresia (BA) is a fibroinflammatory disease of the bile ducts, which causes obstruction of the biliary tree. It presents only in the neonatal period, and is fatal if surgical treatment is not offered in a timely manner. The incidence of BA varies considerably depending upon geographic location: 1:5000 births in Taiwan and 1:20,000 births in Northern Europe, with an equal sex distribution. BA is a panbiliary disease with both intrahepatic and extrahepatic biliary ducts affected, although the manifestations at presentation result from obstruction of the extrahepatic biliary tree. The theorized pathophysiology of BA development includes: perinatal infections (e.g. cytomegalovirus, reovirus, or rotavirus), immune dysregulation, genetic susceptibility, and maternal factors (e.g. diabetes mellitus).

The obliteration of the biliary ducts occurs postnatally in the majority of infants, while a minority has a prenatal onset. Within the subgroup of patients with prenatal onset disease, other congenital malformations can be found in up to 20% of patients. While BA has been associated with congenital defects such as esophageal or jejunal atresia, one specific constellation of abnormalities has been described: biliary atresia splenic malformation (BASM). BASM abnormalities always include splenic malformations (asplenia, polysplenia, or double spleen). However, other findings such as intestinal malrotation, situs inversus, absent inferior vena cava, preduodenal portal vein, cardiac abnormalities (e.g. ventricular septal defect), and pancreatic abnormalities are common as well. An increased index of suspicion is required to avoid missing one of these diagnoses.

2. Clinical Presentation

A case: A 40-day-old infant presents to their primary care physician with persistent neonatal jaundice. The infant's stools are beige in color. On examination, the infant has hepatomegaly but otherwise appears completely well with no dysmorphic features.

At presentation, parents frequently describe a persistence of their infant's neonatal jaundice past two weeks of life, and closer questioning reveals the concomitant presence of pale (acholic) stools (Table 1). These infants typically appear to be completely healthy despite the persistent jaundice. If infants present at a later age, greater > three months of life, hepatosplenomegaly or ascites may be discovered on physical examination. These findings indicate progression of disease due to obstructed biliary ducts, subsequent cholestasis, and liver cirrhosis. Furthermore, poor weight gain or failure to thrive may occur as a result of a lack of bile acids in the lumen of the small intestine, which in turn results in fat malabsorption (refer to *The Cholestatic Infant* chapter).

3. Differential Diagnosis and Investigations

The infant with a conjugated hyperbilirubinemia requires assessment of liver enzymes and liver function tests. An elevated gamma-glutamyl transferase (GGT) concentration (> 100 IU/L) is a first clue to the presence of a biliary tract abnormality. An international normalized ratio (INR) may be elevated due to vitamin K malabsorption secondary to fat malabsorption. Investigations to assess the differential diagnosis of



infantile conjugated hyperbilirubinemia are also necessary (refer to *The Cholestatic Infant* chapter).

An assessment of the biliary ducts should begin with an abdominal ultrasound investigation to assess for masses or a choledochal cyst. Findings in BA can include hepatomegaly, and an absent or contracted gallbladder. Occasionally, the ultrasonographer may report a highly specific finding known as the “triangular cord sign,” which refers to a hyperechogenic solid biliary remnant at the bifurcation of the portal vein and liver hilum. However, absence of this sign does not exclude BA, and thus should not be relied upon to make the diagnosis.

Subsequent investigations for BA will depend on the age of presentation of the cholestatic infant as surgical intervention has a better outcome when performed within approximately 60 days of life. Thus, less invasive investigations may be attempted, such as the radioisotope study hepatobiliary iminodiacetic acid (HIDA) scan, in children presenting within the first four weeks of life. If adequate hepatic uptake of the tracer and subsequent excretion into the intestine is clearly visualized, the diagnosis of BA can be ruled out. However, in the setting of severe cholestasis, hepatic uptake of the tracer may be poor, and therefore assessment of its excretion into the intestinal lumen can be uninterruptable. As pretreatment with phenobarbital for 3-5 days has been recommended to promote tracer excretion, this would significantly delay the diagnosis of BA. HIDA scans should not be the primary test modality in patients presenting later in life (≥ 6 weeks).

A liver biopsy can provide supportive clues to help establishing a diagnosis of BA. Characteristic findings of biliary obstruction include cholestasis with bile plugs, ductular proliferation, and portal fibrosis. However, a cholangiogram is the definitive test in the diagnosis of BA (Figure 1). This involves the injection of a contrast dye into the biliary tract, and the radiographical identification of passage of dye into the intestine. Interventional radiologists can perform this percutaneously, however, this is not widely attempted. Typically, the cholangiogram is performed intra-operatively, which is considered the gold standard diagnostic procedure.

4. Management

Surgical treatment is required to avoid progressive biliary cirrhosis and end-stage liver disease. The procedure of choice is a Kasai portoenterostomy, which involves the excision of the extrahepatic biliary ducts and the anastomosis of a jejunal Roux loop to the cut surface at the porta hepatis. Restoration of bile drainage into the intestine allows for resolution of hepatic cholestasis and improvement of nutrient absorption. In our centre, following this procedure, infants are treated with ursodeoxycholic acid (at a dose of 20 milligrams/kilogram/day) to promote bilirubin clearance as well as prophylactic antibiotics to prevent the development of cholangitis. The duration of treatment with ursodeoxycholic acid is variable among paediatric centres, with long-term administration offered in many cases. Furthermore, their anthropometrics are followed closely to determine the need for calorie supplementation. Fat-soluble vitamin levels are also closely monitored, as these children almost universally require vitamin supplementation.

A proportion of patients will continue to have persistent hyperbilirubinemia immediately after the Kasai procedure, or will experience a recurrence of jaundice years later, as an indication of progressive cirrhosis. These patients may develop signs of end stage liver disease such as ascites, bleeding esophageal varices or general hepatic dysfunction. In these cases, liver transplantation is the only life-saving option. Indications



for liver transplantation include: signs of portal hypertension, hepatic dysfunction, failure to thrive, persistent cholestasis, and recurrent cholangitis. Approximately 50% of children with BA will undergo liver transplantation by the age of two years. Children with a history of BA should be followed closely by a hepatologist at a minimum interval of every four to six months with a clinical examination and liver biochemistry measurements to detect signs of progressive liver disease.

5. Prognosis

Without surgical treatment, infants with BA do not survive past two years of age due to progressive cirrhosis and complications of end-stage liver disease. Numerous studies have correlated improved outcomes, and decreased transplantation rates post Kasai, with younger age at procedure. Screening tools have been proposed to improve early detection of BA, such as stool color charts that can be used by parents to recognise acholic stools. However, despite increased awareness of the optimal timing of Kasai and better attention to post-Kasai medical management, 70-80% of children with BA eventually require liver transplantation regardless of the initial outcomes of surgery. A study of twenty-two BA patients who survived into adulthood with their native liver revealed that 96% had features of portal hypertension and 63% were cirrhotic, demonstrating the significant disease burden associated with this diagnosis. The longer-term outcomes of BA remain to be determined as children with BA managed in the current era survive into adulthood.

Percutaneous cholangiogram demonstrating injection of radiopaque dye into the gallbladder and lack of definition of the biliary tree due to biliary obstruction (Figure 1a). HIDA scan in biliary atresia is significant for appropriate uptake of radiolabelled tracer into the hepatocytes (prominent signal in the right upper quadrant), without any tracer excretion into the intestines (Figure 1b). Note the accumulation of dye in the bladder (low-midline abdomen) as it is excreted renally. This should not be confused with intestinal uptake.

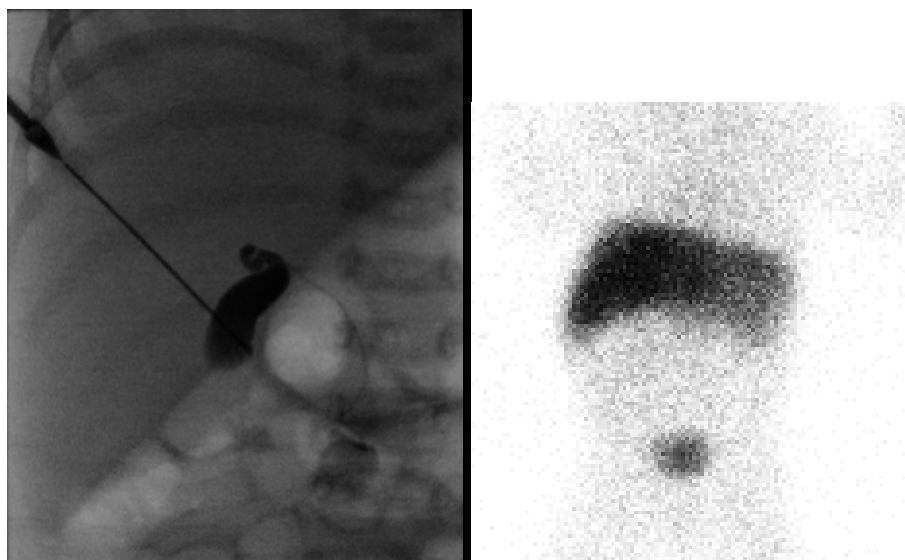


Figure 1: Photo of Cholangiogram in BA



Chapter 33: Approach to Failure to Thrive

M. Mouzaki



1. Overview

Failure to thrive (FTT) refers to faltering growth. Malnutrition is thought to primarily affect children from developing countries; its prevalence, however, in hospitalized children from the developed world ranges anywhere from 6-19%. There are no good prevalence data for outpatients with FTT. Common gastrointestinal conditions, such as inflammatory bowel disease and cystic fibrosis are frequently associated with malnutrition. Recognizing FTT promptly is crucial for long-term outcomes, including psychosocial development. Appropriate tools for the assessment and identification of FTT should be used, and underlying medical conditions (e.g. syndromes) that lead to altered growth patterns should be recognized and not misdiagnosed as FTT.

2. Clinical Approach and Definition

A case: 18-month-old male is referred to your clinic because his weight has been crossing percentiles (50th to 25th to now 10th percentile) over the past 10 months. The mother feels that he is a 'fussy eater' and states that he spits up during feedings as well. He does not have diarrhea and is otherwise developing normally.

Growth charts have been developed to assist in determining growth patterns and detecting faltering growth. The most widely used are the Center of Disease Control (CDC) and World Health Organization (WHO) charts (Figures 1, 2; <http://www.who.int/childgrowth/standards/en/>). In Canada, practitioners are advised to use the WHO charts from infancy to 19 years of age due to the high quality of the data used to create these charts.

A patient, whose weight plots below the 3rd percentile on a WHO chart, is **underweight**. Long-term energy deprivation leads to a decrease in length- or height-for-age as well, which if it plots below the 3rd percentile is called **stunting**. Lastly, weight-for-length or Body Mass Index (BMI) below the 3rd percentile is indicative of **wasting**. Classification systems have been developed to assess the severity of malnutrition; the Wellcome classification system is seen in Table 1.

Table 1. Wellcome classification system

	Weight-for-Length percentage (current weight divided by the appropriate weight for length)	Length percentage (length divided by appropriate length for age)
Normal	90-110	95-105
Underweight	80-89	90-94
Malnourished	70-79	85-89
Severely malnourished	>70 or edema	<85



Since growth charts are the only available tool for practitioners to diagnose FTT, it is of paramount importance to know how they were developed to avoid incorrect assessments (see figure legends). For example, breast fed infants grow faster the first 3 months of life, while formula fed infants have an accelerated growth between 6-18 months. Using CDC charts for breast feeding infants may raise unnecessary concerns regarding FTT, as it may appear that the weight of these infants are crossing percentiles (downwards) during the 5-7th month of age, when they would be found to be growing appropriately on a WHO chart. This is a common source of inappropriate concerns and investigations at this age.

Apart from growth charts for otherwise healthy children, various other charts have been developed for the assessment of growth in the setting of fairly common medical conditions, such as specific syndromes. This is because different patterns of growth are associated with the presence of a specific chromosomal abnormality. It is incorrect to use regular growth charts for these children, as they will invariably lead to inaccurate assessments. Examples of such charts are those for patients with Trisomy 21, Turner's, Noonan's, Prader-Willi or Russell-Silver syndrome, as well as those constructed for children with cerebral palsy etc. It is of importance to note that growth charts have been smoothed with statistical methods to provide a more linear estimate of growth. In reality, infants and children grow in inconsistent patterns with peaks and troughs. For that reason, three rather than two serial points are required to correctly assess growth trends.

3. Differential Diagnosis and Investigations

Once the diagnosis of FTT is established using the correct tools, it is important to investigate the underlying cause. The physiological processes leading to faltering growth can be separated into three categories: 1) lack of energy/nutrients due to poor intake; 2) adequate intake but poor digestion or absorption of ingested food; or 3) adequate intake but increased energy expenditure limiting the availability of energy for growth. The differential diagnoses for each category are summarized in Table 2.



Table 2: Differential diagnosis of failure to thrive

Poor Intake	Maldigestion / Malabsorption	Increased Energy Demands / Other systemic conditions
<u>Behavioral / Social problems</u> Over-dilution of formula, neglect, abuse, developmental delay, financial concerns / poor access to food, anorexia nervosa/ bulimia	<u>Maldigestion</u> Lactose intolerance, pancreatic insufficiency, enterokinase deficiency	<u>Cardiopulmonary</u> Cystic fibrosis, congenital heart disease, heart failure, severe reactive airways disease
<u>Anatomical issues</u> Cleft palate, esophageal strictures, decreased gastric capacity, pyloric stenosis	<u>Malabsorption</u> Celiac disease, cow's milk protein allergy, inflammatory bowel disease, chronic enteric infections, cholestasis	<u>Renal</u> Renal failure, renal tubular acidosis
<u>Motility issues</u> Esophageal dysmotility, GERD, severe colonic dysmotility (e.g. chronic intestinal pseudo-obstruction syndrome; CIPOS)		<u>Immunologic</u> Chronic infections (parasites, HIV, TB), malignancy, immunodeficiencies (e.g. CGD, IPEX), rheumatological conditions (e.g. SLE, JIA)
		<u>Endocrinologic</u> Diabetes mellitus, hyperthyroidism, Addison's disease
		<u>Metabolic / Congenital</u> Inborn errors of metabolism

Abbreviations: GERD: Gastro-Esophageal Reflux Disorder; CGD: Chronic Granulomatous Disease; IPEX: Immune dysregulation, Polyendocrinopathy, Enteropathy, X-linked; SLE: Systemic Lupus Erythematosus; JIA: Juvenile Idiopathic Arthritis



