

PRACTICE REVIEW IN HEPATOPANCREATICOBILIARY DISEASES AND NUTRITION

A. B. R. Thomson

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PRACTICE REVIEW IN HEPATOBILIARY AND PANCREATIC DISEASES

*This book complements
Practice Review in Gastroenterology*



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THE WESTERN WAY

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GI Practice Review 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

The participants are provided with assignments in advance of the three day GI Practice Review. There is much work for them to complete before as well as afterwards, so they learn to manage their time effectively, and to complete the assigned tasks proficiently and on time. They learn to work in teams to achieve answers from small group participation, and then to share this with other small group participants through effective delegation of work. 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 GI 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

Like any good story, there is no real beginning or ending, just an in-between glimpse of the passing of time, a peek into a reality of people's minds, thoughts, feelings, and beliefs. The truth as I know it has a personal perspective which drifts into the soul of creation. When does life begin, when does an idea become conceived, when do we see love or touch reality? A caring, supportive, safe, and stimulating environment creates the holding blanket, waiting for the energy and passion of those who dream, invent, create – disrupt the accepted, challenge the conventional, ask the questions with forbidden answers. Be a child of the 60's. Just as each of us is a speck of dust in the greater humanity, the metamorphosis of the idea is but a single sparkle in the limitlessness of the Divine Intelligence. We are the ideas, and they are us. No one of us is truly the only parent of the idea, for in each of us is bestowed the intertwined circle of the external beginning and the end....

....during a visit to the Division of Gastroenterology at the University of Ottawa several years ago, the trainees remarked how useful it would be to have more than two hours of learning exchange, a highly interactive tutorial with concepts, problem solving, collegial discussion, the fun and joys of discovery and successes. Ms. Jane Upshall of BYK Canada (Atlanta, Nycomed), who had sponsored two of these visiting Professorships, encouraged the possibility of the development of a longer program. Her successor, Lynne Jamme, supported the initial three day educational event for the trainees enrolled in the GI training program at the University of Ottawa. With her entrepreneurial foresight, wisdom, and enthusiasm, the idea began. Lynne's commitment to an event which benefited many of the future clinicians, who will care for ourselves and our loved ones, took hold. Then, thanks to the GI program directors in Ottawa and the University of Western Ontario, Nav Saloojee and Jamie Gregor, more trainees were exposed, future GI fellows talked with other trainees, and a grass roots initiative began. Had it not been for Nav and Jamie's willingness to take a risk on something new, had they not believed in me, then there would have been no further outreach. Thank you, Lynne, Nav, and Jamie. You were there at the beginning. I needed you.

By 2008, all but one GI program in the country gave their trainees time off work to participate in the three day event, GI Practice Review (GI-PR). The course is 90% unsponsored, and is gratis to the participants, (except for the cost of their enthusiastic participation!) I am happy to give back to the

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subspecialty that gave me so much for 33 years. I hope GI-PR is helpful to all trainees. I know that from these future leaders there will arise those who will continue to dedicate and donate their time, energy, and ability to the betterment of those who contribute to the continued improvement of our medical profession. The clinicians, the teachers, the researchers.

In the short span of six years, more than 250 fellows, coming from all the 14 training programs in Canada, have participated in the small group sessions in the GI practice review. I thank the training program directors who have supported GI-PR. Special appreciation as well to their many staff physicians who worked without their trainees for the three days of each program.

The idea for the electronic and hard copy summary of the “list of facts” came from the trainees who wished for an aide memoir. But the GI-PR is about more than lists and facts - it is about problem formulation, case discussions, review of endoscopy, histopathology, motility, diagnostic imaging. It is about having fun working together to learn. The subterfuge to gain interest in the basic sciences is the use of clinical scenarios to show the way to the importance of first principles. While the lists are here, the experience is in the performance.

The child will grow, the images will expand, the learning of all aspects of our craft will develop and flourish amongst persons of good will. Examinations will become second nature, as each clinical encounter, each person, each patient, becomes our test, the determination of clinical competence, of caring, of compassion. May these three C's become part of each of our live's narrative. And from this start comes Capstone Academic Publishing, an innovation for the highest quality and value in educational material, made available at cost, speaking in tongues, in the languages of many cultures, with the dialect of the true North strong and free, so that knowledge will be free at last.

Outstanding medical practice and true dedication to those from whom we receive both a privilege and pleasure of care, comes from much more than the GI-PR can give you, much more than Q & As, descriptions of diagnostic imaging or endoscopy stills or videos, histopathology or motility. True, we need all of these to jump over a very high bar. But to be a truly outstanding physician, you need to care for and care about people, and you must respect the dignity and rights of all others. You must strike a balance between love



and justice, and you place your family and friends at the top of your wish-list of lifetime achievements.

For the skeptics who ask “What do you want from me?” I simply say “You are the future; I trust that in time you too will help young people to be the best they can be.”