WHO GROWTH CHARTS FOR CANADA

GIRLS

BIRTH TO 24 MONTHS: GIRLS

Length-for-age and Weight-for-age percentiles

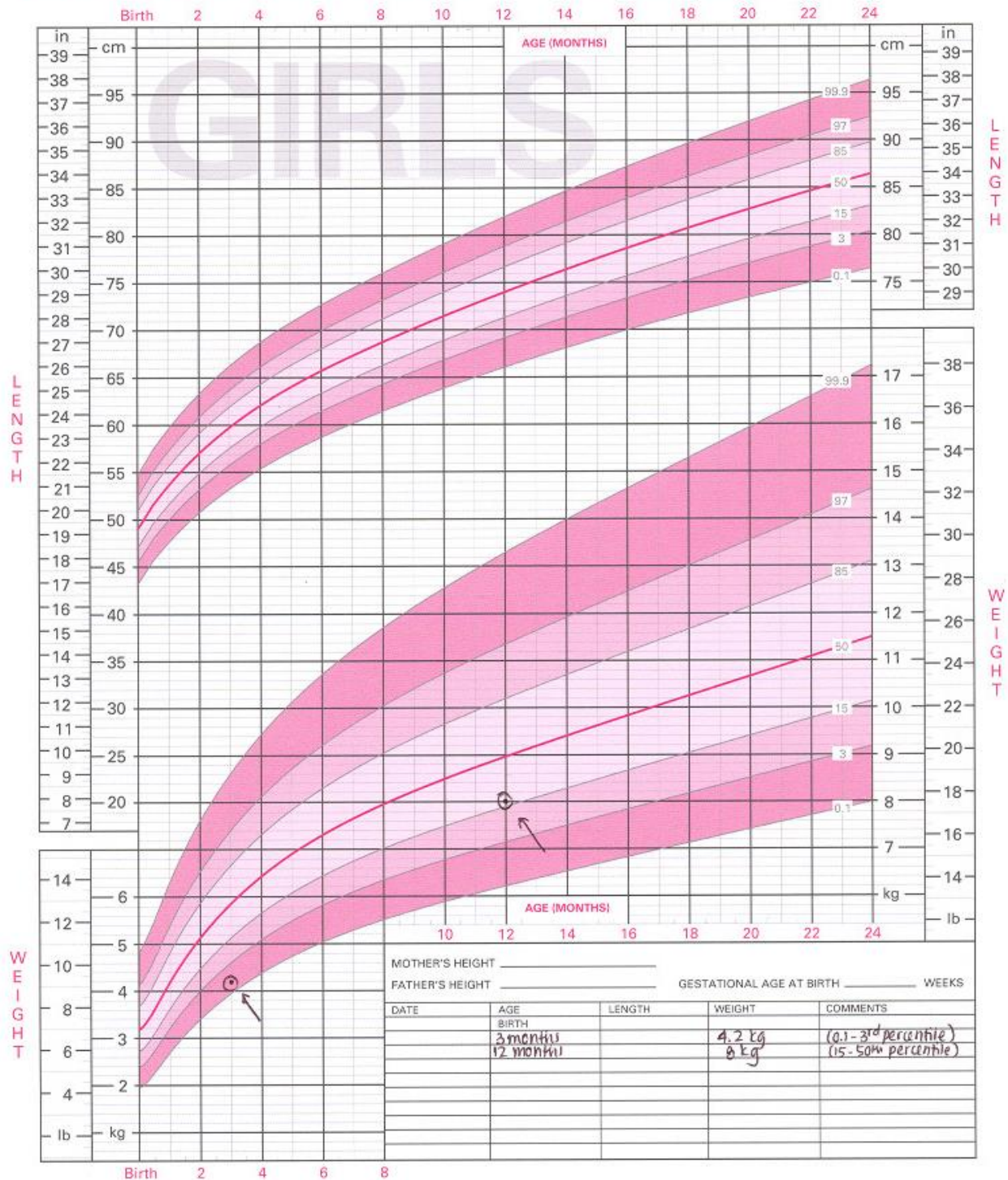
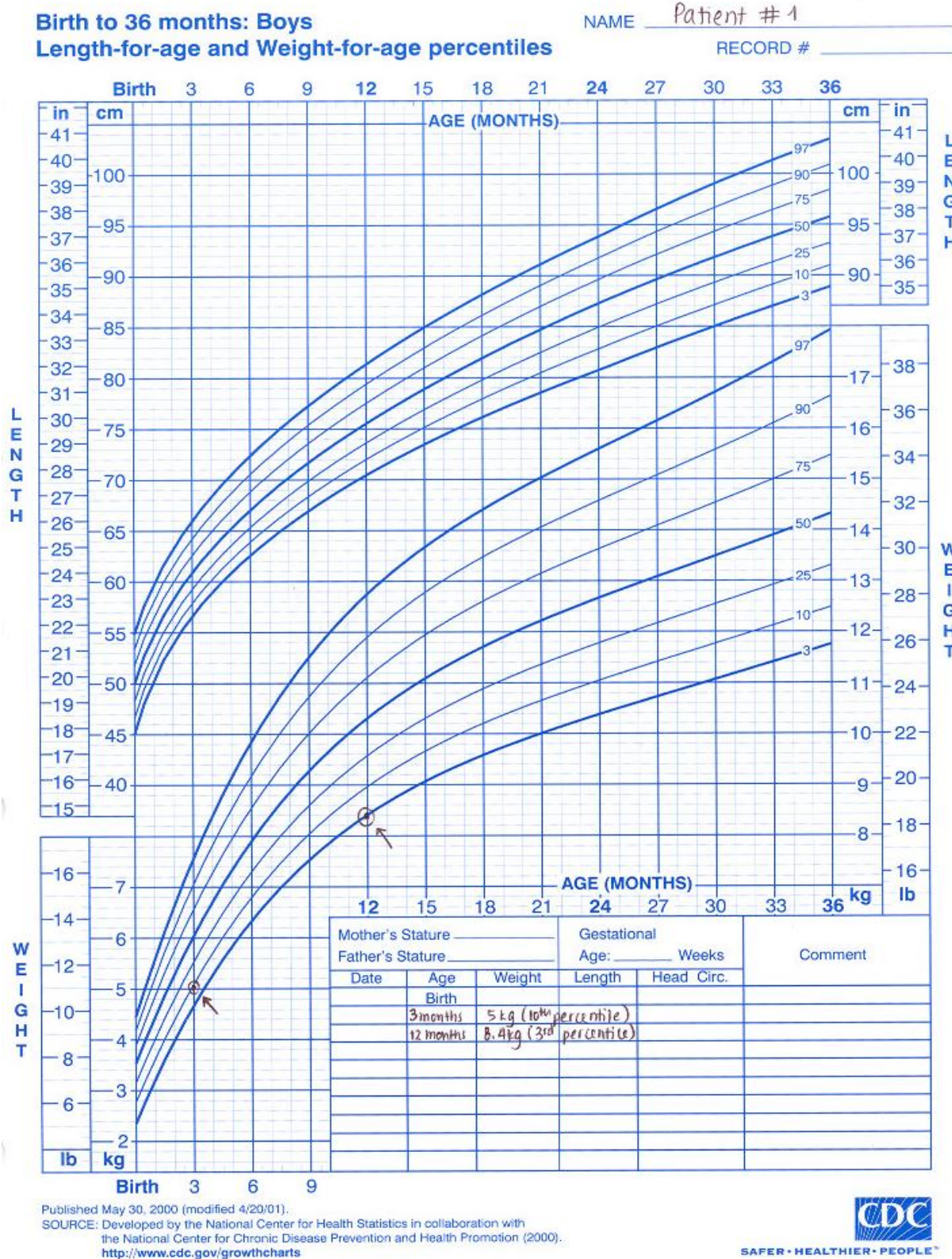
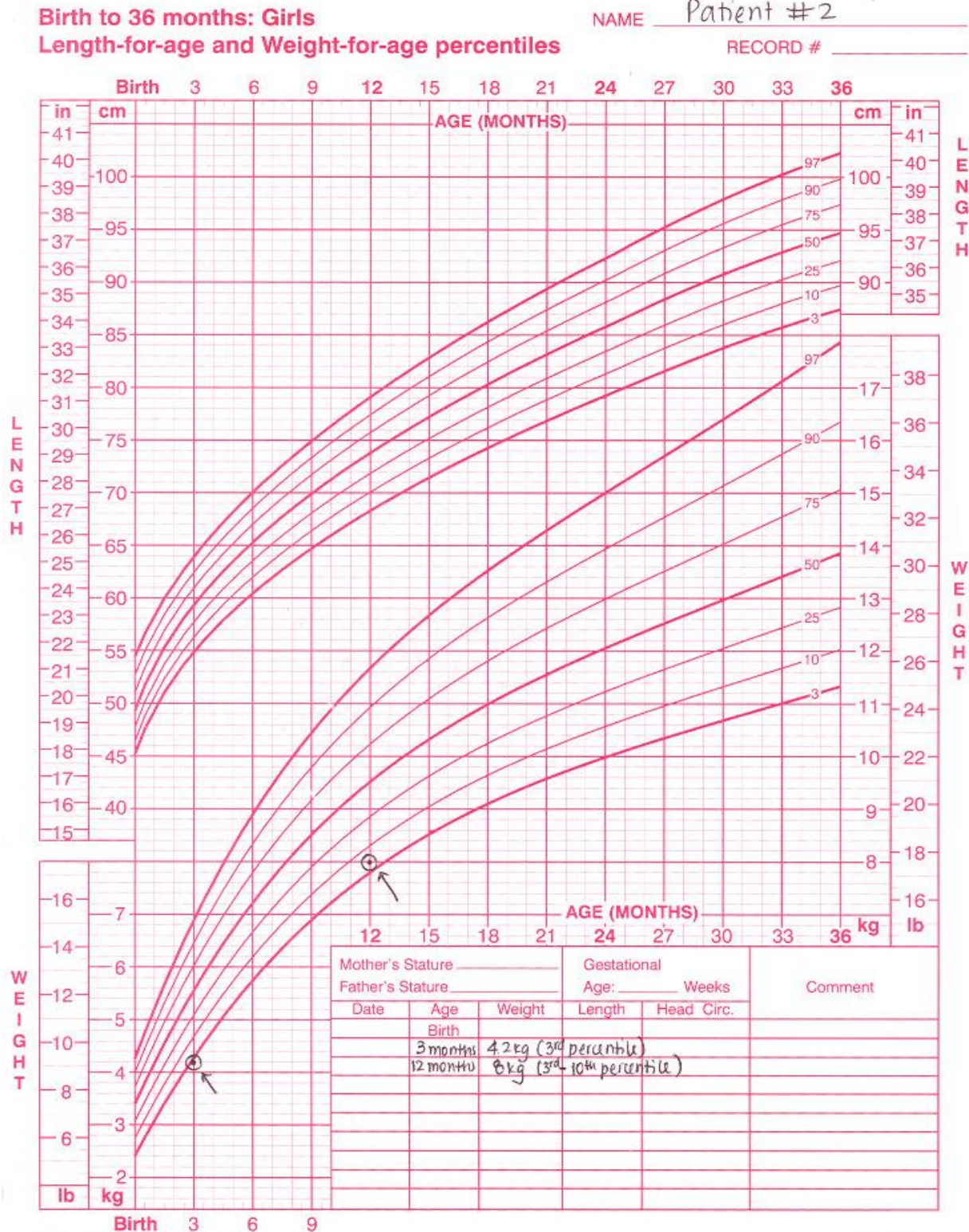
NAME: Patient #2
DOB: _____ RECORD # _____

Figure 1b: Example of WHO growth chart for girls







Published May 30, 2000 (modified 4/20/01).
 SOURCE: Developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion (2000).
<http://www.cdc.gov/growthcharts>



Figure 2b: Example of CDC growth chart for girls



The WHO constructed the 0-2 year old charts with longitudinal data collected from 8,500 infants/toddlers from Brazil, Ghana, India, Norway, Oman, and the United States (US). The characteristics of this cohort were: birth weight of more than 1,500 g, exclusive or predominant breast feeding at 4 months and still receiving some breast milk at 12 months of age, solid food introduction no sooner than at 4 months of age, and non-smoking mothers. The growth patterns of these children are thought to be optimal. The WHO charts from 2-5 years of age were based on cross-sectional data collected from 6,669 children residing in the same areas as the earlier cohort. Lastly, the WHO Reference Charts 2007 are to be used for children/adolescents from 5-19 years of age (<http://www.who.int/growthref/en/>) and were constructed using data from the CDC, while implementing additional statistical strategies to limit extreme growth patterns, especially upward trends indicative of obesity.

The CDC charts were based on cross-sectional data collected from a much smaller cohort residing in the US alone, with variable feeding patterns and environmental exposures, not necessarily reflecting optimal growth.

3.1 Dietary history:

In order to differentiate the various causes that could be contributing to FTT, one should start by obtaining a detailed diet history. In the clinical setting, 24 hour dietary recalls are used more often. During the recall, a trained professional asks about the type, size and composition of the meals consumed by the patient as well as the fluid intake on a typical day. The daily caloric intake of the patient is subsequently estimated and compared to their Estimated Energy Expenditure (EER). The latter can be calculated based on age and gender appropriate equations <http://www.hc-sc.gc.ca/fn-an/nutrition/reference/table/index-eng.php#e eer>. If the estimated dietary intake is below the EER for age, it is likely that the FTT is at least in part secondary to inadequate energy intake.

3.2 Laboratory investigations:

If the history is suggestive of maldigestion/malabsorption, a gross assessment can be initiated by measuring levels of albumin and fat-soluble vitamins. Hypoalbuminemia in the absence of poor dietary intake of protein, diarrhea, albuminuria or liver failure, may be indicative of a malabsorptive process. Low levels of fat-soluble vitamins (A, D, E and K) may suggest fat malabsorption. Other tests that can be used, if available, include: 3 day fecal fat collection (fat malabsorption), fecal elastase (pancreatic insufficiency), fecal alpha-1 antitrypsin clearance (protein malabsorption), stool reducing substances (carbohydrate malabsorption) and fecal electrolytes (secretory diarrhea). Disease-specific tests should be used to investigate for the presence of fairly common conditions, such as celiac disease (anti tissue transglutaminase IgA and IgG, as well as total IgA level) and cystic fibrosis (CF, sweat chloride test and possible *CFTR* mutations screen), especially if the medical history and physical examination raises suspicion for these diseases. Clinical findings should determine the need for any additional tests in the investigation of other conditions that lead to malabsorption/maldigestion of nutrients.



3.3 Indirect Calorimetry

Increased energy expenditure is the characteristic of conditions that belong to the third group of FTT etiologies. Indirect calorimetry is an efficient and fairly inexpensive tool that measures the resting energy expenditure (REE) of subjects based on rates of inhaled oxygen and exhaled carbon dioxide. Calorimetry is useful in identifying patients whose FTT is associated with an increased REE. It is important to note, however, that various conditions associated with FTT alter the REE in opposite direction (i.e. lower REE) and, hence, this tool should only be used as an adjuvant for the assessment of faltering growth. For example, anorexia nervosa leads to a decrease in REE, which is thought to be a normal preservation response. On the other hand, malnourished patients with inflammatory bowel disease may have a normal REE, due to the combined presence of malnutrition and inflammation. Lastly, patients with CF can have an increase in REE, despite significant FTT, which is primarily driven by the enhanced energy cost of the chronic lung disease and increased work of breathing.

4. Management

The treatment of FTT is entirely dependent on the underlying condition(s).

4.1 Dietary

Care providers should ensure that regular feeding times are established and children are sitting in developmentally appropriate seats during meals (e.g. high chair etc.). Patients whose intake is suboptimal should be offered either an increased volume of food or more calorically dense meals. The latter can be achieved by adding butter and/or olive oil to feeds or by increasing the caloric density of the formula that is being used (e.g. from 0.67 kcal/mL to 0.8 kcal/mL etc.). Medium chain triglycerides (MCT) have been used as a means of increasing the caloric content of feeds; practitioners however, should take into consideration that MCT is not a very efficient source of energy and should be used with caution in the setting of FTT. Specifically, MCT has been shown in animal studies to increase energy expenditure and fat oxidation in the liver. In addition, compared to long chain triglycerides (LCT), MCT leads to 20% less weight gain when animals are fed isocaloric diets.

A practical way to estimate energy requirements for catch up growth is the following. Assuming that a quarter of lean tissue consists mainly of proteins, the energy content of protein is 4 kcal/g, in order to gain 1 g of lean mass an intake of 4 kcal would be required. Assuming that each unit of catch up growth consists of 40% fat mass (9 kcal/g) and 60% fat-free mass (4 kcal/g), the energy cost of catch up growth would be $(0.4 \times 9) + (0.6 \times 4) = 4.2$ kcal/g of new tissue. That should be given on top of the energy requirements for age. Provisions of adequate protein to meet requirements for age, in addition to the aforementioned calories, will allow for optimal catch up growth.

Care should be undertaken to prevent re-feeding syndrome when starting nutritional rehabilitation of malnourished children. This condition is a metabolic imbalance characterized by hypokalemia, hypophosphatemia and hypomagnesemia, which occur a few days post initiation of aggressive feeding following a period of poor intake/starvation. The anabolic effects of insulin are at the center of the pathogenesis of this condition. Prevention of re-feeding syndrome is achieved by initially supplying the patient with the calories that they had been tolerating prior to the intervention, or if this is not know



applying the basal metabolic rate for age. Calorie intake can then be increased by 10% every day. In severely undernourished patients electrolyte (potassium, phosphorus and magnesium) and glucose levels should be controlled daily for the first 3-5 days. Multivitamin supplementation as well as additional use of micronutrients, such as folic acid, zinc and copper, may be warranted. It is important to note that children with hypoalbuminemia may initially lose weight during the re-feeding stage, due to enhanced diuresis; this phase is followed by weight gain if sufficient calories are continuously provided. The WHO provides a stepwise approach to the short- and long-term management of severely malnourished children; however, this applies primarily to children followed at low-income settings:

(http://www.who.int/nutrition/publications/severemalnutrition/guide_inpatient_text.pdf).

4.2 Alternate ways of feeding

Anatomic abnormalities of the mouth or esophagus can be either repaired surgically or bypassed with the use of gastrostomy or gastrojejunostomy (GJ) tubes. These feeding tubes allow for supplemental feeds, without interfering with oral intake. Enteral tubes may also assist with dysmotility syndromes resistant to medical treatment, the majority of which affect the gastroduodenal region. Multiple formulas and dietary supplements are now available for enteral nutrition. Among other things, they vary in the type of protein they contain (e.g. casein vs. whey; full protein vs. hydrolyzed protein vs. amino acid based), the source of carbohydrate and the amount and type of fat they contain (e.g. LCT vs. MCT) If enteral feeding is not possible, parenteral nutrition should be considered.

4.3 Psychosocial support

A significant proportion of cases of FTT in developed countries are secondary to psychosocial issues. Counselors and social worker involvement can aid in identifying resources to support low-income families, who cannot afford the cost of food and also assist in detecting other social stressors that may be contributing as well. Behavioral therapy is necessary for patients with behavioral feeding problems and psychiatric involvement is required for patients with anorexia or bulimia nervosa. Lastly but most importantly, the medical team caring for children who are failing to thrive should educate the parents and involve them in decision-making process, in an effort to maintain long term success.

To conclude, failure to thrive is a common problem even in the western world. Thorough history and physical are usually sufficient to assist the medical team in reaching a diagnosis. Regardless of the underlying condition, children are able to grow if provided with adequate calories. Close monitoring and a multidisciplinary approach are occasionally required to support patients with FTT and their families.





Chapter 34: Approach to obesity

M. Mouzaki



1. Overview

Obesity has been termed by the WHO to be a 'global epidemic' with rising incidence in various parts of the world. In Brazil, almost 20% of children between 7-18 years of age are overweight, with half of them being in the obesity range. In South West France, 10% of children 5-7 years and 16% of children of 7-11 years are overweight and obese. Recent data from the United States support an unchanged prevalence of obesity in the past decade with the numbers reaching approximately 10% in the infant/toddler ages and 17% in older children. The only reported increase is that of the BMI of 12-19 year old males. Similar numbers are reported in Canada, with obesity reaching 8% of children 6-11 years of age and 11% in 12-18 year-old children.

2. Clinical Approach and Definition

A case: A 14 year old male presents to your clinic with a chief complain of knee pain. He also describes waking up tired and his mother tells you he snores at night. His BMI is on the 96th percentile for age. His blood pressure in clinic is above the 99th percentile for age, gender and height. On exam you see striae on the lateral sides of the abdomen and acanthosis nigricans on the neck. The liver is palpable 1 cm below the right costal margin.

Overweight and obese patients are usually identified at the primary care office when their weight, height and body mass index (BMI; weight divided by height squared, kg/m²) are plotted on an age and gender appropriate growth chart. They are usually asymptomatic but after careful questioning they may report musculoskeletal pain (hip, knee, ankle, back), daytime fatigue (which may be associated with snoring and sleep apnea), headaches (which may be due to increased intracranial pressure), regurgitation of food, as well as emotional comorbidities, such as depression.

Various definitions have been used to describe overweight and obesity. The American Academy of Paediatrics defines obesity is a BMI $\geq 95^{\text{th}}$ percentile for age (or BMI ≥ 30 kg/m², whichever is lower) and overweight a BMI $\geq 85^{\text{th}}$ percentile for age. The World Health Organization (WHO) defines obesity as a BMI z-score > 3 , and overweight as a z-score > 2 (z-scores are defined as: [value-mean]/standard deviation, and are used instead of percentiles in this setting). For children younger than 2 years of age, weight-for-height (WFH) charts are used instead; obesity is defined as a WFH $> 95^{\text{th}}$ percentile. These definitions represent statistical data rather than specific cutoffs associated with active or future health risks. Reported associations between abdominal girth and obesity-related metabolic and cardiovascular complications have led to the definition of abdominal obesity, which is a waist circumference (WC) $\geq$ the 90th percentile for age. Metabolic syndrome is a term used to describe a constellation of findings associated with obesity; its definition for children, as proposed by the international diabetes federation, is the presence of abdominal obesity in addition to 2 or more factors, as shown in Table 1 (<http://www.idf.org>). The parameters used to describe the metabolic syndrome in children have been derived from adult studies; data on children are limited.



Table 1. International Diabetes Federation-proposed definition of metabolic syndrome in children

Age (years)	Waist Circumference (WC)	Triglycerides	High Density Lipoprotein (HDL)	Blood Pressure	Fasting Plasma Glucose
6-10	≥90 percentile for age				
10-16	≥90 percentile for age OR adult cut-off	≥ 1.7 mmol/L (≥ 150 mg/dL)	< 1.03 mmol/L (< 40 mg/dL)	Systolic ≥130 OR Diastolic ≥85 mmHg	≥ 5.6 mmol/L (100mg/dL) OR known DM2
>16 (adult criteria)	Males: ≥ 94 cm* Females: ≥ 80 cm*	As above OR on treatment for hyperlipidemia	As above for males; < 1.29 mmol/L (<50 mg/dL) for females OR on treatment for low HDL	As above OR on treatment for hypertension	As above

* Japanese, South and South-East Asians, ethnic South and Central American descent should use a cut-off of 90 cm for males and 80 cm for females; DM2: Type 2 Diabetes Mellitus

2.1 Risk Factors

Genetic background has been thought to contribute to obesity and that is supported by studies in twins. Maternal obesity, even in the absence of gestational diabetes, as well as excess gestational weight gain and smoking during pregnancy, have been linked to higher BMI z scores later on in life. Paternal obesity has also been shown to have a similar effect. Fetal macrosomia, or a birth weight in the small for gestational age range, are both risk factors for the development of overweight or obesity during childhood and adolescence. Later on in life, the degree of physical inactivity is directly proportional to BMI, as is prolonged screen time (>2 hours per day) and nighttime television watching. The latter is also associated with shorter duration of sleep, which is another, independent risk factor for the development of obesity. Low socioeconomic status and certain dietary patterns, e.g. skipping breakfast, having few large meals rather than multiple smaller meals throughout the day, have also been linked to obesity.

3. Diagnostic Diagnosis and Investigations

The vast majority of children have exogenous obesity, secondary to excessive caloric intake. Certain metabolic, endocrinologic or genetic conditions can predispose to obesity as well, as summarized in Table 2.



It is recommended that every child that presents to a paediatric practice should have their weight and height measured and depending on the age, weight-for-height (for < 2 years of age) or BMI (2-18 years of age) calculations should follow. Visual inspection alone does not accurately detect overweight and obesity, especially in younger children. Once a BMI > 84th percentile is identified, primary care providers should obtain detailed information on dietary patterns: type of foods consumed and cooking styles, frequency of breakfast consumption, number of meals eaten outside the household, volume of sugar-sweetened beverages and fresh fruit juice consumed per day, activity levels, as well as inheritable medical risk (family history of obesity, hyperlipidemia, hypercholesterolemia, heart disease, stroke, NAFLD). Every subject should have their blood pressure checked and assessed based on age-appropriate cut-offs (http://www.nhlbi.nih.gov/guidelines/hypertension/child_tbl.pdf).

Table 2. Conditions associated with obesity

Obesity with Delay	Developmental Prevalence	Obesity without Delay	Prevalence
Prader-Willi Syndrome (hypotonia, short stature, hyperphagia, hypogonadism)	1:15,000-1:30,000	Leptin Receptor Deficiency / Congenital Leptin Deficiency (hyperphagia, no dysmorphic features)	Few cases reported
Albright's Hereditary Osteodystrophy (short stature, brachydactyly, round facies)	<1:100,000	Prohormone Convertase Deficiency (congenital diarrhea, FTT early on in life, hypoglycemia)	Few cases reported
Fragile X syndrome (elongated face, large ears, macroorchidism)	1:4,000	Alstrom syndrome (blindness, hearing loss, hyperinsulinism)	<500 cases reported
Congenital hypothyroidism (undiagnosed for a prolonged period of time)	1:2,370 births	Hypothyroidism (developing later on in life)	1-2:100
Bardet-Biedl Syndrome (retinitis pigmentosa, polydactyly, hypogonadism)	1:120,000	Cushing Syndrome (primary or secondary)	1:500,000
Cohen Syndrome (microcephaly, hypotonia)	>100 cases in the world	POMC Deficiency (red hair, adrenal insufficiency)	Few cases reported



3.1 Complications/Comorbidities

Increased body fatness is frequently associated with comorbidities, such as insulin resistance or type 2 diabetes mellitus, hypertension, hypercholesterolemia, hyperlipidemia, obstructive sleep apnea, non-alcoholic fatty liver disease (NAFLD), polycystic ovarian syndrome, musculoskeletal abnormalities (e.g. Slipped Capital Femoral Epiphysis [SCFE; fracture through the physics of the femoral head], Blount's disease [tibia vara]), as well as various psychosocial issues (Table 3). The major concern is that there is an increased risk of cardiovascular events and death with a BMI>84th percentile or with the presence of metabolic syndrome alone, regardless of BMI. Also, NAFLD is quickly emerging as a significant health issue; it currently ranks third as an indication for liver transplantation in adults.

Table 3. Potential complications of exogenous obesity and associated findings on History & Physical Examination (H&P)

System	Complications	Findings on H&P
CNS	Idiopathic Intracranial Hypertension	Headaches, papilledema
CV	Hypertension, LV hypertrophy	High blood pressure
RESP	Obstructive Sleep Apnea	Enlarged tonsils, increased neck adiposity, daytime sleepiness
GI	NAFLD, cholecystitis, GERD, inguinal or midline hernias	Hepatomegaly, abdominal pain if acute cholecystitis, hernias
MSK	Slipped Capital Femoral Epiphysis, Blount's disease, Pes planus	Joint pain, primarily at lower back, hips, knees and/or ankles; limited mobility at hip, abnormal gait
ENDO	Insulin Resistance	Acanthosis nigricans
	Polycystic Ovarian Syndrome	Acne, menstrual irregularities

Abbreviations: CNS: Central Nervous System, CV: Cardiovascular, RESP: Respiratory, GI: Gastrointestinal; MSK: musculoskeletal; ENDO: endocrine, LV: Left Ventricle; NAFLD: Non-alcoholic fatty liver disease, GERD: Gastro-Esophageal Reflux Disease

Apart from medical complications, obesity in childhood has also been associated with a poorer quality of life (QOL) and a decreased ability to perform daily activities. Overweight and obese children have a decreased total, physical and psychosocial QOL, which is inversely correlated with their BMI. Despite that, a recent meta-analysis showed that parental perception of their children's QOL is worse compared to what children themselves report.



Screening for hyperlipidemia and hypercholesterolemia should be undertaken in every patient whose BMI is >84th percentile, even in the absence of any risk factors. Interpretation of the results is shown in **Table 4**.

Table 4. Interpretation of lipid levels

Interpretation	Total Cholesterol	LDL Cholesterol
Acceptable	<170 mg/dL (4.4 mmol/L)	<110 mg/dL (2.8 mmol/L)
Borderline	170-199 mg/dL (4.4-5.1 mmol/L)	110-129 mg/dL (2.8-3.3 mmol/L)
High	≥200 mg/dL (5.2 mmol/L)	≥130 mg/dL (3.4 mmol/L)

Abbreviation: LDL: Low Density Lipoprotein

Screening for type 2 diabetes mellitus is recommended for patients with a BMI>84th percentile and risk factors, such as Black, Hispanic or Native American descent, family history of diabetes, cardiovascular risk factors (e.g. hypertension) and/or comorbidities (such as obstructive sleep apnea or the presence of acanthosis nigricans). A BMI >94th percentile should prompt screening, even in the absence of any risk factors. The presence of two risk factors and a BMI at or above the overweight range should prompt further investigations with a fasting glucose test. The American Diabetic Association recommends that this type of screening start at the age of 10 years or at the onset of puberty (whichever comes first) and to be repeated every two years. A fasting glucose ≥ 100mg/dL (5.6 mmol/L) is suggestive of pre-diabetes, whereas fasting glucose ≥ 200mg/dL (11 mmol/L) is indicative of diabetes and these patients should be referred to a paediatric endocrinologist. Diabetes mellitus is tightly linked to metabolic syndrome (Table 1).

Screening for NAFLD with transaminase (AST, ALT) levels should be considered for every patient with a BMI>84th percentile and additional risk factors (similar to those for diabetes) and for those with a BMI>94th regardless of the presence of risk factors, starting at the age of 10 years or at the onset of puberty (whichever comes first). They should be repeated every 2 years thereafter. Abnormal levels on two separate occasions should prompt further work-up with an abdominal ultrasound, assessing for hepatic steatosis, as well as further laboratory work-up to exclude other causes of transaminase elevation and/or steatosis, such as ceruloplasmin for Wilson's disease; anti-smooth muscle, anti-liver/kidney/muscle and anti-nuclear antibody levels for autoimmune hepatitis, antibody for hepatitis C virus, alpha-1 antitrypsin levels for alpha-1 antitrypsin deficiency, anti-tissue transglutaminase IgA and total IgA for celiac disease. Traditionally ALT/AST ratio is higher than 1 in NAFLD; a ratio <1 may be suggestive of cirrhosis.



3.2 Indirect calorimetry

Some practitioners use indirect calorimetry to measure the resting energy expenditure (REE) of overweight and obese patients. This tool is not always available; however its use is aimed at ruling out endocrine causes of obesity that alter the REE, as described below, as well as a tool that aids in identifying caloric intake goals. It is important to note that despite parental beliefs that children's obesity is secondary to a 'slow metabolism', exogenous obesity is characterized by an increased REE, as a result of the overall increased lean body mass of overweight patients. As such, an increased REE in the setting of obesity is likely secondary to exogenous obesity, whereas normal or low REE in patients with abnormally high BMI is suggestive of endocrine (e.g. hypothyroidism, hypopituitarism) causes of obesity. Weight loss in obese subjects leads to normalization of their REE and that should be taken into consideration when caloric intake goals are set.

4. Management

The management of patients with a BMI > 84 requires the participation of the entire family, as it is based on lifestyle interventions. Health Canada's Food Guide provides detailed information on healthy dietary choices (<http://www.hc-sc.gc.ca/fn-an/food-guide-aliment/index-eng.php>). Further dietary and activity recommendations are summarized in Table 5. If the first level of lifestyle changes fails to improve the degree of obesity or the cardio-metabolic risk factors, the family may benefit from planned diets, meetings with dietitians and counseling or group therapy (depending on the dynamics of the family). The progress should be monitored frequently, however, the effort should not focus on reaching a target weight but rather on attaining a healthier physical state. Indirect calorimetry results may be used as an initial caloric intake goal, understanding that this should be decreasing as the children are losing weight. Patients with severe obesity (BMI > 99th percentile) or with multiple comorbidities may be referred to a multidisciplinary team that specializes in the management of obesity. Subspecialists should be involved in the management of severe complications (cardiologist for hyperlipidemia, endocrinologist for diabetes mellitus, gastroenterologist for NAFLD, occupational therapist for musculoskeletal symptoms etc.). In recent years, bariatric surgery has also been used in the management of patients with severe and complicated obesity that is resistant to medical treatment.



Table 5. Lifestyle recommendations for children with obesity

Diet	Activity
Limit the consumption of sugar-sweetened beverages	At least 1 hour of moderate to vigorous activity per day
Portion control	Walk to school or other destinations
Avoid eating outside, especially in fast-food restaurants	Participate in structured physical activities (dance, martial arts etc.)
Family meals 5-6 times per week (not in front of the TV)	Screen time (TV, computer etc.) < 2 hours per day
Consume a healthy breakfast daily	

The management of exogenous obesity is challenging and most dietary interventions fail to have a sustained effect over time. Motivation and determination for change on behalf of all the family members is required for this condition to be addressed effectively and with long-term results.



Chapter 35: Alternate Ways of Feeding: Enterostomy Tubes and Parenteral Nutrition

M Mouzaki



1. Overview

Patients with altered anatomy or dysmotility of the gastrointestinal (GI) tract, or those with severe neurocognitive impairment, occasionally require alternate routes of feeding. Gastric (G), gastro-jejunal (GJ) or jejunal (J) tubes are widely used in this setting with success. Intestinal failure defined as the 'inability to maintain protein-energy, fluid, electrolyte or micronutrient balance, while on a conventionally used diet requires the use of parenteral nutrition (PN).

2. Enteral Nutrition

A case: 3-year-old female with spastic quadriplegia, hypertonia and gastroesophageal reflux disease presents with failure to thrive. The parents report difficulties with feeding as she chokes, gags and vomits almost with every feed. A feeding study is just completed and is suggestive of aspiration with any type of oral feeding. You are considering the insertion of a gastrostomy tube.

A variety of formulas are available for feeding children with enterostomy tubes. The most commonly used ones contain intact protein, as well as carbohydrate and fat levels that mimic those of regular diet. When fed intragastrically, children with severe dysmotility benefit from whey-, rather than casein-based formulas, as whey protein leads to more rapid gastric emptying. Semi-elemental and elemental formulas (defined by the presence of oligopeptides and free amino acids, respectively) are available for children with food allergies. Despite the lack of evidence, they are also used in clinical practice for children with significant dysmotility, resistant to medical management. Apart from the protein content, there are other formulas that differ in the amount of long- to medium- chain triglycerides (MCT). Higher MCT formulas are used for patients with intolerance to long chain triglycerides, such as those with chylous ascites/chylothorax and cholestasis. Lastly, the use of blenderized diets is becoming increasingly popular for patients with enterostomy tubes. These are composed of regular foods that are processed (blenderized) in order to be able to pass via the tube without causing obstruction and are thought to improve feeding tolerance.

2.1. Enterostomy tubes

2.1.1. Types

G-tubes are the enterostomy tubes most commonly used in practice, which allow for feeding directly into the stomach. Patients with severe gastroesophageal reflux disease (GERD), refractory to medical management, history of aspiration pneumonias or anatomic abnormalities of the stomach or duodenum, may benefit from a GJ tube. The latter enters via the stomach and reaches the proximal jejunum, which is where the feeds are delivered. J tubes are used less frequently as they are more labor-intensive to insert.



2.1.2. Indications:

- A. Anatomical (e.g. craniofacial dysmorphisms), neuro-cognitive (e.g. severe cerebral palsy [CP]) or behavioral issues that render the patient unable to take adequate nutrition orally
- B. Failure to thrive and inability to consume the necessary calories orally or anorexia secondary to chronic illness
- C. Tracheal aspiration with oral feedings
- D. Unpalatable diets (e.g. formulas used in metabolic conditions)
- E. Large volume of unpalatable medications

2.1.3. Investigations prior to insertion:

Prior to making the final decision to insert an enterostomy tube, it is important to have ruled-out anatomic abnormalities of the GI tract. An upper GI series is usually recommended, as it assists in detecting gastric or intestinal anomalies that could be contributing to the concurrent symptomatology (e.g. emesis). In addition, a radionuclide gastric emptying study assists in guiding feeding practices (e.g. delayed gastric emptying may imply better feeding tolerance with continuous compared to bolus feeds or may indicate the need for jejunal feeds if there are significant symptoms with gastric feeding). In reality, most patients receive nasogastric or nasojejunal feeds for a few weeks prior to the tube insertion, which allows for decision-making regarding the type of tube to be used, assessment of weight gain while on this mode of feeding, as well as feeding tolerance. Apart from the technical aspects of the pre-insertion investigations, ethical considerations should affect decision-making as well. This is particularly important in patients who are terminally ill or who may be placed at increased risk with tube feeding. The latter has been reported in a cohort study of patients with cerebral palsy who were shown to have increased risk of death when fed via a G-tube. This needs to be investigated further. The last step prior to inserting an enterostomy tube is obtainment of informed consent from the patients and/or their parents. This is possible after having conveyed concise information regarding the technique used and the potential complications associated with the insertion which is discussed below.