May good luck, good health, modesty, peace, and understanding be with you always. Through medicine, all persons of the world may come to share caring, respect, dignity, and justice.

Sincerely,

Alan Thomson

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 behavior and wisdom and art, without those special people who turn our minds to the practical - of getting the job done!

Thank you, Naiyana and Duen, for translating those scribbles (called my handwriting), into the still magical legibility of the electronic age. Sarah, thank you for your hard work and creativity.

My most sincere and heartfelt thanks go to the excellent persons at JP Consulting, and CapStone Academic Publishers. Jessica, you are brilliant, efficient, dedicated, and caring. Thank you most sincerely.

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, generous, kind and forgiving. For what I was trying to say and to do was to make my professional life focused on the four C's and an "H"; competence, caring, compassion, and composure, as well as humour - and to make my very private personal life dedicated to family - to you all.



Dedication

Dedicated to Jeannette Rita Cécile Mineault

My life began when I met you:

Your wit, your charm, your laughter,

Your love for children, your caring, your common sense.

As always, all ways, thank you for saying I do.

For the parents who gave us life

For the children and grandchildren who give us hope

For the teachers who gave us knowledge

For the partners who give us confidence, encouragement and meaning





LIVER



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General

Useful background: **Histology**

➤ Hepatocytes

- Polygonal cells, 20 to 30 µm in diameter
- Organized into “plates” of cells, 1-2 hepatocytes thick
- The nuclei of the hepatocytes have round nuclei
- The nuclei vary in size, and 30% of hepatocytes may have 2 nuclei
- These proteins are coated by COP (coatamers) to form vesicles
- These vesicles move from cis, to medial- and then to trans Golgi stacks (trans- Golgi network), and then to the cell membrane for exocytosis.
- Protein synthesized from the RER traffic to Golgi complex the cis side of outer membrane of nucleus is in continuity with the ER (endoplasmic reticulum).
- The ER contains cisternae
 - Rough ER (RER)
 - Attached ribosomes
 - Protein synthesis
 - Smooth ER (SER)
 - Lipid synthesis
 - Detoxification
 - Calcium regulation
- The endothelial cells of the sinusoids have fenestrae (pores).
- The size of the fenestrae can be changed
- The individual hepatocytes are joined by desmosomes (“..... specialized membrane structures that anchor intermediate filaments to the plasma membrane and link cells in the tight junctions”).
- Ca²⁺ and calmodulin act on filaments of actin to change the size of the fenestrae

➤ Kupffer cells

- Kupffer cells are tissue macrophage
- The Kupffer cells includes
 - Remove old red blood cells



- Function
 - Line the sinusoids along with the sinusoidal membranes of the hepatocytes arise
 - Tissue macrophages arise from monocytes and bone marrow stem cells
 - Secrete lymphokine mediators
 - The Kupffer cell lymphokine mediators influence the hepatocytes to synthesize
 - Proteins
 - Mediators of inflammation
 - Prostaglandins
 - LDL (low-density lipoproteins)
- Stellate cells (HSC, hepatic stellate cells; aka Ito cells) surround the wall of the sinusoids (perisinusoidal)
- 1. Give 10 functions of the hepatic stellate cells..
 - Control the diameter of the lumen of the sinusoids
 - May become activated and express desmin and actin
 - HSCs are activated by
 - Sinusoidal endothelial cells
 - ↑ fibronectin
 - Convert latent TGF-B to active fibrogenic active TGF-B
 - Intestinal LPS (lipopolysaccharides → absorbed in portal blood → binds to hepatocyte TLR4 (toll-like receptor 4)
 - LPS bound to TLR4, in the presence of MyD88 (myeloid differentiation response protein) activates NFkB (nuclear factor kappa B)
 - NFkB-downregulates pseudotumor Bambi (bone-morphogenic protein and the actin membrane-bound inhibitor)
 - Kupffer cells
 - Chemokines expression by HSC attracts kupffer cells
 - Kupffer cells secrete TGF-B
 - Hepatocytes
 - Platelets and WBC
 - Downregulation of Bambi-sensitized HSCs to TGF-B
 - HSCs alter cytoskeleton assembly increase extracellular matrix proteins (collagenous and non-collagenous glycoproteins, proteoglycans and glycosaminoglycans).
 - Receptors for vitamin A
 - Store vitamin A