2.1.4. Technique of insertion:

Enterostomy tubes can be inserted either by interventional radiologists using fluoroscopy (percutaneous radiological gastrostomy; PRG), paediatric gastroenterologists using an endoscopic approach (percutaneous endoscopic gastrostomy; PEG) or general surgeons during a laparoscopic or open procedure. PRGs are the most efficient to insert and do not necessarily require the use of general anesthesia. PEG insertion allows for visualization of the mucosa during the endoscopy. The surgical approach is the most invasive but it is occasionally necessary, as in the case of unfavorable anatomy, for example, that makes the percutaneous route challenging or even potentially dangerous (see complications section below).

2.1.5. Complications

The prevalence of major and minor complications depends on the technique used as well as the experience of the medical team and is thought to reach 5% and 74% respectively. The surgical approach is the one associated with the highest risk of complications, but both PEG and PRG can lead to complications as well. These include



colonic perforation with peritonitis/sepsis, gastro-colo-cutaneous fistula formation, GI bleeding, aspiration pneumonia, infection at the site and intussusception (the latter primarily seen with GJ tubes). Minor complications that are primarily associated with tube maintenance, include tube occlusion / migration, gastric leakage at the insertion site, premature removal of the tube (prior to the maturation of the tract) and formation of granulation tissue at the stoma.

2.1.6. Long-term outcomes:

Feeding tubes are inserted for nutritional support. Some children may only require short-term nutritional support until health is restored, e.g. children treated with malignancies, whereas for most children (e.g. those with cerebral palsy) an enterostomy tube supports long-term nutritional management. Tube placement alone does not guarantee adequate nutrition and weight gain still needs to be monitored.

3. Parenteral Nutrition

Nutrition delivered directly into the venous system is often required for patients who are not allowed to eat for prolonged periods of time (2-3 days for infants and >5days for older children) or children with intestinal failure, severe GI dysmotility, or chronic conditions associated with feeding intolerance (e.g. emesis during chemotherapy). It can also be used as a treatment strategy, such as in the setting of chylous ascites. Solutions with an osmolarity <1050 mOsmol/L or a glucose concentration $\leq 12.5\%$ may be delivered via a peripheral line. This is usually a short-term approach, as it does not allow for provision of adequate calories in most cases. Long-term parenteral nutrition requires the insertion of a central line (peripherally inserted central catheter [picc], port-a-catheter or central venous line [CVL]). This allows for provision of higher fluid rates, greater osmolarity and ultimately better nutritional support.

3.1.1. Energy

Due to the fact that the process of digestion and absorption are bypassed with the use of parenteral nutrition, the energy requirements are decreased by 25% in the neonatal period and 7-15% in children/adolescents compared to enteral feeding. Energy requirements are dependent on comorbidities (e.g. burns/sepsis increase the requirements), as well as other factors, such as the use of medications (e.g. paralytic agents decrease the requirements). Prediction equations are used to estimate the basal metabolic rate of patients (Table 1). These however, can be inaccurate in critically ill patients for whom energy expenditure should be measured with indirect calorimetry instead.

Table 1: World Health Organization equations for estimation of basal metabolic rate

Age range (years)	Kcal/day males	Kcal/day females
0-3	$60.9 * \text{weight} - 54$	$61.0 * \text{weight} - 51$
3-10	$22.7 * \text{weight} + 495$	$22.5 * \text{weight} + 499$
10-18	$17.5 * \text{weight} + 651$	$12.2 * \text{weight} + 746$

World Health Organization. Energy and Protein Requirements. Technical Report Series 724. Geneva, Switzerland; World Health Organization; 1985



3.1.2. Macronutrients

Dextrose: The dosing of macronutrients is dependent on the age of the patient and may be tailored to the underlying medical condition. Dextrose used in parenteral nutrition is in the monohydrate form and provides 3.4 kcal/mL. Dextrose is the primary source of calories. The initial dose should aim at preventing hypoglycemia but should be low enough to avoid hyperglycemia and stimulate adequate insulin secretion. High doses of dextrose can increase carbon dioxide release, with subsequent respiratory acidosis in patients with parenchymal lung disease or those who cannot regulate their respiratory rate (e.g. paralyzed and intubated patients). Chronic provision of high dextrose doses can also enhance de novo lipogenesis, contributing to hepatic steatosis. Daily increases in the glucose infusion rate allow for optimization of carbohydrate intake and ultimately energy provision (Table 2).

Table 2: Carbohydrate initiation and increase schedule

mg/kg/min	Preterm children	Full term – Older children	Adolescents
Initial dose	5-8	5-8	3-5
Daily increase	1-2	1-3	1-3
Final dose	10-16	11-12	5-8

Fat: In North America, the solution most commonly used as a source of fat is Intralipid (IL). The later is derived from soybean oil and is primarily composed of ω -6 polyunsaturated fatty acids (PUFA), as well as some monounsaturated fatty acids (MUFA), saturated fatty acids and phospholipids. Clearance of IL is dependent on the activity of the lipoprotein lipase, located in the vascular endothelium. In order to assess for tolerance to IL, the dose is started at a low level (0.5-1g/kg/day) and is gradually increased (by 1g/kg/day) to a target level (3-4g/kg/day in terms/preterms and 2-3g/kg/day in older children and adolescents). At least 0.5 g/kg/day of IL is needed to prevent essential fatty acid deficiency, which is manifested clinically with a scaly rash (mimicking zinc deficiency), hair loss and thrombocytopenia. Prolonged use of high doses of IL can contribute to 'fat overload syndrome', which is associated with fever, respiratory insufficiency, platelet dysfunction, as well as hypertriglyceridemia and cholestasis. Fever and sepsis can be associated with poor lipoprotein lipase function and hence IL intolerance; the IL solution must be halved or stopped in such cases until intralipid or triglyceride level can be obtained. Patients with egg or soy protein allergies may react to IL, because of its soybean source and the potential for contamination with egg phospholipid.

Protein: Protein should not be used as an energy source, but rather as an anabolic fuel. Various amino acids solutions are available, with somewhat different amino acid compositions. It was initially thought that parenteral protein should be started at a low dose and then be increased as tolerated, to prevent metabolic acidosis and hyperammonemia. It is now clear that there is no risk of starting at the target protein level.



In addition, for certain populations (e.g. premature infants) this strategy prevents catabolism at a crucial point in life, which may have long-term consequences. Target protein levels are 3.5 g/kg/day for premature infants, 3-3.5 g/kg/day for term infants and 1.5-2 g/kg/day for older children. Urea levels are used as a marker of protein tolerance, but they are of little value in patients with renal impairment.

3.1.3. Micronutrients

Electrolytes, minerals, trace elements and vitamins are also added in parenteral nutrition. Age, underlying medical issues and the duration of parenteral nutrition dictate the dose. Tables with detailed recommendations regarding the use of these micronutrients are included in the American Society of Parenteral and Enteral Nutrition (ASPEN) guidelines (<http://ncp.sagepub.com/content/early/2012/06/27/0884533612446706.full.pdf>).

3.1.4. Complications:

Complications seen with the use of parenteral nutrition can be divided into short- and long-term. Short-term complications include phlebitis, thrombosis, line occlusion, breakage, migration, infections /sepsis, re-feeding syndrome (see failure to thrive chapter), hyper- or hypoglycemia and hyperlipidemia. The most extensively studied long-term complication associated with the use of parenteral nutrition is intestinal failure associated liver disease. Even though parenteral nutrition is thought to contribute to that, other factors, such as impaired intestinal barrier, recurrent septic episodes, lack of enteral feeding and dysmotility have been implicated as well.

3.1.5. Strategies to minimize complications:

From a nutrition standpoint, strategies aimed at decreasing the development and progression of intestinal failure-associated liver disease are:

- Prefer use of enteral feeds over parenteral nutrition, cycle infusions (i.e. running it over < 20 hours per day)
- limit the use of IL (use fish oil or combination emulsions, e.g. SMOF lipid instead or in addition)
- decrease dextrose rates
- limit amino acid dose to the minimal requirement for optimal growth
- limit micronutrients that may be toxic in the long-term use (e.g. copper or manganese); but avoid deficiencies

In a few cases, patients progress to liver failure due to the combined effects or frequent septic episodes (from line infections or bacterial translocation from the gut), lack of enteral feeding and poor enterohepatic circulation, use of hepatotoxic medications and chronic use of parenteral nutrition. Liver transplant is an option in that setting. Combined liver/small intestinal transplant may be considered for those with intestinal failure (predominantly short bowel syndrome or severe intestinal dysmotility disorders) leading to chronic parenteral nutrition dependence. Centers with experience in hepatic/small intestinal transplantation should be following these patients.

Metabolic bone disease improves with the optimization of calcium, phosphate, vitamin D and K dosing, as well as the removal of aluminium from the infusate.



Chapter 36: Specific Nutritional Challenges

M. Mouzaki



1. Overview

There are groups of patients, who are at risk of nutritional deficiencies, either due to restrictive eating practices (e.g. vegetarians, vegans) or because of malabsorption (e.g. short gut syndrome, post bariatric surgery). Practitioners who will increasingly encounter these patients need to be aware of special nutritional considerations.

A case: 10 month old exclusively breast fed infant, born to a vegetarian mother presents with lethargy, pallor and edema. Height and head circumference are below the 3rd percentile for age; weight is between the 3-10th percentile. Laboratory investigations reveal normocytic anemia, hypoalbuminemia and a MRI of the brain reveals brain atrophy.

2. Dietary Challenges

2.1 Vegetarians / Vegans

Classic vegetarians do not consume meat, fowl, fish and related products (e.g. dairy and eggs). Lacto-ovo vegetarians do consume dairy and eggs and ovo vegetarians avoid dairy but consume eggs. The diet of vegetarians consists primarily of grains, legumes, fruits, vegetables, seeds and nuts and is thought to be healthy and nutritionally adequate, if balanced appropriately. Vegans avoid all products of animal origin and hence, in addition to the vegetarian diet, they do not consume foods, such as honey and gelatin. The aforementioned restrictions increase the likelihood of certain deficiencies, such as vitamin B12, vitamin D, calcium, iron, zinc, ω -3 fatty acids, as well as protein and energy, which are discussed below.

2.2 Short bowel syndrome (SBS)

Nutritional deficiencies in the setting of SBS are dependent on the location and the length of the resected intestine. Medical professionals taking care of patients with SBS should have a clear understanding of the remaining anatomy to prevent and treat nutritional deficiencies. Table 1 summarizes the sites where specific nutrients are absorbed along the intestinal tract.

Apart from specific nutrient deficiencies, malabsorption due to the overall decrease in intestinal surface area and the shorter transit time can contribute to protein energy malnutrition as well. In addition, patients with SBS may also have a component of maldigestion, secondary to hypergastrinemia that can subsequently lead to precipitation of bile acids and impaired pancreatic enzyme activity in the duodenum. Significant losses of sodium through the gastrointestinal tract, contribute to poor growth unless replaced vigilantly. Loss of the ileocecal valve may also predispose to nutritional deficiencies as it allows for bacteria to migrate and grow into the small bowel and compete with the host for the use of various nutrients (small intestinal bacterial overgrowth). Lastly, absence of the colon not only leads to water and electrolyte losses but it also limits the ability to use short chain fatty acids (which are synthesized in the colon by the intestinal microbiota during the fermentation of non-digestible carbohydrates) as an additional energy source.



Table 1. Intestinal location of nutrient absorption

Duodenum	Jejunum	Ileum
Calcium	Calcium	
Iron	Iron	
Phosphate	Phosphate	
Magnesium	Magnesium	Magnesium
Copper	Chromium	
Selenium	Manganese	
B vitamins (Thiamine, Riboflavin, Niacin, Biotin, Folate)	B vitamins (Thiamine, Riboflavin, Niacin, Biotin, Folate)	Folate, Vit B12
Fat soluble vitamins (A, D, E, K)	Fat soluble vitamins (A, D, E, K)	Vitamin K, bile acids
	Vitamin C	Vitamin C

Most patients with SBS receive parenteral nutrition, at least initially. This allows for adequate replenishment of malabsorbed nutrients and, if done appropriately, prevents deficiencies. Enteral feeds and nutrient supplementation after the cessation of parenteral nutrition are dependent on the remaining anatomy, as well as other comorbidities that the patient may have. A team approach involving paediatric gastroenterologists, surgeons, dietitians, occupational therapists and pharmacists is paramount for the optimal care of these patients.

2.3 Bariatric surgery

Similarly to SBS, bariatric surgery can predispose to nutritional deficiencies when segments of the intestinal tract are bypassed in an effort to induce weight loss.

One of the most commonly used bariatric procedures in the paediatric population is the adjustable gastric band. This procedure does not lead to malabsorption or maldigestion, as no part of the gastrointestinal tract is being bypassed. It does, however, alter the meal choices of patients, who cannot consume large portions of solid foods, and as a consequence depending on their food choices may develop iron and/or vitamin D deficiencies.

Gastric bypass is the second type of bariatric surgery used in adolescents. With this operation the stomach, duodenum and proximal jejunum are bypassed and the most common deficiencies seen include iron, vitamin D, vitamin B12 and folate. Protein-energy malnutrition and dehydration have also been seen in adults and beri-beri (thiamine deficiency) has been reported in adolescents post-gastric bypass surgery. Multivitamins, as well as calcium and iron (the latter is particularly important in menstruating females) should be supplemented in patients post-gastric bypass.



3. Critical nutrients

3.1 Vitamin B12 (cobalamin)

Vitamin B12 is an essential cofactor in methionine synthesis from homocysteine, as well as the conversion of methylmalonyl-CoA to succinyl-CoA. Signs of cobalamin deficiency include megaloblastic anemia and neurologic impairment with lateral and posterior column degeneration of the spinal cord, developmental delay and neuropsychiatric complications. In infants, brain atrophy with microcephaly has also been reported. Biochemically, the diagnosis of cobalamin deficiency is based on serum vitamin B12 levels but more sensitive tests, such as homocysteine and methylmalonic acid levels are also used.

The major dietary source of vitamin B12 is meat and animal products. Cobalamin found in seaweeds and algae is not metabolically active. Regular consumption of dairy, as in the case of lacto-ovo vegetarians, limits the risk of vitamin B12 deficiency. Children born to vegetarian or vegan mothers may become cobalamin deficient as early as at 2 months of age, because infant stores are dependent on maternal stores during pregnancy. If there is no regular consumption of dairy, children should be given products fortified with vitamin B12 (e.g. soy milk) or be started on vitamin supplements to prevent hematologic complications, as well as significant and occasionally irreversible neurological complications. Cyanocobalamin is the synthetic (not naturally occurring form of vitamin B12) that is used in supplements and food fortification. It is synthesized by bacteria and is not derived from animals, hence can be consumed by vegans/vegetarians. The Recommended Dietary Allowance (RDA) for cobalamin ranges from 0.7 mcg/day during the first couple of years of life to 2 mcg/day in adolescence.

3.2 Vitamin D

Vitamin D receptors are expressed in every cell of the body. Apart from its established role in calcium homeostasis it appears to be involved in immune regulation, as well as a multitude of metabolic and cardiovascular conditions. Serum levels of 25-hydroxy-vitamin D reflect vitamin D status.

The major dietary sources of vitamin D are dairy products and fortified cereals. Cutaneous synthesis of vitamin D also occurs after sufficient exposure to sunlight (UVB radiation). Neonates and infants are less efficient in the synthesis of vitamin D, as are people living in higher latitudes, those with darker skin pigmentation and those that use sun-blocking agents. Vegetarian and vegan children are at risk of developing vitamin D deficiency unless consumption of fortified products, such as juice, soymilk or cereals, is adequate. Supplementation with vitamin D is recommended if the later does not occur. Cholecalciferol is more bioavailable than ergocalciferol and should be used for supplementation. The RDA for vitamin D is 400 IU/day early on in life and 600 IU/day in childhood and adolescence.

3.3 Calcium

Apart from participation in cellular signaling cascades, calcium is necessary for bone mineralization. Vegetarian and vegan diets place people at risk of calcium deficiency, both due to inadequate calcium content and also because of the presence of 'anti-nutrients', such as phytates and oxalates in plant foods that limit the bioavailability of calcium. Fiber also contributes to the latter. Bone fractures and even rickets have been



reported in infants consuming limited amounts of calcium, even in the setting of adequate vitamin D levels.

Rich plant sources of calcium include broccoli, Chinese cabbage and okra. A great proportion of calcium consumed by most vegetarians and vegans is derived from fortified soymilk and fruit juices. The RDA for calcium is 200mg/day in the first 6 months of life and increases to 1300 mg/day in older children and adolescents.

3.4 Iron

Iron deficiency is the most common nutritional issue in children consuming strict vegetarian or vegan diets. Similarly to calcium, the reason for that is two-fold: first, these diets lack heme iron, which is the most bioavailable source, and second, non-heme iron found in plant-based diets is made even less bioavailable by the presence of phytates, calcium and fiber. Interestingly, despite the fact that iron deficiency and low iron stores (reflected by serum ferritin levels) are more prevalent in vegetarians and vegans, iron deficiency anemia is not more frequent than in non-vegetarians. It appears like a degree of adaptation occurs over time, with increased absorption of iron in the setting of poor dietary intake. It is currently recommended that vegetarians consume 1.8 times the RDA for iron to prevent nutritional deficiencies.

3.5 Zinc

Zinc is an important trace element and an integral part of multiple enzyme systems in the body. Zinc deficiency leads to impaired growth and wound healing, immune dysregulation and decreased plasma protein levels. In addition, a scaly, periorificial skin rash (also seen in patients with acrodermatitis enteropathica, who have a genetic condition leading to poor zinc absorption) is characteristic of zinc deficiency. Serum zinc level is the laboratory test used in clinical practice to assess zinc status; however, it may not always accurately reflect zinc stores. Alkaline phosphatase is an enzyme whose synthesis is dependent on zinc, and hence low levels may indicate zinc deficiency.

Red meat is a significant source of dietary zinc; the protein consumed with meat also aids in increasing the bioavailability of zinc. Various plant sources, such as whole grain cereals, soy, peas, nuts and lentils are rich in zinc as well, but the presence of phytates limits its absorption. Despite the increased zinc requirements in vegetarian or vegan diets due to the presence of 'anti-nutrients', zinc supplementation is not recommended, as signs of deficiency have only been reported infrequently. Infant and adult cereals fortified with zinc are a good source of this micronutrient for infants and children consuming vegetarian or vegan diets.

3.6 ω -3 fatty acids (FA)

Linoleic (ω -6 FA) and α -linolenic (ω -3 FA) are the essential fatty acids in humans. Elongation of the ω -6 FA leads to arachidonic acid, as well as various other proinflammatory molecules. Elongation of ω -3 FA leads to eicosapentanoic and docosahexanoic acids that have anti-inflammatory properties. Essential fatty acid deficiency can lead to poor growth, immune dysregulation and rashes; similar to those induced by zinc deficiency. Vegetarian and vegan diets have adequate amounts of ω -6 FA but are restrictive in ω -3, as the primary source of the latter is fish. Consumption of algae, walnuts and canola oil prevents essential fatty acid deficiency in the setting of vegetarian or vegan diets.



3.7 Protein / Growth:

The protein quality of foods refers to the proportion of essential amino acids. Animal proteins are thought to have higher quality than plant-derived proteins, and only a balanced vegetarian/vegan diet provides sufficient amounts of essential amino acids for protein synthesis and growth. An example is that soy products are limiting in sulfur amino acids (methionine, cysteine), whereas corn, wheat and rice are limiting in lysine. Variety in the plant-based diet can prevent protein malnutrition. Overall, vegetarian children have similar growth patterns as their omnivorous counterparts; however, vegan diets in childhood have been associated with a leaner and shorter phenotype. Strong longitudinal data to support the latter are lacking.



Chapter 37: OSCE – Practice in Gastroenterology and Hepatology

A.B.R. Thomson



OSCE Questions in Gastroenterology Chapter

1. Perform a focused physical examination to determine the causes of stomatitis.
2. Take a directed history to determine the causes of halitosis.
3. Perform a focused physical examination to determine the causes of salivary gland swelling.
4. Perform a focused physical examination to determine the causes of parotid gland enlargement.
5. Take a directed history for dysphagia.
6. Take a directed history to determine the causes of RUQ pain.
7. Take a directed history and perform a focused physical examination for appendicitis, and stratify the risk and need for surgery.
8. Perform a focused physical examination to determine the causes of abdominal masses.
9. Take a directed history and perform a focused physical examination for the cause of abdominal bruit.
10. Take a directed history for bowel obstruction.
11. Take a directed history for diarrhea.
12. Take a directed history to determine the cause of infertility in men with inflammatory bowel disease.
13. Take a directed history of alcohol abuse.
14. Perform a directed physical examination for alcohol withdrawal (SSH-DTs: shake, seize, hallucinates, DTs).
15. Perform a focused physical examination hepatosplenomegaly.
16. Perform a physical examination for acute liver disease (acute hepatitis and fulminant liver failure).
17. Perform a focused physical examination for signs of chronic liver disease (portal hypertension).
18. Take a directed history and perform a focused physical examination for ascites.
19. Perform a focused physical examination to determine the cause of pruritus.
20. Prepare a patient for informed consent for the use of steroids (GCS, glucocorticosteroids) in a patient with IBD, explaining the adverse effects.
21. Provide a patient with informed consent prior to their having possible bariatric surgery.
22. Prepare a patient for informed consent for the use of nonsteroidal anti-inflammatory drugs, explaining the potential adverse effects.
23. Perform a directed examination of an abdominal x ray ('flat plate')



Mouth

1. Perform a focused physical examination to determine the causes of stomatitis.

➤ General

- Malnutrition: protein, vitamins, minerals (esp. iron)
- Smoking
- Alcoholism
- Infections
- Drugs
 - Antibiotics
 - Atotoxic drugs
 - Phenytoin
 - Heavy metals
- Trauma
 - Poorly fitting dentures
- Tumour

➤ Systemic diseases

- GI
- Crohn's
- Ulcerative colitis
- Celiac disease
- MSK
 - Behcet's
 - Reiter's
 - Lupus
- Hematology
 - Leukemia and its treatment
 - Neutropenia
 - Iron deficiency

➤ Skin diseases (associated, including angular stomatitis)

- Eczema
- Erythema multiforme (Stevens-Johnson)
- Pemphigus vulgaris
- Pemphigoid
- Benign pemphigoid of mucous membranes
- Epidermolysis bullosa
- Lichen planus
- Dermatitis herpetiformis



- HIV/AIDS associated infections
 - Viral
 - Herpes simplex
 - Herpangina
 - Hand, foot and mouth disease
 - Exanthemata
 - Bacterial
 - Pyorrhea and alveolar abscess
 - Vincent's angina
 - TB
 - Syphilis
 - Fungal
 - Candidiasis
 - Actinomyocosis

Adapted from: Burton J.L. *Churchill Livingstone* 1971, pages 36 and 37.

2. Take a directed history to determine the causes of halitosis.

- Infection
 - Poor oral hygiene
 - Putrid (due to anaerobic chest infections with large amounts of sputum)
- Metabolic
 - Feter hepaticus (a sweet smell)
 - Ketosis (diabetic ketoacidosis results in excretion of ketones in exhaled air, causing a sickly sweet smell)
 - Uremia (fish breath: an ammoniacal odour)
- Drugs
 - Alcohol (distinctive)
 - Paraldehyde
 - Cigarettes, tobacco

Adapted from: Talley N. J., et al. *MacLennan & Petty Pty Limited* 2003, Table 5.8, page 161.

Useful background: Causes of gum hypertrophy

- Gingivitis
 - from smoking
 - calculus
 - plaque
 - Vincent's angina (fusobacterial membranous tonsillitis)



- Drugs (Phenytoin)
- Pregnancy
- Scurvy (vitamin C deficiency: the gums become spongy, red, bleed easily and are swollen and irregular)
- Leukemia (usually monocytic)

Adapted from: Talley N. J., et al. *MacLennan & Petty Pty Limited* 2003, Table 5.6, page 161.

Useful background: Causes of pigmented lesions in the mouth, including tongue

- Drugs/Toxins
 - Heavy metals: lead or bismuth (blue-black line on the gingival margin), iron (hemochromatosis- blue-grey pigmentation of the hard palate)
 - Drugs
 - Antimalarials
 - Oral contraceptive pill (brown or black areas of pigmentation anywhere in the mouth)
- Endocrine
 - Addison's disease (blotches of dark brown pigment anywhere in the mouth)
- Tumor
 - Malignant melanoma (raised, painless black lesions anywhere in the mouth)
- Genetic
 - Peutz- Jeghers syndrome (lips, buccal mucosa or palate)

Source: Talley N. J., et al. *MacLennan & Petty Pty Limited* 2003, Table 5.7, page 161.

Useful background: The tongue

- Brown mottling of enamel (Fluorosis)
- Stippling of gums (Pb, bismuth poisoning)
- Furred tongue-fever (acute abdomen, uremia, cholemia)
- Magenta-colored tongue, angular stomatitis, cheilosis (cracked lips).
- Red side and tip of tongue (nicotinic acid deficiency)
- Dipapillating glossitis (antibiotic therapy).
- Large tongue-myxedema, acromegaly, amyloid, Down syndrome
- Jaundice (frequently appears first and disappears last from frenum of tongue)
- Scrotal tongue (normal or in Down syndrome)



- Geographical tongue-patchy redish depapillation surrounded by “fur” (of no importance)

Source: Mangione S. *Physical Diagnosis Secrets*. Hanley & Belfus, Philadelphia, 2000,, page 122 and pages130 to 133.

Salivary gland

3. Perform a focused physical examination to determine the causes of salivary gland swelling.

- Unilateral swelling
 - Ductal calculus, with staphylococcus or streptococcus viridians infection
- Bilateral swelling
 - Malnutrition; anorexia nervosa/ bulimia, starvation, Kwashiorkor
 - Alcoholism
 - Keratoconjunctivitis sicca (dry eyes and mouth)
 - Autoimmune (Sjögren’s syndrome)
 - Mikulicz’s syndrome (non-autoimmune keratoconjunctivitis sicca): TB, lupus, sarcoid, Waldenstrom’s macroglobulinemia
 - Diabetes
 - Thyrotoxicosis
 - Infection- mumps, HIV
 - Infiltration (leukemia, lymphoma)
 - Drugs (PTU, sulfonamides, lead, mercury, iodide)

Adapted from: Mangione S. *Physical Diagnosis Secrets*. Hanley & Belfus, Philadelphia, 2000, page 144; Talley N. J., et al. *MacLennan & Petty Pty Limited* 2003, Table 5.5, page 160.

4. Perform a focused physical examination to determine the causes of parotid gland enlargement.

- Bilateral
 - Infection
 - Mumps (may be unilateral)
 - Sarcoidosis
 - Infiltration
 - lymphoma
 - Immune
 - Mikulicz syndrome (painless enlargement of all three salivary glands, probably an early stage of Sjogren’s syndrome)



- Drugs / toxin
 - Alcohol-associated parotitis
- Malnutrition
- Severe dehydration
- Unilateral
 - Tumor
 - Mixed, parotid, occasionally bilateral
 - Infiltration (check for signs of VII nerve palsy)
 - Duct blockage, e.g. salivary calculus

Adapted from: Talley N. J., et al. *MacLennan & Petty Pty Limited* 2003, Table 5.5, page 160.

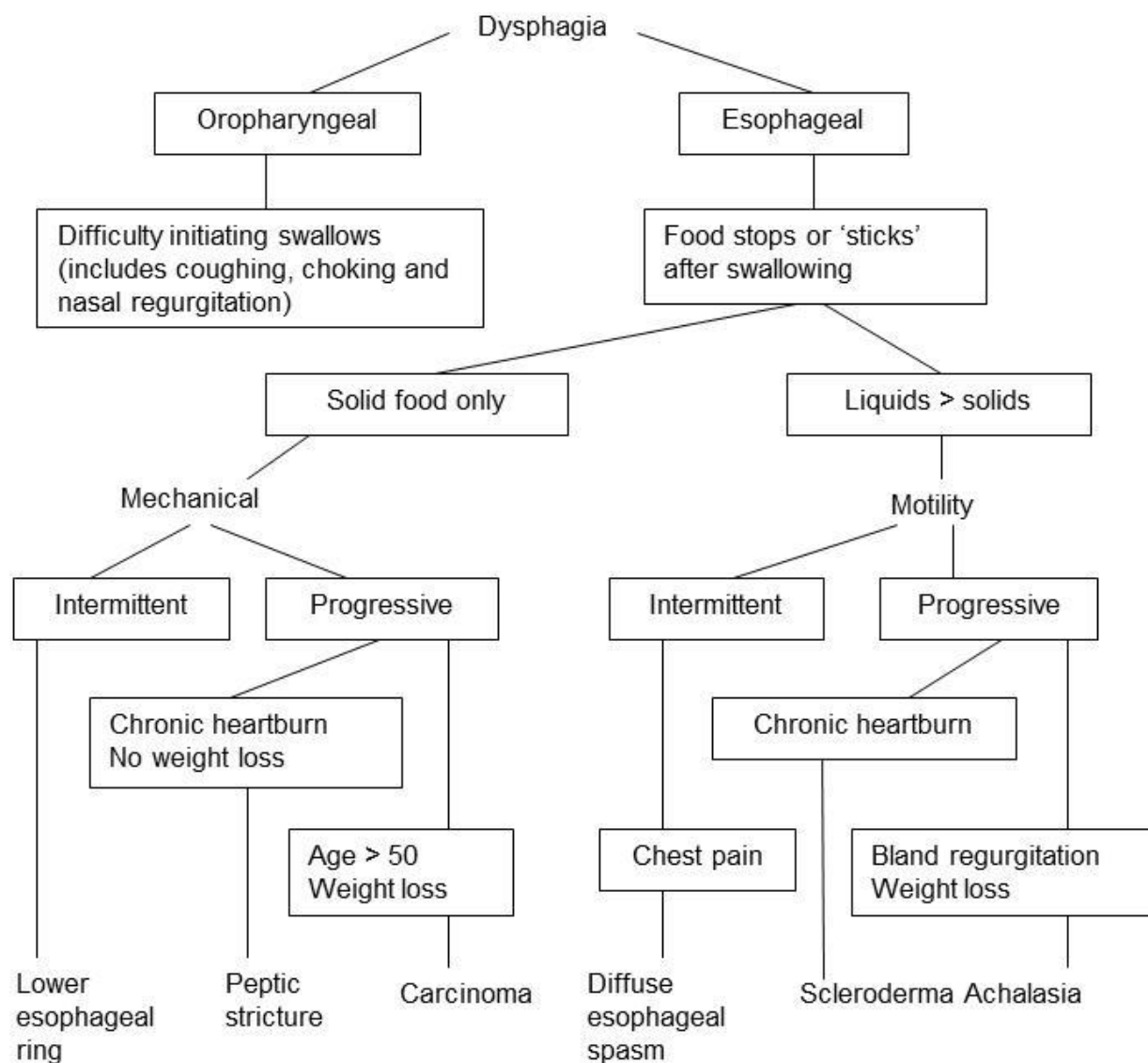
Dysphagia

- Oropharyngeal diseases
 - Symptoms
 - Choke, cough, nasal regurg' drool, wheeze, CNS signs
 - Food sticks immediately after swallowing
 - Felt in the neck
 - Tests
 - VFSS - ENT consult
 - FEES fiberoptic endoscopic evaluation of swallowing
 - Modified barium swallow bolus challenge esophagram (bolus transfer assessment)
 - "buried BE" (submucosal squamous metaplasia) baseline (no Px) 25%
After RFA 6%

What is "the best"? The "best" four clinical signs for bowel obstruction are: visible peristalsis, distended abdomen, hyperactive and/or abnormal bowel sounds.



Useful background: Approach to the person with dysphagia



Adapted from: AW Cockeram. *Can J gastroenterol* 1998;12(6):409-414.



5. Take a directed history for dysphagia.

➤ Algorithm for symptomatic assessment

- Solids
 - Suggests mechanical (e.g. stricture, ring, malignancy)
- Liquids
 - Suggests motility problem (e.g. achalasia, diffuse esophageal spasm [DES], scleroderma)
- Progressive
 - Stricture
- Intermittent
 - DES
 - Lower esophageal ring
- Painful
 - Esophagitis
- Painless
 - NERD (normal endoscopy reflux disease)
- Nasal/ ENT symptoms
 - Suggests oropharyngeal or CNS cause

➤ Causes

- CNS
 - E.g. CVA, Parkinsonisms
- Lung
 - Compression
- Stomach
 - Tumor
 - Gastric retention
- Colon
 - Constipation (rare)
- Drugs
- Pregnancy
- Diet
- MSK
 - Scleroderma
 - Skeletal muscle disease

➤ Complications

- ENT
- Hemorrhage
- Obstruction
- Perforation
- Malnutrition
- Quality of life
- Drug treatment
- Lifestyle modification



SO YOU WANT TO BE A GASTROENTEROLOGIST!

Q: In the person with heartburn but a normal EGD (esophagogastroduodenoscopy), what are the performance characteristics of the Bernstein test?

A: ○ Indication

- Assess esophageal acid sensitivity in persons with NCCP or NERD.
- Sensitivity 0-59%*
- Specificity 59-94%

*Lack of association between symptoms induced by acid perfusion of esophagus compared with symptoms following spontaneous reflux in same individual, suggesting that heartburn following acid perfusion and spontaneous heartburn are induced by different stimuli.

Abdominal pain and masses

6. Take a directed history to determine the causes of RUQ pain.

- Heart
 - CHD
 - Pericarditis
- Lung
 - Pleurisy
 - Pneumonia
 - PE
- Aorta
 - Dissection /rupture
- Stomach/ duodenum
 - GU
 - DU
- Liver
 - Hepatitis
- Gallbladder
 - Cholecystitis
 - Choledocholithiasis
- Pancreas
 - Pancreatits
- Kidney
 - Colic

Abbreviations: CAD, coronary artery disease; DU, duodenal ulcer; GU, gastric ulcer; PE, pulmonary embolism



SO YOU WANT TO BE A GASTROENTEROLOGIST!

Q1: A sexually active woman of reproductive potential presents with acute abdominal pain three weeks after a missed menses. What are the most likely diagnoses?

- A1:
- Ectopic pregnancy
 - PID (pelvic inflammatory disease)
 - Ovarian cyst or torsion

Q2: What are the names of the two signs of abdominal wall discolouration which suggest the presence of an ectopic pregnancy and ruptured AAA?

- A2:
- Cullen's Sign: Purple-blue discoloration around umbilicus peritoneal hemorrhage; caused by acute pancreatitis, ectopic pregnancy
 - Grey-Turners Sign: Flank discolouration retroperitoneal hemorrhage; caused by acute pancreatitis, ruptured abdominal aortic aneurysm (AAA), strangulated bowel

Adapted from: Filate W., et al. *The Medical Society, Faculty of Medicine, University of Toronto*, 2005, page 37.