- Sinusoidal cells
 - Sinusoidal cells (aka HSECs [hepatic sinusoidal epithelial cells])
 - HSECs overlap, and form fenestrae by having
 - No junctions
 - No basement membrane
 - The spaces of Disse
 - Is between the lining of the sinusoidals and the hepatocytes
 - Contains plasma and collagen
 - This collagen in the space of Disse (type I, III and V) forms the scaffolding (skeleton) of the liver.
 - “There is bidirectional exchange of liquids and solutes between the plasma [in the portal vein blood] and hepatocytes at the sinusoidal surface [of the hepatocytes] (Feldman M., et al. Sleisenger and Fordtran’s Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier, Philadelphia, 2010, page 1207).
 - The skeleton is comprised of
 - Microfilaments
 - Polymers of G-actin
 - Acts as highways for trafficking of intracellular proteins
 - α/β polymerized dimers of tubulin
 - ATP-driven motor proteins
 - Intermediate filaments
 - Lamins
 - Cytokeratins
 - Hepatocytes: CK8, CK18
 - Bile duct epithelium: CK8, CK18, CK19
 - Vimetin
 - Plectin
 - Pit cells (aka liver NK [natural killer] cells)
2. Give 4 functions of the hepatic pit cells.
- Express Ox-8 antigen
 - Kill tumor cells
 - Remove hepatocytes infected by virus
 - Intracytoplasmic membrane-bound sacs that contain protein kinase for protein degradation (autophagic lysosomal pathway)



- CMA (chaperone-mediate autophagy). “..... is a selective mechanism for the degradation of altered cytosolic proteins in lysosomes” (Feldman M., et al. Sleisenger and Fordtran’s Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier, Philadelphia, 2010, page 1216).
- The ubiquitin / proteasome pathway
 - Binds to misfolded proteins and directs proteasome-dependent proteolysis.
 - Regulate cytoplasmic protein trafficking
- Cell membrane
 - Dynamic polarization due to exo- / endocytosis
 - Endocytosis is non-selective, or selective by way of RME (receptor-mediated endocytosis).
 - Molecules, ligands bind to their membrane receptor and are taken up into the membrane.
 - Clathrin coated vesicles enter the cytoplasm, loose the clathrin coat, travel along the microtubular.
- The canalicular membrane of the hepatocytes
 - Secrets products into the bile canaliculus
 - Flow across the canalicular membrane is unidirectional.
 - Bile flows into the terminal canals of Hering which are lined and formed by hepatocytes and cholangiocytes.
 - Both the canalicular and sinusoidal membranes of the hepatocyte have microvilli.
- The central vein (aka terminal hepatic venule) is at the periphery of the acinus
 - Between the portal tract and the central vein are 3 zones of hepatocytes
 - 1. Periportal
 - 2. Intermediate
 - 3. Perivenular
- Terminology
 - Riedel lobe
 - A variant of normal development, leading to a large right lobe of the liver.



3. Give 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 (men who have sex with men)
- Extrahepatic manifestations
- Following acute hepatitis-failure of recovery, whether clinical or biochemical or both
- Abnormal liver enzyme or function tests, or positive hepatitis B or C viral 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

Useful background:

➤ Direction of flow of blood in veins of abdominal wall

- Flow below umbilicus is down into saphenous veins.
- Above umbilicus flow is upwards into veins of thoracic wall.
- In portal hypertension, dilated veins show normal direction of flow
- In IVC obstruction, flow in veins below umbilicus is reversed, ie. flows upwards

➤ Umbilicus is common site of infiltration by cancer metastases

➤ Spider nevi are telangiectases

- Leuconychia-white nails, beginning at the lunula-may be normal; seen in cirrhosis, leprosy, arsenic poisoning, vasomotor disturbance of fingers



- Finger clubbing with portal cirrhosis.
- Dupuytren contracture is suggestive of alcoholic cirrhosis
- Patients with hemolytic jaundice do not have pruritus or bradycardia
- Parotid enlargement is common in liver disease, as is fever, even in absence of infection (look for spontaneous bacterial peritonitis)
- Knobby liver with umbilication – 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
 - Peritoneal deposits
 - Cutaneous and endocrine changes
 - Spider nevi, palmar erythema, Dupuytren's contractures
 - Gynecomastia, testicular atrophy, impotence
 - Amenorrhea
 - Parotid enlargement

4. Give 5 cutaneous signs of chronic liver disease.

- Jaundice
- Dupuytren contracture
- Spider angiomas
- Palmar erythema
- Telangiectasia
- Hyperpigmentation
- Loss of lunulae
- White nails
- Clubbing
- Excoriations
- Xanthelasma
- Xanthomas



5. Give 15 clinically significant extrahepatic manifestations of acute and chronic liver disease.

- CNS: depression, anxiety, hepatic encephalopathy (HE)
- Lung: portopulmonary hypertension, hepatopulmonary syndrome, pleural effusion, congestive heart failure, aspiration
- Heart: prolonged QT (from low Mg 2+); endocarditis; peripheral intravascular vasodilation, ↓ systemic vascular resistance, ↑ HR, ↑ BP, ↑ CO, vitamin K,
- Blood: Coagulopathy (DIC, fibrinolysis), thrombocytopenia, Hypersplenism, ↓ thrombopoietin, immune mediated destruction, ITP (especially with use of 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
- Bone: osteoporosis, osteomalacia: cholestasis, liver Tx, malnutrition, alcohol, tobacco, ↓ motility, hypogonadism, malabsorption
- Renal: hyponatremia, ascites, hepatorenal syndrome, glomerulosclerosis (HCV), nephritic syndrome, amyloid
- Muscle: spastic paraparesis (from demyelination of corticospinal tracts and posterior columns), wasting; arthritis (hemosiderosis)
- Gonads; hypergonadism, amenorrhea