Appendicitis and peritonitis

Useful background: Terminology

- McBurney's point tenderness
 - Tenderness 1/3 along line from ASIS to umbilicus
- Rovsing's sign
 - LLQ palpation causes RLQ pain (indirect tenderness)
- Rectal tenderness
 - In patients with appendicitis whose inflammation is confined to the pelvis, rectal examination may reveal tenderness, especially on the right side, and some patients with perforation may have a rectal mass (i.e. pelvic abscess).
- Psoas sign
 - The patient lies down on their left side and the clinician hyperextends the right hip. Painful hip extension is a positive psoas sign, suggesting acute appendicitis.
- Obturator sign
 - Flex the patient's right hip and knee and then internally rotate the right hip; eliciting pain suggests acute appendicitis



7. Take a directed history and perform a focused physical examination for appendicitis, and stratify the risk and need for surgery.

- The symptoms with the highest PLR are right lower quadrant (RLQ) pain (PLR, 7.3 to 8.5), migration of pain (3.2), and pain before vomiting (2.8).
- The signs with the highest PLR are severe RLQ tenderness (7.3 to 8.5), rigidity (3.8), tenderness at McBurney's point (3.4), rebound abdominal tenderness (1.1 to 6.3), rectal tenderness (0.8 to 5.3), Rovsing's sign (2.5), and psoas sign (PLR, 2.0 to 2.4).

Abbreviation: likelihood ratio (LR) if finding is present= positive LR (PLR)

Adapted from: McGee S. R. *Saunders/Elsevier* 2007, Tables 48, page 577.

Useful background: Alvarado clinical decision rule (mnemonic "Mantrels") provides guidance to operate for suspected acute appendicitis

- History
 - MAN – migration of pain (1), anorexia-acetone (1), nausea/vomiting (1)
 - TRE – tenderness in RLQ (2), rebound (1), elevated temperature (fever) (1)
 - LS – leucocytosis (2), shift-to-the-left (1)

	PLR	NLR
Alvarado score ≥ 7	3.1	0.26

Abbreviation: NLR, negative likelihood ratio; PLR, positive likelihood ratio.

Source: Simel David L, *Et al.* The Rational Clinical Examination: Evidence- based clinical diagnosis. *JAMA* 2009, Table 5-5, page 62.

Note that many historical points, symptoms and signs on physical examination have a PLR < 2 (and are not included here)

What is "the best"? The "best" clinical tests for appendicitis in a person with RLQ pain are: McBurney's point tenderness, Rovsing's sign, and Psoas sign; the Alvarado score ≥ 7 (is also useful).

Useful background: Performance characteristics of physical findings that suggest the presence of peritonitis

- Finding:
 - Guarding
 - Rigidity
 - Rebound tenderness
 - Percussion tenderness



- Abnormal bowel sounds
 - Positive abdominal wall tenderness test
 - Positive cough test
 - Rectal tenderness
- None of the physical findings which have been taught to be clinically useful to diagnose peritonitis have a positive likelihood ratio (PLR) greater than 3.9. The signs with a PLR > 2 include abdominal rigidity (3.9), guarding (2.6), percussion tenderness (2.4), and rebound tenderness (2.1).

Abbreviation: likelihood ratio (LR) if finding is present = positive LR (PLR)

Adapted from: McGee S. R. *Saunders/Elsevier* 2007, Box 48.1, page 576.

8. Perform a focused physical examination to determine the causes of abdominal masses.

- Upper abdomen
 - Retroperitoneal lymphadenopathy (eg lymphoma, teratoma)
 - Left lobe of the liver
 - Abdominal aortic aneurysm (expansile)
 - Carcinoma of the stomach
 - Pancreatic pseudocyst or tumour
 - Gastric dilatation (e.g. pyloric stenosis, acute dilatation in diabetic ketoacidosis or after surgery)
 - Carcinoma of the transverse colon
 - Omental mass (eg metastatic tumour)
 - Small bowel obstruction
- Right upper quadrant (palpable gallbladder)
 - With jaundice
 - Carcinoma of the head of pancreas
 - Carcinoma of the ampulla of Vater*
 - In-situ gallstone formation in the common bile duct
 - Mucocele of the gallbladder due to a stone in Hartmann's pouch and a stone in the common bile duct (very rare)
 - Without jaundice
 - Mucocele or empyema of the gallbladder
 - Carcinoma of the gallbladder (stone hard, irregular swelling)
 - Acute cholecystitis
- Right lower quadrant
 - Appendiceal abscess or mucocele of the appendix
 - Carcinoma of the cecum or cecal distension due to distal obstruction
 - Crohn's disease (usually when complicated by an abscess)
 - Ovarian tumour or cyst



- Carcinoid tumour
 - Amebiasis
 - Psoas abscess
 - Ileocecal tuberculosis
 - Hernia
 - Transplanted kidney
- Left lower quadrant
- Feces
 - Carcinoma of sigmoid or descending colon
 - Diverticular abscess
 - Ovarian tumour or cyst
 - Psoas abscess
 - Hernia
 - Transplanted kidney
- Pelvis
- Bladder
 - Ovarian tumour or cyst
 - Uterus (e.g. pregnancy, tumour, fibroids)
 - Small bowel obstruction
- Groin
- Above the inguinal ligament
 - Inguinal hernia
 - Undescended testis
 - Cyst of the canal of Nuck
 - Encysted hydrocele or lipoma of the cord
 - Iliac node
 - Large femoral hernia (rare)
 - Below the inguinal ligament
 - Femoral hernia
 - Lymph node
 - Saphena varix (sensation of a 'jet of water' on palpation, disappears when supine)
 - Femoral aneurysm (pulsatile)
 - Psoas abscess (associated with fever, flank pain and flexion deformity)

Adapted from: Talley N. J., et al. *MacLennan & Petty Pty Limited* 2003, Table 5.14 to Table 5.19, pages 174, 175, 179 184 and 199.



SO YOU WANT TO BE A GASTROENTEROLOGIST!

Q: What are the uses of examining the “belly button”?

- A:
- Direction of flow of blood in veins of abdominal wall-flow below umbilicus is down into saphenous veins, above umbilicus is upwards into veins of thoracic wall. In portal hypertension, dilated veins show normal direction of flow, but in IVC obstruction, flow in veins below umbilicus is reversed, i.e. Flows upward.
 - Umbilicus is common site of infiltration by cancer metastases (Sister Mary Joseph’s nodule)
 - Protuberance from ascites (an “out-ie”)

Useful background: Causes of anterior abdominal wall masses

- Umbilicus
 - Malignant deposits – e.g. melanoma, carcinoma
- Rectus sheath
 - Umbilical, paraumbilical hernia, or epigastric hernia
 - Incisional hernia
 - Rectus sheath diaphragm
 - Rectus sheath hematoma
- Skin
 - Lipoma
 - Sebaceous cyst
 - Dermal fibroma
 - Epigastric hernia

Source: Talley N. J., et al. *MacLennan & Petty Pty Limited* 2003,, Table 5.15, page 193.

Useful background: Causes of a palpable mass in the rectum

- In lumen
 - Feces
 - Foreign body
- In rectal wall
 - Hypertrophied anal papilla
 - Rectal or polyp carcinoma or rectal or sigmoid colon carcinoma prolapsed into the pouch of Douglas
 - Diverticular phlegmon (recent or old)



- Outside rectal wall
 - Metastatic deposits in the pelvis
 - Uterine or ovarian malignancy
 - Prostatic or cervical malignancy (direct extension)
 - Endometriosis
 - Pelvic abscess or sarcoma
 - Amebic granuloma

Adapted from: Talley N. J., et al. *MacLennan & Petty Pty Limited* 2003, Table 5.18, page 189.

What is “the best”? The “best” four clinical tests for the presence of peritonitis are: rigidity, guarding, rebound and percussion tenderness.

Abdominal aorta

9. Take a directed history and perform a focused physical examination for the cause of abdominal bruit.

- Kidney
 - Renovascular disease
 - Unilateral renal hypertrophy
 - Bruit is rare in primary systemic hypertension
 - Normal variant (10% of normal persons)
- Liver
 - Hepatitis
 - Cirrhosis
 - Hepatoma (HCC)
 - AV fistula
- Pancreas
 - Neoplasia
- Spleen
 - AV fistula
 - Tortuous arteries
- Vessels
 - AAA (abdominal aortic aneurysm); aka “triple ‘A’”
 - Celiac artery compression, stenosis
 - Chronic intestinal ischemia



- *An AB is rare in a person with essential hypertension. *In persons with renovascular hypertension, an AB is found in 77% with fibromascular disease, and 35% of those with atherosclerotic disease.

Adapted from: Filate W., et al. *The Medical Society, Faculty of Medicine, University of Toronto*, 2005, page 33.

Useful background: Performance characteristics of auscultation and palpation of abdomen for AAA*

- The value of the positive likelihood ratio (PLR) for AAA depends on the size of the lesion (see below), but overall the physical signs which have the highest PLR values include detecting renovascular hypertension (PLR, 38.9), palpating an AAA (8.0), and auscultating an abdominal bruit (5.6).

*sensitivity depends on size of AAA: > 3 cm, ~29%; > 4 cm, ~50%; >5 cm, 75%

Abbreviations: AAA, abdominal aortic aneurysm ; PLR, positive likelihood ratio

Adapted from: McGee S. R. *Saunders/Elsevier* 2007, Box 49-1, page 589; and Box 47-3, page 561.

SO YOU WANT TO BE A GASTROENTEROLOGIST!

Q: What is the clinical use if auscultating an hepatic bruit or friction rub?

- A:
- Hepatic arterial bruit
 - Alcoholic hepatitis
 - HCC (hepatocellular cancer)
 - Metastases
 - Venous hum
 - Portal hypertension(PHT, usually from cirrhosis, aka Cruveilhier-Bamgarten syndrome)
 - Venous hum plus hepatic arterial bruit (PHT+ alcoholic hepatitis, or PHT + HCC)
 - Rub and bruit + venous hum
 - Cirrhosis and HCC
 - Friction rub
 - Infection in and around liver (e.g. gonococcal perihepatitis [Fitz-Hugh-Curtis syndrome])
 - Rub + bruit
 - HCC



Bowel obstruction

10. Take a directed history for bowel obstruction.

- Abdominal pain – where, when, what, why, how
- Associated symptoms
 - Appetite
 - Weight change
 - Nausea, vomiting (bilious, feculent, bloods)
 - Jaundice, dark urine
 - Recent weight
 - Pale stools
 - Bloating
 - Borborigmi
- Changes in bowel movements
 - Constipation/ obstipation/ no flatus
 - Diarrhea
 - Tenesmus
 - Calibre of stool
 - Melena
 - Hemochezia
 - Flatus
- Medical history
 - Previous surgeries
 - Abdominal hernia
 - Gallstones
 - Colorectal cancer
 - Drugs (opiates, anticholinergics, antipsychotics)
 - Diagnoses – inflammatory bowel disease, colorectal cancer, diverticulitis, gallstones, abdominal hernia, vascular ischemia, endometriosis
- Causes/Associations
 - Small bowel
 - Adhesions
 - Hernias
 - Strictures from IBD
 - Gallstone ileus
 - Mesenteric artery syndrome
 - Small bowel tumours
 - Metastatic cancer
 - Cystic fibrosis
 - Volvulus
 - Crohn's disease



- Large bowel
 - Cancer
 - Volvulus
 - Diverticulitis
 - Ileus
 - Narcotics ileus
 - Mesenteric ischemia
 - IIBD with stricture
 - Ogilvie's syndrome
 - Adhesions
 - Intussusception
 - Endometriosis

Adapted from: Jugovic P.J., Et al. Saunders/ Elsevier 2004, pages 58 and 59.

SO YOU WANT TO BE A GASTROENTEROLOGIST!

Q: Which is the better test to assess the size of the liver in a patient with suspected cirrhosis, abdominal ultrasound with doppler, or an ultrasound.

A: ○ Meta-analysis supports transient elastography to diagnose cirrhosis with a high diagnostic accuracy independent from the underlying liver disease (Friedrich-Rust, et al. *GE* 2008;134:960-974), and is not used to assess liver size.

Useful background: Performance characteristics of physical examination for bowel obstruction.

- While there may be numerous abnormal physical findings which have been traditionally thought to be useful to diagnose a bowel obstruction, the four best tests in terms of the value of the value of their positive likelihood ratio (PLR) are the findings on inspection of visible peristalsis (PLR, 18.8) and distended abdomen (9.6) and on auscultation hearing hyperactive (5.0) or abnormal bowel sounds (3.2)

Abbreviation: Likelihood ratio (LR) if finding present= positive PLR

Adapted from: McGee S. R. *Saunders/Elsevier* 2007, Box 48.4, page 579.



Diarrhea

11. Take a directed history for diarrhea.

➤ Stools

- Timing (duration, onset, and course)
- Frequency
- Aggravating/alleviating factors (milk, coffee, drugs)
- Blood
- Fat droplets
- Food particles
- Floating stools
- Foul odour
- Difficult to flush
- Excess flatus

➤ Associated symptoms

- Fever
- Weight loss
- Change in appetite and diet
- Vomiting, nausea
- Urination changes
- Tenesmus
- Extraintestinal symptoms of inflammatory bowel disease
- Arthritis
 - Ulcerative colitis
 - Crohn disease
 - Whipple disease
 - *Yersinia* infection
- Lymphadenopathy
 - Lymphoma
 - Whipple disease
- Neuropathy
 - Diabetic diarrhea
 - Amyloidosis
- Postural hypotension
 - Diabetic diarrhea
 - Addison disease
 - Idiopathic orthostatic hypotension
 - Autonomic dysfunction
- Flushing
 - Malignant carcinoid syndrome



- Hyperpigmentation
 - Whipple disease
 - Celiac disease
 - Addison disease
 - Pancreatic cholera
 - Eosinophilic gastroenteritis
- Dyspepsia
 - Peptic ulcer disease
 - Zollinger-Ellison syndrome
- Risk factors
 - Travel history
 - Outbreak (friends/family)
 - Seafood (food poisoning)
 - Extraintestinal symptoms (eye, skin, and joint)
 - Diet changes
 - Laxative use
 - Steatorrhea
 - Celiac disease
 - Immunosuppression, including HIV/AIDs
 - Medications and allergies
 - Anal intercourse
 - Family history (inflammatory bowel disease (IBD), bowel cancer, celiac disease, lactose intolerance)
 - Personal history of IBD, celiac disease, pancreatic or hepatobiliary disease, bowel surgery
 - Medications

Adapted from: Jugovic PJ., et al. *Saunders/ Elsevier* 2004, pages 25 to 27.

Inflammatory bowel disease

12. Take a directed history to determine the cause of infertility in men with inflammatory bowel disease.

- Medications
- Active inflammatory bowel disease
- Poor nutritional status
- Tobacco use
- Alcohol use
- Postsurgical states

Source: Feagins LA, et al. *American J Gastroenterol* 2009; 104(3):773.



Alcohol abuse

Useful background: The continuum of alcohol abuse

- At risk drinking- drinking more than the recommended levels of alcohol (no more than 2 standard drinks per day to a maximum of 9 standard drinks a week for females and 14 standard drinks for males) but no apparent physical or social problems related to alcohol
- Problem drinking- same as at risk drinking but with one or more alcohol related social or physical problems and no clinical features of dependency
- Alcohol dependency- a maladaptive pattern of alcohol use leading to clinically significant impairment or distress with 3 or more of the following criteria in the past 12 months:
 - Tolerance
 - Use of larger amounts of alcohol for longer periods of time
 - Presence of withdrawal
 - Symptoms, excessive amount of time spent in obtaining alcohol
 - Important activities missed or reduced due to alcohol use
 - Persistent desire but unsuccessful efforts to cut down alcohol

Adapted from: Jugovic P.J., et al. *Saunders/ Elsevier* 2004, pages 103 and 106.

13. Take a directed history of alcohol abuse.

- Alcohol
 - Drinking behavior – where, when, what, who, why
 - CAGE questionnaire
 - Have you ever felt the need to **C**ut down on your drinking?
 - Have you ever felt **A**nnoyed by criticism of your drinking?
 - Have you ever had **G**uilty feelings about drinking?
 - Have you ever had an **E**ye opener (a drink first thing in the morning?)
 - Medical complications and associations
 - Fatigue
 - Seizures
 - Blackouts
 - Sleep disturbances
- Alcohol withdrawal
 - Shakes, seizures, hallucinations, DTs
- Liver – cirrhosis, hepatitis
- Cardiac – hypertension, cardiomyopathy
- GI- esophagitis, gastritis, hepatitis, fatty liver, liver cirrhosis, pancreatitis, peptic ulcers, esophageal or rectal varices, oral and esophageal cancers, malabsorption, UGIB



- Cardiac- alcoholic cardiomyopathy, arrhythmias
- Peptic ulcer disease, variceal or non-variceal upper GI bleeding
- Neurologic- Wernicke's syndrome, Korsakoff's syndrome, cerebellar degeneration, peripheral neuropathy, myopathy
- Hematologic- iron or folate anemia, thrombocytopenia, coagulopathies
- Endocrine- impotence, hyperlipidemia
- Immunologic- immune system impairment
- Electrolytes- symptoms of low serum calcium, magnesium, or phosphate; ketosis
- **Mental**
 - Depression
 - Attempted suicide
 - Family Hx of alcoholism
 - Other substance abuse
 - Stressors
 - Family
 - Spouse
 - Friends
 - Stress
 - Money
 - Social consequences
 - Occupation
 - Family
 - Leisure
 - Financial problems
 - Legal problems
 - Accidents and fights
 - Driving intoxicated

Adapted from: Jugovic P.J., Et al. *Saunders/ Elsevier* 2004, pages 103 and 105.