Abbreviations: GAVE, gastric antral vascular ectasia; PHG, portal hypertensive gastropathy

Hepatic Laboratory Tests

- Liver function tests
 - Bilirubin
 - Albumin
 - INR
- Liver enzymes
 - Aspartate transaminase (AST; SGOT)
 - Alanine transaminase (ALT; SGPT)
 - Gamma-globulin
 - Albumin
 - Alkaline phosphatase (ALP)



- INR
 - Gamma glutamyl transferase (GGT)
 - Hematology
 - Hemoglobin
 - White cell count
 - Platelet count
 - PPT
 - Special tests
 - Serum antibodies
 - Nuclear
 - Smooth muscle
 - Mitochondrial
 - Liver/kidney microsomal
 - HBsAg
 - HBeAg
 - HBeAb
 - Anti-HCV and HCV RNA
 - Serum iron, transferrin, % saturation, genetic testing
 - Serum ferritin concentration
 - Serum ceruloplasmin, as well as blood and urinary copper
 - Alpha-fetoprotein (AFP)
 - Creatinine kinase (if smooth muscle disease suspected as cause of ↑ALT/AST, fasting, LDL and HDL cholesterol, triglycerides)
 - Protein electrophoresis (polyclonal ↑ gamma globulins in AIH)
 - Anti-transglutaminase
 - Note: From the above, be prepared to answer the question blood tests which may be used in primary care which suggest the cause of underlying liver disease
6. Give 6 causes of chronically elevated aminotransferase levels without associated cholestasis, and 6 causes with cholestasis.
- Without cholestasis
- Medication, herbal products, illicit drugs and substance abuse
 - Infection – HBV, HCV
 - Drugs/toxins, alcohol
 - NAFLD, NASH



- Autoimmune liver disease
- Genetic – hereditary hemochromatosis
 - α , AT deficiency
 - Wilson disease
- Celiac disease
- Striated muscle diseases
- With cholestasis
 - Bile duct obstruction
 - Idiopathic ductopenia
 - Primary biliary cirrhosis (PBC)
 - Autoimmune cholangitis (AIC)
 - Primary sclerosing cholangitis (PSC)
 - Sarcoidosis
 - Granulomatous hepatitis
 - Hepatic tumours (primary or metastatic)
 - Medications
 - Diet
 - Drugs
 - Blood products
 - Infection
- Liver tests
 - R value
 - ALT/AP
 - >5, hepatocellular disease
 - <2, cholestatic disease
- ALT, AST
 - ALT, AST in liver, muscle, kidney
 - AST > ALT in ALD (mitochondria produce ↓ AST) fibrosis

“Mediocrity is metric modulation, bringing people
back (regression) to the mean.”

Grandad



7. Give 10 common causes for elevation of **aminotransferases**.

- Marked elevation (up to 20+ fold)
 - Acute hepatitis due to viruses, ischemia or drugs
- Moderate elevation (up to 8 fold)
 - Chronic hepatitis, cirrhosis, cholestatic diseases, and replacement disease
- Minimal elevation (up to 2+ fold)
 - Non-alcoholic liver disease, chronic viral hepatitis (C and B), alcoholism, obesity
 - AST, ALT > 1000
 - Ischemia
 - Drugs
 - Viral hepatitis
 - Autoimmune
 - Budd Chiari
 - CBD stones
 - Macro AST
 - Isolated ↑ AST
- Aminotransferase
 - ALT (aka SGPT, serum glutamic pyruvic transaminase)
 - AST (aka SGOT, serum glutamic oxaloacetic transaminase)
 - Leak into blood when hepatocyte membrane become leaky
 - Increase does not require necrosis, or extent of liver damage.
 - Many causes of ↑ ALT, but a few causes increase > 1000 U/L
 - Viral hepatitis
 - Drugs / toxins
 - Ischemia
 - Autoimmune hepatitis
 - Fulminant Wilson disease
 - Acute Budd-Chiari syndrome
 - Acute obstruction of biliary tree



- Usually, ALT > AST, except in
 - ALD (alcoholic liver disease NAFLD/ NASH)
 - Development of fibrosis
- Transaminitis is not specific for liver disease
 - Thyroid
 - Hyper- / hypothyroidism
 - Muscle
 - Acute rhabdomyolysis
 - Myopathy
 - Extreme exercise
 - GI disease
 - Celiac disease
 - Others
 - Macro – AST

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The ALT is usually higher than AST, except with alcoholic liver disease (ALD), non-alcoholic steatohepatitis (NASH), acute rhabdomyolysis, myopathy, severe exercise, hypothyroidism or macro-AST.

- Give the explanation for AST > ALT in ALD.
 - In ALD there is ↓ pyridoxal 5' – phosphate (P5P)
 - P5P is used to synthesize ALT and AST
 - More P5P is needed to synthesize ALT and AST
 - When P5P↓, as in ALD, there will be less synthesis of ALT, so AST > ALT



8. Give 10 laboratory evaluations of conjugated hyperbilirubinemia in children.

- Total and direct serum bilirubin
- Alkaline phosphatase, aminotransferases, γ -glutamyl transpeptidase
- Prothrombin time or INR, serum albumin (factor V levels, if available)
- Complete blood cell count, differential
- Urine culture (blood/cerebrospinal fluid, if indicated)
- Serology for cytomegalovirus, rubella, herpes simplex, herpes type 6, toxoplasmosis, syphilis (adenovirus, Coxsackie virus, reovirus III, parvovirus B19, if available)
- Urine for reducing substances, serum galactose-1-phosphate uridylyltransferase, serum/urine amino acids and organic acids
- Sweat chloride, genotyping for cystic fibrosis
- α_1 -antitrypsin level and Pi phenotype
- Urine for bile acid metabolites
- Serum ferritin
- TSH
- T4, glucose, cortisol

Source: Robertson, M. and Martin, SR. Approach to the Jaundiced Neonate. *First Principles of Gastroenterology* 2005. pg. 733

- Isolated $\uparrow$ AP (normal ALT, AST; also normal GGT)
 - Renal cell carcinoma
 - Systemic mastocytosis
 - Paget disease
 - RA (rheumatoid arthritis; sometimes also $\uparrow$ GGT)
- $\uparrow$ AP plus GGT
 - Temporal arteritis
 - Metastatic CRC (colorectal) cancer
 - RA (rheumatoid arthritis; sometimes isolated $\uparrow$ AP, i.e. AP but not GGT)
 - Granulomatous liver disease



➤ Alkaline phosphatase (AP)

- ↑ AP in cholestatic liver diseases because of
 - ↑ synthesis
 - ↑ leakage into serum
- An isoenzyme of AP made by intestine ↑ after a fatty meal in persons with blood group B or O.
- ↓ AP in fulminant Wilson disease and hemolysis

9. Give 6 causes of reduced serum **alkaline phosphatase** concentration.

- Endocrine
 - Hyperthyroidism
 - Hypoparathyroidism
 - Hypophosphatemia
- Stomach
 - Pernicious anemia (atrophic gastritis)
 - Milk alkali syndrome
- Bowel
 - Small bowel disease (+ / - alcoholism) associated with
 - Deficiency
 - Magnesium
 - Vitamin C
 - Zinc
 - Vitamin B6
 - Folic acid
 - Excesses
 - Vitamin D
 - Celiac disease
 - Protein-calorie malnutrition
- Liver
 - WD (Wilson disease)

➤ Gamma glutamyl transpeptidase (GGT)

- Sensitive but not specific for liver disease
- May be increased with
 - Alcohol
 - Drugs, e.g. HAART, phenytoin, barbiturates



10. Give 10 common causes for elevation of **gamma glutamyltranspeptidase (GGT)**.

- Hepatobiliary disease
- Replacement disease
- Enzyme induction
- Miscellaneous causes
 - Anorexia
 - Hyperthyroidism
 - Guillain-Barre syndrome
 - Myotonic dystrophy
 - Obesity
 - Diabetes mellitus

➤ Performance characteristics

	Sens	Spec
- AST / ALT > 1, as an indication of cirrhosis in HCV	44% to 75%	> 94%
- GGTP		
- As an indicator of alcohol use	52% to 94%	Low
- As an indicator of bile duct stones	NPV ~ 98%	

Abbreviation: NPV, negative predictive value; Sens, sensitivity; Spec, specificity

11. Give the laboratory tests which help distinguish between the 2 types of cholestasis, bland versus mixed.

Laboratory finding	Types of cholestasis	
	Bland	Mixed
↑ AP > 2x ULN	+	
↑ ALT / AP < 2	+	
↑ ALT > 2x ULN		+
↑ ALT / AP > 5		+



➤ **Prothrombin time**

- Influenced by clotting factors II, V, VII, X
- Prolonged PT with vitamin K deficiency (reduced II, VII, IX, X) and DIC
- Serum T_{1/2} of 6 hours of factor VII, making PT useful to detect rapid changes in liver function