14. Perform a directed physical examination for alcohol withdrawal (SSH-DTs: shake, seizure, hallucinates, DTs).

Time after stopping alcohol	Name of withdrawal syndrome	Clinical picture
- 6-8 hours	Shakes	- Tremor - Nausea/vomiting - Insomnia, agitation - Tachycardia (autonomic hyperactivity), fever
- 8 hours to 2 days	Seizures	- Multiple tonic-clonic seizures
- 1-2 days	Hallucinations	- Visual hallucinations
- 3-5 days	DTs	- Fluctuating LOC, coma, agitation/anxiety, death

- Autonomic hyperactivity (tachycardia, pyrexia, sweating, tremor, irritability)
- Depressed mood
- Nausea, vomiting
- Insomnia
- Anxiety
- Seizures
- Delirium tremens
- Hallucinations (usually visual, but auditory and tactile are possible).

SO YOU WANT TO BE A HEPATOLOGIST!

Q: Patients with NAFLD may have elevated serum levels of ALT and AST. What level of these liver enzymes should signal the need to refer the patient for a liver transplantation (L-Tx)?

A: No level! The decision to refer the NAFLD patient for L-Tx is based on there risk factors for progressing to NASH, and not on the level of their ALT or AST. In fact, ~ 60% of persons with NASH-cirrhosis have normal transaminases.



Benefit	AEs
○ ↓ adipokinins	↑ BMI
○ ↑ adiponectin (a protector of the liver)	↑ CV event
○ ↑ β oxidation	↑ osteoporosis
○ ↓ TG, ↓ VLDL	↑ bladder cancer
○ Converts “bad” into “good” fat	
○ ↓ insulin resistance	

➤ Caution: Autoimmune markers may be falsely positive in NAFLD

Hepatosplenomegaly

Useful background: Causes of hepatomegaly

- Raised venous pressure
 - Congestive cardiac failure
 - Constrictive pericarditis
 - Tricuspid stenosis
 - Hepatic vein thrombosis
- Degenerative conditions
 - Fatty infiltration and early cirrhosis
- Storage disorders
 - Amyloidosis
 - Gaucher's
 - Niemann-Pick's
 - Histiocytosis X
 - Glycogen storage disease
 - Haemochromatosis
 - Hurler's (Gargoylism)
- Infections
 - Viral
 - Infective and serum hepatitis
 - Infectious mononucleosis
 - Bacterial
 - Hepatic abscess
 - TB
 - Syphilis
 - Weil's disease
 - Protozoal
 - Amoebic abscess
 - Malaria
 - Toxoplasmosis
 - Kala-azar
 - Fungal
 - Histoplasmosis
 - Parasitic
 - Hydatid cyst

Source: Burton J.L. *Churchill Livingstone* 1971, pages 43 and 44.



15. Perform a focused physical examination hepatosplenomegaly.

➤ Liver

- Palpable liver in patients with chronic liver disease
- Palpable liver in epigastrium in patients with chronic liver disease
- Liver edge firm to palpation in patients with chronic liver disease
- Palpable liver in patients with jaundice, detecting hepatocellular disease
- Palpable liver in patients with lymphadenopathy, detecting serious disease
- Liver tenderness in patients with jaundice, detecting hepatocellular disease nonobstructive jaundice

➤ Spleen

- Palpable spleen in returning travellers with fever, detecting malaria
- Palpable spleen in patients with non-obstructive jaundice, detecting hepatocellular disease
- Palpable spleen in patients with chronic liver disease, detecting cirrhosis

- Because of the wide values of the reported sensitivity and specificity for detecting hepatosplenomegaly, none of the values of the positive likelihood ratios (PLR) are much greater than 2: palpation of a firm liver edge in a person with chronic liver disease (PLR, 2.7), palpable liver in the epigastric area in a person with chronic liver disease (2.6), or any palpable liver again in a person with chronic liver disease (2.0).
 - A palpable liver is not necessarily enlarged, but increases the likelihood of hepatomegaly (LR if present, 2.5 [95% CI, 2.2-2.8]). A non palpable liver edge does not rule out hepatomegaly, but reduces its likelihood (LR is absent, 0.45 [95% CI, 0.38-0.52]).
- The likelihood of a high PLR for splenomegaly depends on the clinical setting for example, in a returning traveler and fever where there is splenomegaly from malaria (PLR,6.6), with much lower values to detect hepatocellular disease in a person with non-obstructive jaundice (2.9), or detecting cirrhosis in the person with chronic liver disease (2.3).

Adapted from: McGee S. R. *Saunders/Elsevier* 2007, Box 47.2, pages 556 to 559.



Useful background:

- Causes of a hard knobbly liver
 - Carcinoma metastases
 - Post-necrotic cirrhosis
 - Congenital cystic liver
 - Hydatid cysts
 - Hepar lobatum (syphilis)
- Causes of hepatosplenomegaly
 - Infective e.g. infectious mononucleosis
 - Myeloproliferative e.g. myelofibrosis, chronic myeloid leukaemia
 - Some causes of portal hypertension e.g. Budd-Chiari syndrome
 - Reticuloses
 - Storage diseases e.g. Gaucher's disease, amyloidosis
 - Anemia e.g. PA, sickle cell anemia in children

Source: Burton J.L. *Churchill Livingstone* 1971, page 44.

What is “the best”? In the patient with chronic liver disease, the best tests for determining if there is hepatomegaly are palpating a firm liver edge, palpating the liver in the epigastrium, or just palpating an enlarged liver.

SO YOU WANT TO BE A GASTROENTEROLOGIST!

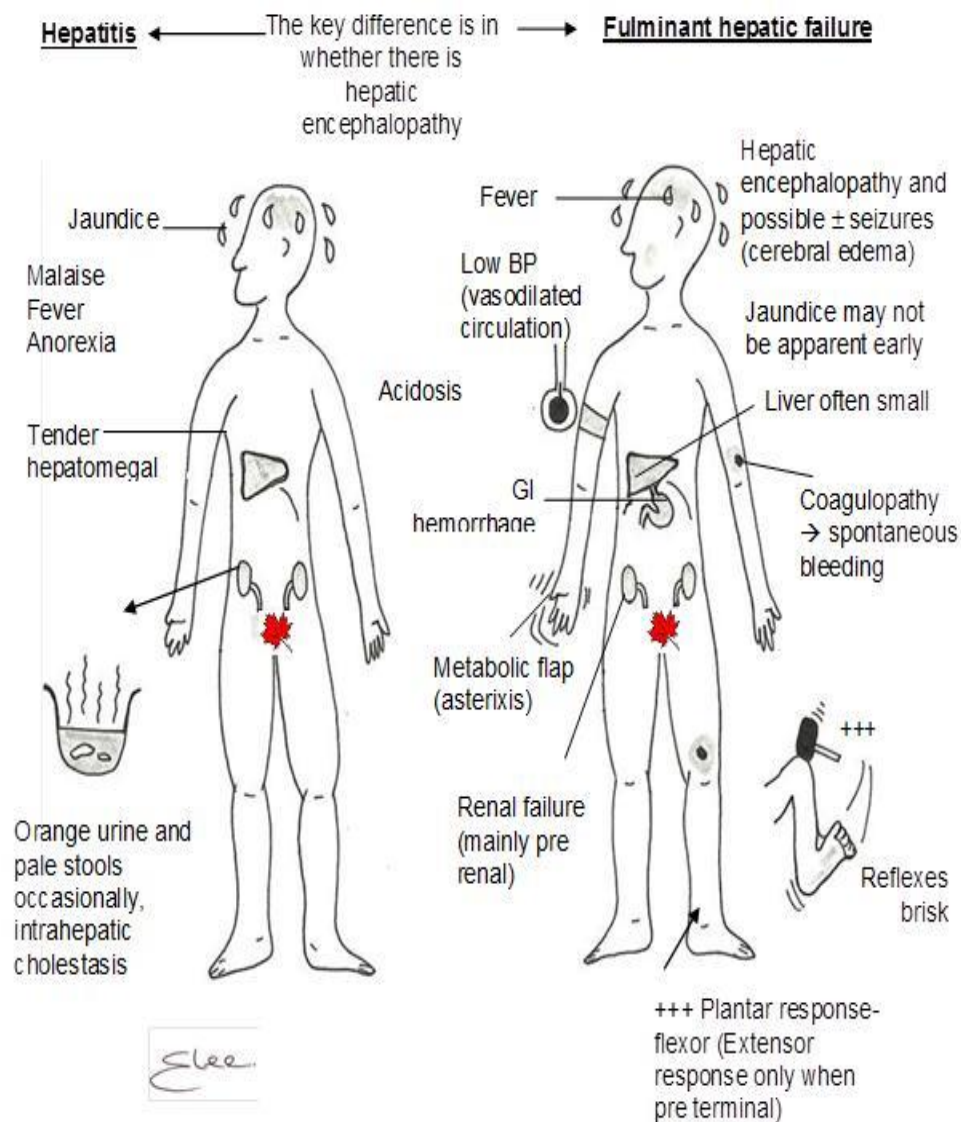
Q: How can you attempt to differentiate between involuntary or malingering pain?

A: Try to distract patient by pretending to auscultate but pushing in the stethoscope, and watch the patient's face for signs of discomfort



Acute and chronic liver disease

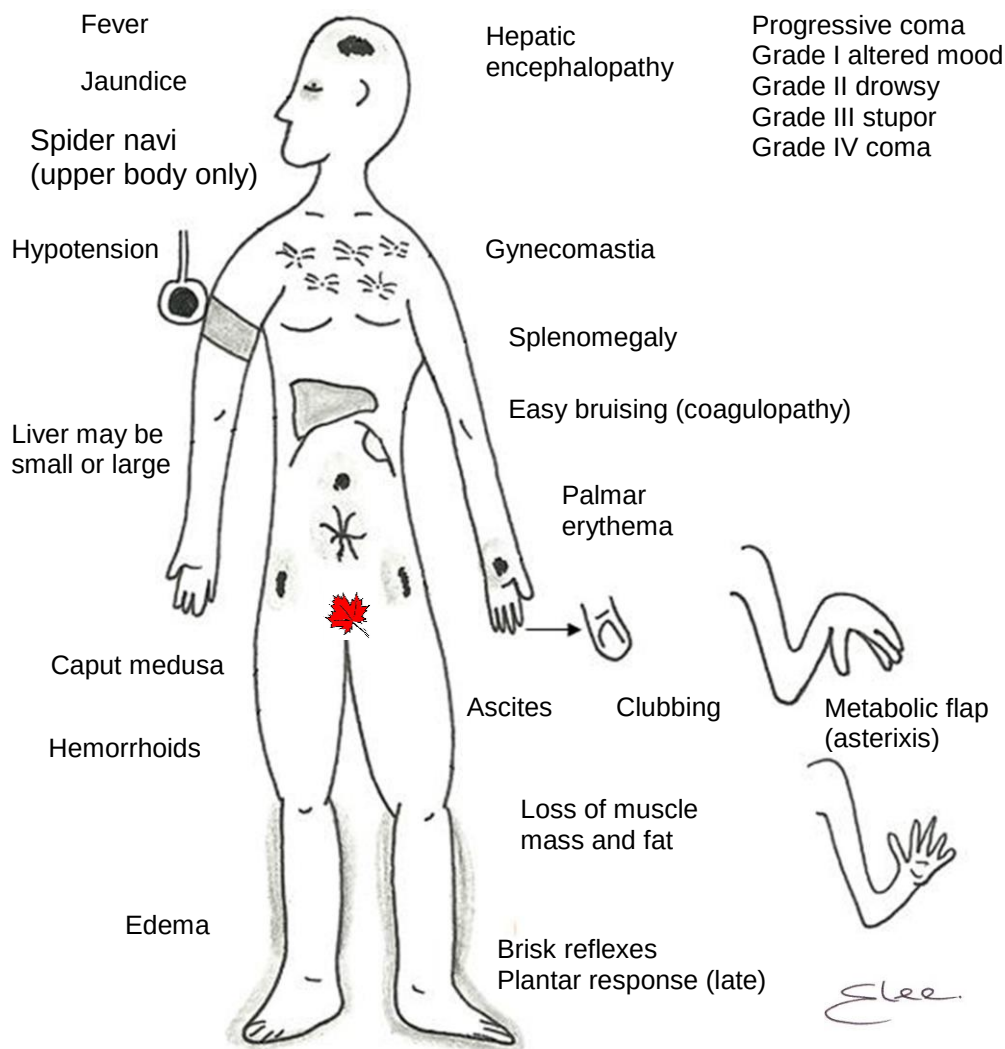
16. Perform a physical examination for acute liver disease (acute hepatitis and fulminant liver failure).



Adapted from: Davey P. *Wiley-Blackwell* 2006, page 234.



17. Perform a focused physical examination for signs of chronic liver disease (portal hypertension).



Causes of acute deterioration in known chronic liver disease

- Drugs (including alcohol)
- Electrolyte disturbance
- Sepsis (especially spontaneous bacterial peritonitis)
- GI bleed
- Hepatoma

*Note that the signs of hepatic encephalopathy (HE), hypotension, fever, acidosis and coagulopathy may occur in acute liver failure. The liver may normal size or small early on. Jaundice may be present. The patient may also experience seizures, which is not a feature of HE.

Adapted from: Davey P. *Wiley-Blackwell* 2006, page 234.



Useful background: Findings cirrhosis in patients with chronic liver disease

- There are numerous findings on physical examination of a patient with chronic liver disease which give a positive likelihood ratio in the 2's or 3's (spider angiomas, 3.7; peripheral edema, 3.0; liver edge firm to palpation, 2.7, or just palpable in the epigastrium, 2.6; palmar erythema, 2.6; splenomegaly (2.3 or hepatomegaly, 2.0), but it is the presence of encephalopathy, ascites, and dilated abdominal wall veins (PLR of 8.8, 6.6 and 5.4, respectively), which have the best performance characteristics.

Abbreviation: likelihood ratio (LR) if finding present = positive PLR

Adapted from: McGee S. R. *Saunders/Elsevier* 2007, page 80.

- Ascites

18. Take a directed history and perform a focused physical examination for ascites.

Item	PLR	NLR
➤ History		
○ Increased girth	4.2	0.2
○ Recent weight gain	3.2	0.4
○ Hepatitis	3.2	0.8
○ Ankle swelling	2.8	0.1
○ Heart failure	2.0	0.7
➤ Physical		
○ Bulging flanks	2.0	0.2
○ Flank dullness	2.0	0.3
○ Shifting dullness	2.7	0.3
○ Fluid wave	5.0-6.0	0.4

Note that a history of alcoholism or carcinoma, and the * Puddle sign and auscultatory percussion have a PLR < 2, and are not included here.

Abbreviations: CI, confidence interval; PLR, positive likelihood ratio; NLR, negative likelihood ratio

Adapted from: Simel D. L., et al. *McGraw-Hill Medical* 2009, Table 6-2, page 68 and Table 6-5, page 69.



Useful background: Factors which increase the pretest probability of finding ascites (existing disease)

- Heart
 - CHF
 - Pericarditis
- Liver – cirrhosis
- Kidney – nephrotic syndrome
- GI
 - Protein losing enteropathy
 - Malabsorption
 - malnutrition
- Cause
 - Systemic infection
 - Blunt abdominal trauma

What is “the best” test? Only the finding of a fluid wave and shifting dullness have a LR>2 for the detection of ascites.

Useful background: Findings predicting hepatocellular jaundice in patients with jaundice

- The peripheral findings on physical examination of dilated abdominal wall veins (17.5), palmar erythema (9.8) and spider angiomas (4.7) have the highest values for positive likelihood ratios (PLR) for predicting a hepatocellular cause of jaundice. The PLRs for the presence of ascites and palpable spleen are much lower, 4.4 and 2.9, respectively. All other findings have PLR less than 2.0.

Abbreviation: LR, likelihood ratio; if finding present = positive LR: PLR

Adapted from: McGee S. R. *Saunders/Elsevier* 2007, page 79.



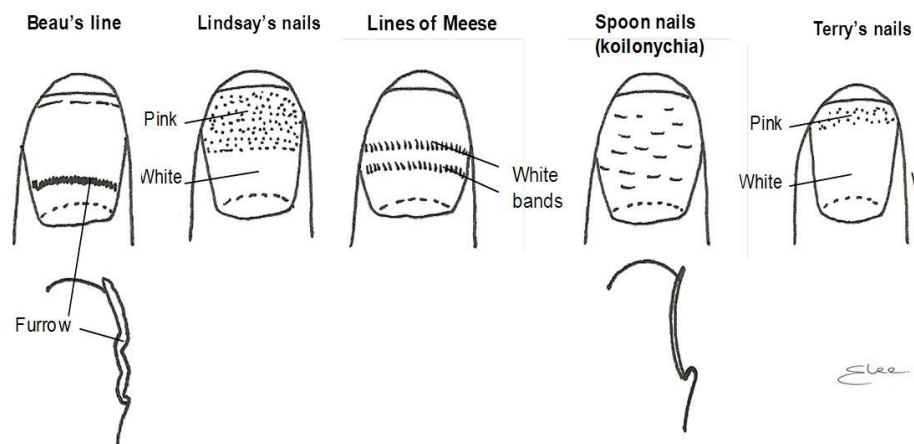
Fingernails

Useful background: Conditions altering the normal appearance of the fingernails

- Azure half moons in nail beds: the nails of Wilson's disease (hepatolenticular degeneration). The lunulae are not white but light blue.
- Beau's lines: transverse grooves on the fingernails of patients recovering from a serious illness such as myocardial infarction.
- Brittle nails: seen in various dysmetabolic states such as hyperthyroidism, malnutrition, and iron or calcium deficiency. They are characterized by irregular, frayed, and torn nail borders.
- Leuconychia-white nails, beginning at the lunula-may be normal; seen in cirrhosis, leprosy, arsenic poisoning, vasomotor disturbance of fingers
- Mees lines (also called Reynolds or Aldrich lines): transverse white lines distal to the cuticle. They are seen in arsenical or thallium poisoning, cancer chemotherapy, Hodgkin's lymphoma, and other systemic disorders, such as severe cardiac or renal disease.
- Muehrcke's lines: two arcuate white lines parallel to the lunula and separated by normal nail. Because they are located in the nail bed (not the nailplate). Muehrcke's lines do not progress with the growth of the nail. They are seen in patients with hypoalbuminemia (<2 gm/100 ml) and disappear with its resolution.
- Nail pitting: an early (but non-specific) sign of psoriasis.
- Red half moons in nail beds (variety of Terry's nails): characterized by a lunula that is not white but red. They also are called the nails of cardiac failure.
- Splinter hemorrhages: linear red hemorrhages, extending from the free margin of the nail bed toward the proximal margin; typical finding of subacute bacterial endocarditis, or trichinosis, trauma.
- Terry's nails: characterized by whitening of the proximal 80% of the nail, leaving a small rim of peripheral reddening. They are seen in older people or patients with heart failure, cirrhosis, or non-insulin dependent diabetes.
- Yellow nail syndrome: characterized by a yellowish colour of the plates due to abnormal lymphatic circulation.



Abnormality	Characteristics	Common associations
➤ Onycholysis	○ Separation of nail from nail bed	○ Fungal infection ○ Thyrotoxicosis ○ Psoriasis ○ Drugs
➤ Lindsay's nails	○ ½ and ½ nails, pink white proximally and brown distally	○ Chronic liver disease ○ Azotemia
➤ Terry's nails	○ White nail beds with 1-2 mm of distal border of the nail	○ Cirrhosis ○ Hypoalbuminemia



Adapted from; Mangione S. Hanley & Belfus 2000, page 412.; and Filate W., et al. *The Medical Society, Faculty of Medicine, University of Toronto*, 2005, Table 5, page 15.



Pruritus

19. Perform a focused physical examination to determine the cause of pruritus.

- Various skin diseases
 - Infection
 - Eczema
 - Urticaria
 - Lichen simples
 - Dermatitis herpetiformis
- Systemic
 - Hepatic
 - Obstructive jaundice
 - Recurrent pruritus of pregnancy
 - Blood disorders
 - Reticuloses
 - Leukaemia
 - Polycythaemia
 - Fe-deficiency
 - Mastocytosis
 - Endocrine
 - Diabetes mellitus
 - Diabetes insipidus
 - Myxoedema
 - Hyperthyroidism
 - Gout
 - Carcinoid
 - Neurological
 - Tabes
 - GPI
 - Thalamic tumour
 - Carcinoma (especially lung, stomach, colon, breast, prostate)
 - Chronic renal failure (probably due to secondary hyperparathyroidism)
 - Psychogenic
 - Drugs
 - Cocaine
 - Morphine
 - Allergic drug reactions

Adapted from: Burton J.L. *Churchill Livingstone* 1971, page 122.



20. Prepare a patient for informed consent for the use of steroids (GCS, glucocorticosteroids) in a patient with IBD, explaining the adverse effects.

- Psyche
 - Depression, hallucinations, psychosis, insomnia, aggravation of pre existing mood, instability or psychotic tendencies
- Neurological
 - Transient worsening of myasthenia gravis
 - Syncope
 - Seizures
 - Pseudotumor cerebri (with GCS withdrawal)
 - Neuritis
 - Paresthesias
- Eyes
 - Cataracts (posterior subcapsular)
 - Glaucoma
 - Activation of ocular herpes simplex
 - May enhance establishment of secondary ocular infections due to fungi or viruses
- Face
 - Puffiness
- Dermatological
 - Buffalo hump striae
 - Necrotizing angitis
 - Impaired wound healing
 - Petechiae, ecchymoses
 - Facial erythema
 - Hirsutism
 - Acne
 - Allergic dermatitis, urticaria, angioneurotic edema
 - Perianal burning
 - Hypo/ hyper pigmentation
 - Scarring, induration
 - Sterile abscesses
 - Cutaneous/ subcutaneous atrophy
- MSK
 - Muscle wasting (steroid myopathy)
- Cardiovascular
 - Hypertension
 - Thromboembolism, fat embolism



- Hypercholesterolemia
- Accelerated atherosclerosis
- K⁺ deficiency → cardiac arrhythmias
- Cardiac rupture after MI
- GI
 - Stomach/ duodenum possible activation of peptic ulcer disease
 - Cautions concurrent use of steroids with ASA/NSAIDs in persons with increased INR
 - Anorexia/ nausea/ vomiting
 - Increased/ decreased appetite- change in body weight
 - Increased/ decreased BMs
 - Ulcerative esophagitis
 - Perforation of small bowel/ colon (especially in IBD)
- Adrenal glands
 - Suppression, risk of adrenal insufficiency if GCS is quickly withdrawn)
- Kidney
 - In the presence of a fixed or decreased GFR, edema may develop
 - Use with caution in presence of renal insufficiency, acute glomerulonephritis and chronic nephritis
 - Sodium and water retention- edema
 - Aggravation of CHF
 - Hypokalemic alkalosis
 - Hypocalcemia
- Bone
 - Osteoporosis, fractures, avascular (aseptic) necrosis (more likely in rheumatoid arthritis or lupus)
- Endocrine
 - Pancreas
 - Type II diabetes, adipose cells
 - Obesity
 - Increased requirement for insulin or oral hypoglycemics in diabetics
 - Secondary adrenocortical and pituitary responsiveness in stress situations
 - Menstrual irregularities
 - Increased sweating
 - Protein catabolism
- Infections
 - Activation of amebiasis, TB
 - Suppression of patch tests



- Enhanced risk of steroid AEs with cirrhosis or hypothyroidism
- Children
 - Suppression of growth
- Drug interactions look up numerous drug interactions in CPS (2011, page 623)
- Hematology
 - ↑WBC, ↓ lymphs, ↓ platelets
 - Thrombophlebitis
- Pregnancy
 - Possible increase of oral cleft in fetus
 - Possible hypercortisolism effects in fetus of pregnant mothers on high dose steroids

21. Provide a patient with informed consent prior to their having possible bariatric surgery.

- Perioperative surgical complications
 - Surgery/ anesthesia
 - Anastomatic leaks
 - Hernia
 - Lung
 - Pulmonary embolism
 - Aspiration
 - Heart
 - Dysrhythmia
 - Cardiac arrest
 - GI
 - Hemorrhage
 - Incidental splenectomy
 - Small-bowel obstruction
 - Dumping syndrome
 - Flushing, palpitations, light-headedness, fatigue, diarrhea
 - Strictures
 - Cholelithiasis
 - Nutrition
 - Deficiencies Fe, B12, Ca, folate; vitamins A, D, E, K
 - Electrolyte disturbance
 - Protein deficiency
- Risks of not having obesity corrected

Adapted from: Ghosh A.K. *Mayo Clinic Scientific Press* 2008, Table 13-13, page 516.



22. Prepare a patient for informed consent for the use of nonsteroidal anti-inflammatory drugs, explaining the potential adverse effects.

➤ Gastrointestinal

- Constipation or diarrhea
- Peptic ulcer disease; anemia, bleeding, perforation
- Colitis
- ↑, ↓ bowel habit
- Hemorrhage from diverticulae
- Obstruction
 - “diaphragm” disease

➤ Renal

- ↓ renal blood flow
- ↓ glomerular filtration rate
- ↑ creatinine clearance
- Pyuria
- Interstitial nephritis
- Papillary necrosis
- Nephrotic syndrome
- Hyperkalemia
- Type IV renal tubular acidosis
- Fluid retention

➤ Hematologic

- Bone marrow suppression
 - Agranulocytosis
 - Aplastic anemia
- Iron deficiency anemia
- Platelet-aggregating defect

➤ Cardiac

- Peripheral edema
- Pulmonary hypertension

➤ Neurologic

- Delirium/ confusion
- Headache
- Dizziness
- Blurred vision
- Mood swings
- Aseptic meningitis



- Dermatologic
 - Urticaria
 - Erythema multiforme
 - Exfoliative syndromes (toxic epidermal necrolysis)
 - Stevens Johnson syndrome
 - Oral ulcers
 - Dermatitis
- Pulmonary
 - Nasal polyps
 - Pulmonary infiltrates
 - Noncardiac pulmonary edema (aspirin toxicity)
 - Anaphylaxis
 - Bronchospasm
- Drug interactions
 - ↑ effect of warfarin
 - ↑ antihypertensive effect of diuretics, beta -blockers, angiotensin-converting enzyme inhibitors
 - Influence drug metabolism
 - Methotrexate (high doses only)
 - Lithium
 - Oral hypoglycemic agents

Adapted from: Ghosh A.K. *Mayo Clinic Scientific Press* 2008, Table 24-21, page 999.

Gallbladder

Useful background: Terminology

- Murphy's sign ○ Breathing in suddenly stops with RUQ palpation, suggesting cholecystitis
- Courvoisier's sign ○ Painless, palpable distended gallbladder, suggesting pancreatic cancer
- Cullen's sign ○ Bruising of periumbilical area from retroperitoneal due to acute hemorrhagic pancreatitis or ectopic pregnancy
- Gray-Turner's sign ○ Bruising of the abdomen and flanks due to acute hemorrhagic pancreatitis, ruptured abdominal aortic aneurysm or strangulated bowel
- Rebound tenderness ○ Pain on quick withdrawal of palpation, suggesting peritonitis



Useful background: Performance characteristics for the palpation of gallbladder

Finding	PLR	NLR
➤ Palpable gallbladder		
○ Detecting obstructed bile ducts in patients with jaundice	26.0	0.7
○ Detecting malignant obstruction in patients with obstructive jaundice	2.6	0.7

Note that Murphy's sign and back tenderness have a PLR <2, and are not included here as signs for cholecystitis.

Abbreviation: NLR, negative likelihood ratio; PLR, positive likelihood ratio.

Adapted from: McGee S. R. *Saunders/Elsevier* 2007, Box 47.3, page 561. 'Sweet Nothings'

- Gall bladder (GB) may be often enlarged without a palpable liver; feel GB better with patient on left side.
- Obstructive jaundice plus palpable GB-unlikely to be due to stones (unless stones in cystic duct or Hartmann's pouch).
- Finger clubbing with portal cirrhosis. Dupuytren's contracture in alcoholic cirrhosis
- Patients with hemolytic jaundice do not have pruritus or bradycardia
- Biliary cirrhosis-1°, 2°-GB disease, methyltestosterone, chlorpromazine; very occasionally due to severe infection, hepatitis
- Parotid enlargement is common in liver disease, as is fever, even in absence of infection (look for spontaneous bacterial peritonitis)
- Knobbly liver with umbilication – is pathognomonic of hepatic metastases (2°); jaundice with hepatic 2° is usually due to lesions at hepatic fissure; ascites due to portal vein obstruction by glands, or peritoneal deposits
- Impossible to insert a finger between kidney and erector spinae muscle; there is a band of resonance anteriorly over an enlarged kidney
- Pancreatic cysts may be palpable, but tumors rarely are
- Ovarian tumors may be palpated in the midline, including at the umbilicus
- Distended bladder is symmetrical, unless a diverticulum is present



Abdominal X-ray

23. Perform a directed examination of an abdominal x ray ('flat plate').

- General
 - Patient demographics (age, sex)
 - Type of study, study date and time
 - Patient's clinical history, if any provided
 - Obtain previous films for comparison
 - Critique quality of film
- Supraphrenic structures
 - Pleural effusions
 - Consolidation
 - Rib fractures
- Bones
 - Lower thoracic spine, hips, pelvis
 - Lumbosacral vertebrae
 - Lytic or sclerotic lesions
 - Degenerative changes
- Soft tissue
 - Fat stripe
 - Flank stripe
 - Psoas muscles
- Gas pattern
 - Intestinal dilation (Small bowel, <3 cm; large bowel [transverse colon] <5 cm), cecum < 7 cm)
 - Air fluid levels
 - Mucosal thickening
 - Intramural gas
 - Extraintestinal
 - Pneumoperitoneum
 - Pneumobilia
 - Portovenous gas
 - Abscess

Adapted from: Jugovic P.J., et al. *Saunders/ Elsevier* 2004, pages 191 and 192.



Useful background: Causes of calcification on abdominal X-ray

- Lumen of bowel - Fecoliths
- VEIN - Phleboliths
- Nodes - Calcified lymph nodes
- Stones (Calculi) renal, gall bladder, prostatic
- Glands - Calcified pancreas, adrenal, liver (see below), kidney, aorta, psoas muscle, costal cartilage
- Tumor - Calcified tumor-dermoid, fibroid
- Fetus
- Abdominal wall - Calcification in abdominal wall, e.g. cysticerci
- Foreign body on abdominal wall

Adapted from: Burton J.L. *Churchill Livingstone* 1971, page 49.

Useful background: Causes of radiological hepatic calcification

- Infection
 - Hydatid cysts
 - Amoebic abscess
 - TB
 - Histoplasmosis
 - Gumma
 - Brucellosis
- Tumor
 - Hepatoma (HCC)
- Veins
 - Hemangioma
- Intrahepatic bile ducts
 - Calculi

Adapted from: Burton J.L. *Churchill Livingstone* 1971, page 49.



Malnutrition

Useful background:

- Likelihood ratios of malnutrition screening tool for adult malnutrition, as compared with subjective global assessment

Combination of findings	PLR	NLR
➤ Serum albumin < 3.0 g/dL	3.3	0.88
➤ LAW criteria	6.1	0.10
➤ Malnutrition screening tool (score ≥ 2)	13	0.27

	Item score
➤ Have you lost weight without trying?	
No	0
Unsure	2
Yes	Use question.2 instead
➤ If No.1 is 'yes', use the question, How much weight (kg) have you lost?	
None	0
1-5	1
6-10	2
11-15	3
>15	4
Unsure	2
➤ Have you been eating poorly because of a decreased appetite?	
No	0
Yes	1
➤ Malnutrition screening score	Sum of above

Note that many historical points, symptoms and signs on physical examination have a PLR < 2 (and are not included here)

Abbreviations: LAW criteria: discriminant function using Lymphocyte count, Albumin, percentage Weight loss; NLR, negative likelihood ratio; PLR, positive likelihood ratio

Source: Simel D. L., Rennie D. *McGraw-Hill Medical* 2009, Table 28-5 and 28-6 page 380.



Useful background: Increased pretest probability for presence of malnutrition

- ↓ Intake
 - ↓ appetite
 - Psychiatric illness
 - Conditions requiring a change to a suboptimal solid diet (eg liquid diets, tube diets)
 - Elderly patients
- ↓ digestion/ absorption
 - Gastrointestinal tract illness
- ↑ requirements
 - Malignancy
 - Disorders affecting metabolism
- ↑ losses
 - Patients with unintentional weight loss of more than 5%, a major category of individuals for whom additional testing is warranted.

Adapted from: Simel D. L., Rennie D. *McGraw-Hill Medical* 2009, page 381.



Suggested practice case scenarios for OSCE examinations

Primary Stem	Secondary Stem	Diagnosis
➤ Abdominal pain	○ Is an alcoholic	- Pancreatitis
	○ With jaundice and R upper quadrant pain	- Acute cholelithiasis
	○ With jaundice and fever in a diabetic	- Ascending cholangitis
	○ Acute epigastric with guarding	- Perforated DU
	○ Chronic epigastric	- DU and H-pylori
	○ Acute epigastric with hypotension in elderly male	- Rupture AAA
	○ Diffuse pain with atrial fibrillation & diarrhea	- Intestinal ischemia
	○ Lower abdominal pain & fever in older person	- Diverticulitis
	○ Lower abdominal pain & fever	- Appendicitis
➤ Hematochezia	○ Massive rectal bleeding in elderly person	- Diverticulosis
	○ Spotting blood & mucous in young person	- IBD
	○ Blood in stool of older person	- Rectal CA
➤ Abdominal mass	○ Renal mass	- PKD/Renal cell carcinoma
	○ Cecal mass	- Ca, Crohn's disease
	○ Pulsatile midline mass	- Abdominal aortic aneurysm
	○ LUQ mass	- Splenomegaly
➤ Diarrhea	○ Acute following travel	- Giardia
	○ In elderly	- Drugs
	○ With blood in stool	- Bacterial
	○ Chronic diarrhea in Asian	- Lactose intolerance



- Chronic diarrhea, microcytic anemia & rash in Caucasian - Celiac
- Chronic diarrhea, bronchospasm, murmur & flushing - Carcinoid
- Floating stools, pain, weight loss, alcohol abuse - Pancreatic insufficiency

➤ Abnormal lab tests

Primary Stem	Secondary Stem	Diagnosis
➤ Jaundice	○ Painless with pruritus, in older person	- Pancreatic cancer
	○ Painless with pruritus , fatty diarrhea in middle aged female	- Primary biliary cirrhosis
	○ Painless with pallor	- Hemolytic anemia
➤ Abdominal distension	○ Signs of portal hypertension	- Ascites
	○ Heartbeat	- Pregnancy
	○ Android obesity	- Cirrhosis 2° chronic hepatitis
	○ Large kidneys	- Syndrome X
	○ Massive splenomegaly	- PKD

➤ Other

Source: Kindly provided by Dr. P Hamilton (U of Alberta)



Suggested Reading and References

For complete information on Guidelines, Meta-analyses, Systematic Reviews, Technical Reviews, General Reviews, as well as selected classical and recent references, please see the online version of this text at: www.giandhepatology.com





INDEX

Note: Page numbers followed by f or t represent figures and tables respectively. I refers to Volume I, II refers to Volume II.

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