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- Give reasons why the validity of using PT or INR (international normalized ratio) in liver patients has been challenged.
 - Each lab measuring INR has their own standardization of the PT based on the thromboplastin reagent that lab uses to calculate ISI (international sensitivity index), from which the INR is calculated.
 - “.... The ISI [has been] validated only for patients taking a vitamin K antagonist
 - Dose not reflect bleeding risk in hepatic disease
 - Measures procoagulant clotting factors
 - Does not measure anticoagulant clotting factors (e.g. protein C and thrombin)
 - Protein C and antithrombin are elevated with liver disease
 - PTT (partial thromboplastin time) used to assess bleeding risk in liver disease, PT / INR used to determine if there is coagulopathy

Patients with liver disease may have a prolonged PT / ↑ INR due to deficiency of vitamin K –dependent coagulation factors (II, VII, IX, X) or DIC.

- Give the laboratory test which is used to distinguish between a deficiency of vitamin K, and DIC.
 - Factor VII
 - ↓ in DIC
 - N / ↑ in liver disease



Clinical Tips

- An elevated serum bilirubin, AP (alkaline phosphatase) or GGT does not necessarily indicate drug-induced liver injury (DILI), but instead may be an adaptive response through the induction of microsomal enzymes in the hepatocytes.

Please refer to Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier, Philadelphia, 2010, Table 86.2, page 1423 for a "Clinicopathologic Classification of Drug-Induced Liver Disease".

- ↓ AP, ↓ AP / bilirubin ratio, and ↓ uric acid in serum → think of Wilson disease

12. Give the **genetic abnormalities** in three of the following hepatic conditions:

➤ ALD (alcoholic liver disease)

- Genotypes of the aldehyde dehydrogenase (ALDH2-*2 allele) and the P4502E1 (C2 allele)
- Polymorphism of TNF2 at position -238 (G→A)
- A→e mutation in exon 1 of the Cytotoxic T-lymphocyte antigen-4 (CTLA-4) gene

➤ Cholelithiasis

- ABC B4 gene (PC transporter)
- ABC B11 gene (bile salt export pump)
- CYP7A1 (cholesterol 7α-hydroxylase)
- FXR farnesoid x
- E4 allele of APOE (apolipoprotein E)
- N TCP (Na⁺ dependent taurocholate cotransporting peptide)
- TNF receptor 2
- SHP (small heterodimer partner)

➤ PBC (primary biliary cirrhosis), environmental: smoking, HRT (hormone replacement therapy), UTI (urinary tract infection), toxic waste sites, Chlamydia, pneumonia, betaretrovirus, novosphingobium aromaticivorans)



- MHC class II HLA-DR8 allele
- CTLA-4 gene
- IL-I
- PSC (primary sclerosing cholangitis)
 - HLA A1-B8-DRB1*0301-DQA-1*0501-DQB1*0201, and DRB*1301-DQA-1*0103-DQB1*0603
 - Genetic polymorphisms: TNF α ; stromelysin, matrix metalloproteinase 3; MHC class I polypeptide-related sequence A, chemokine C-C motif receptor 5; intracellular adhesion molecule-1, CD54
- α 1-AT (alpha 1 – antitrypsin deficiency)
 - Mutation in codon 342 of the 1-AT gene, changing a single amino acid from lysine to glutamate

Abbreviation: HRT, hormone replacement therapy

Printed with permission: Juran BD, and Lazaridis KN. *Clin Gastro Hepat* 2006; 4: 548-57.

Surgery and Liver Disease

13. Give 10 management considerations in the **pre- and post-operative care** of the patient with advanced liver disease (based on MELD score).
 - Risk stratification
 - Diagnose and treat
 - Hepatic encephalopathy (HE)
 - Correction of reversible metabolic factors (eg. hyponatremia, hypocalcemic alkalosis)
 - Oral lactulose administration, titrated to ~3-4 bowel movements per day
 - Administration of nonabsorbable antibiotics
 - Avoidance of nephrotoxic insult (eg. NSAIDs, narcotics, benzo's)
 - Supportive care
 - Correction of reversible metabolic factors
 - Esophageal varices



- EGD +/- banding or non-specific β -blockers
- Treat ascites / SBP / HRS
 - Ascites, peripheral edema
 - Oral diuretic therapy with spironolactone and/or furesomide
 - Fluid restriction (if sodium concentration is <120 mmol/l)
 - Avoidance of excessive saline administration
 - Albumin infusion (with paracentesis volumes >5 l)
 - Antibiotics for spontaneous bacterial peritonitis
 - Steroids, as indicated
 - 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
- Diet
 - Maintenance of an adequate protein intake (1-1.5 g/kg per day)
 - Promotion of a balanced diet
 - Dietary sodium restriction (<2 g daily)
- Pain control
 - Dilaudid (0.5-1 mg q 4 h prn) or PLA
 - Acetaminophen
 - Avoid benzodiazepines, NSAIDs, narcotics
- Assess pulmonary function (e.g. for dyspnea, O_2 desaturation)
 - Supplemental oxygen

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

Post-operative Hepatic Dysfunction is Common, please see Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier, Philadelphia, 2010, Table 87.4, page 1449, "Causes of Post-operative hepatic Dysfunction".



- Summary approach to **predicting post-operative mortality**
 - Child-Pugh classification
 - MELD ((model for end-stage liver disease) score
 - Presence of PHT (portal hypertension)
 - Co-morbidities
 - For high risk surgery, consider performing the surgery at a centre with hepatobiliary experience, including liver transplantation (L-Tx)
 - Consider pre-operative assessment for L-Tx (liver transplantation), in case patient does not do well post-operatively

14. Give the **Child-Pugh classification** of liver disease.

Parameter	1	2	3
○ Ascites	None	Slight	Mod/severe
○ Encephalopathy	None	Slight/mod (1-2)	Mod/severe (3-4)
○ Bilirubin (mg/ dl)	<2 (<34)	2-3 (34-50)	>3 (>50)
○ Albumin (mg/ dl)	>3.5 (>35)	2.8-3.5 (28-35)	<2.8 (<28)
○ PT (INR)	1-3 (<1.7)	4-6 (1.7-2.2)	>6 (>2.2)

Total score	Child-Pugh classification
5-6	A
7-9	B
10-15	C

Adapted from: Kim WR, et al. *Hepatology* 1999;29(6):1643-8.; and Durand F, Valla D. *J Hepatol* 2005;42.

“Life isn't about waiting for the storm to pass. It's
about learning how to dance in the rain...”

Vivian Greene



15. Give the peri-operative mortality rates (MR) in persons with cirrhosis.

<u>Child's</u>	<u>Surgical MR (%)</u>
A	5-10
B	30
C	70-80

- 30-day perioperative mortality, 30% (total):
 - Worsening Ascites, 7%
 - Pneumonia, 8%
 - Infection, 8%
 - Bleeding, 10%

Source: Sterling RK. Evaluation and management of the surgical patient with cirrhosis: when they have to go to the operating room. *ACG Annual Scientific Meeting Symposia Sessions* 2009; 71-77.

16. Give the use of the **MELD score** to predict perioperative complications.

- MELD score
 - 5-20
 - 1% increase in mortality with each 1 point increase
 - >20
 - 2% increase in MR for each MELD point increase
- If MELD < 11 (especially < 8), acceptable risks
- If MELD > 20, elective surgery should be postponed
- If MELD 12-20, complete L-TX evaluation in case of deterioration
- Derived from creatinine, bilirubin, INR
- Correlates with mortality rate for
 - Liver transplantation
 - Liver resection
 - Other abdominal operations
 - Cardiac surgery



➤ Summary of findings: “MELD Plus”

- MELD, ASA class, and age were most important
 - www.mayoclinic.org/meld/mayomodel9.html
 - C-statistic is 0.80 (30d) and 0.84 (90d)
- Emergency surgery predicted duration of hospitalization ($p < 0.001$) but not mortality
- ASA class V best to predict 7d mortality
- MELD is best beyond 7 days

Adapted from: Teh SH, Nagorney DM, Stevens SR et al. Risk factors for mortality after surgery in patients with Cirrhosis. *Gastroenterology* 2007;132:1261-9.

Fatty Liver Disease

➤ Natural history of NAFLD

NAFL $\xrightarrow{20\%}$ NASH $\xrightarrow{\sim 1\% / \text{year}}$ cirrhosis, HCC $\xrightarrow{\sim 4\% / \text{year}}$ decompensation

- About 2/3 of NAFLD are SS (NNFL) and 1/3 are NASH
- Only 10-15% weight reduction reduces hepatic fat (Harrison SA, Day CP. *Gut* 2007;1760-9)
- Agents tested to treat NAFLD, but not being of consistent benefit, include UDCA, vitamins C and E, thiazolidinediones, statins, ARBs (angiotensin receptor blockers), ghrelin-leptin modulators, and antioxidants such as SNACS-nitroso-n-acetyl cysteine. Vitamin E supplementation shows promise.
- Bariatric surgery achieves weight reduction and benefits many parameters of NASH (Mummadi RR, et al. *Clin Gastroenterol Hepatol* 2008;1396-1402.)

Abbreviations: ARBs, angiotensin receptor blockers; NAS, NASH activity score; NNFL, non-NASH fatty liver; SS, simple steatosis

Printed with permission: Cortez-Pinto H, and Camilo ME. *Best Practice & Research Clinical Gastroenterology* 2004;18(6): pg 1097.



➤ NAFLD and NASH may be distinguished using Kleiner's scoring system, also known as "NAS" (NASH activity score) (Kleiner DE, et al. *Hepatology* 2005;41:1313-21.)

➤ Based on:

1. Simple steatosis
2. Steatosis plus inflammation alone
3. Steatosis plus ballooning
4. Steatosis plus fibrosis (Matteoni CA, et al. *Gastroenterology* 1999;116:1413-9.)

- NAFLD worsens the prognosis of liver disease associated with HCV and HH (hereditary hemochromatosis).
- Obesity (↑ BMI)
- T2DM (type 2 diabetes mellitus)
- Dyslipidemia
- Metabolic syndrome

➤ Pathogenesis

17. Give the **pathogenesis** of NAFLD (non-alcoholic fatty liver disease) and NASH (non-alcoholic steatohepatitis).

- GI Tract

- ↑ intake / absorption
 - ↑ fat to liver
- Fat, CHO
 - CHO to liver
 - ↑ lipogenesis (↑ TG in liver)
 - ↑ insulin resistance
- Bacterial toxins
 - ↑ ROS
 - ↑ oxidative stress

- Adipocyte

- ↑ FFA / ROS
 - Activation of macrophages / immune system → ↑ lipoptosis
 - ↑ insulin-resistant adipocytes → ↑ FFAs

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- Liver
 - Metabolism
 - ↑ insulin, ↑ insulin-resistance
 - ↑ leptin, ↑ leptin resistance
 - ↓ adiponectin
 - Mitochondria
 - ↓ β oxidation of FFA
 - ↑ synthesis of FFA
 - ↓ respiratory chain complexes
 - ↓ ATP
 - ↑ ROS, ↑ PPAR γ , ↑ TNF- α
 - ↑ DNA damage
 - ↑ SREBP1 / ↑ CHREBP → ↑ TG synthesis
 - ↓ Apo B-100 (also ↓ β oxidation) → ↓ fat transport out of liver → ↑ TG in liver
 - ↑ CYP 2E1
 - ↑ leak of electrons → ↑ ROS, ↑ RNS → ↑ NF- κ B → ↑ TNF- α
 - ↓ ATP
 - ↓ antioxidant
 - ↑ membrane lipid peroxidation
 - ↑ protein / DNA oxidation
 - ↑ hepatic insulin
 - ↑ synthesis of PL, CE
 - Dysregulated cytokine production (↑ pro- / ↓ anti-inflammatory cytokines)
 - Hepatocytes
 - IL-8, IL-18
 - Neutrophil chemotactic peptide
 - Angiogenesis factor
 - Kupffers cells
 - NF- κ B → TNF- α
 - IL-10
 - Sinusoidal endothelial cells
 - Adhesion molecules
 - Stellate cells
 - TGF- β → fibrosis
 - ↑ intestinal permeability → ↑ LPS
 - ↑ LPS
 - ↑ apoptosis of hepatocytes → ↑ release of IL-8 (neutrophil chemoattractant), IL-18 (primes TNF α release, and type 1 helper T cell response)
 - ↑ TNF- α inducible IL-6, IL-8, IL-18, MCP-1 (monocyte chemoattractant protein 1)



- As well as ↑ pro-inflammatory cytokines, there is ↓ anti-inflammatory cytokines

“hepatocyte apoptosis may sustain proinflammatory cytokine production and cell injury or death” (Feldman M., et al. Sleisenger and Fordtran’s Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier, Philadelphia, 2010, page 1387).

- Inflammasomes (proinflammatory multiprotein complexes: redox state)
 - Nod-like receptor (NLR) protein or a PYHIN protein – sense pathogen-associated molecular pattern (PAMPs) or damage-associated molecular patterns (DAMPs)
 - Are key to the production of the proinflammatory cytokines IL-1 β IL-18.
 - Reactive oxygen species (ROS) activate the NLRP3 inflammasome and their generation is triggered by many PAMPs.
 - Increased ROS generation is a proinflammatory insult in the progression of NAFLD.
 - Inflammasome-dependent processing of IL-1 β and IL-18 could be important in NAFLD / NASH
- Stellate cell activation
 - Activation of hepatic stellate cell (HSC)
 - Pro-inflammatory cytokines
 - Angiotension
 - Oxidative stress
 - Growth factors
 - Extracellular matrix
 - PDGF (platelet-derived growth factor)
 - Connective tissue growth factor
 - Leptin-associated production of TGF- β by kupffer cells
- A signaling pathways regulating HSC activation
 - PDGF
 - PDGF signals partially through ERK activation and also through AKT via mTOR mediated protein synthesis regulation.
 - PDGF activation also allows for influx of Ca²⁺ ions, which contributes to gene regulation
 - In addition to PDGF, several other growth factors can activate tyrosine receptors which lead to Akt activation and then either mTOR or JNK activation.



- TGF β
 - TGF β recruits Smad 2/3, leading to their phosphorylation and stimulation of fibrogenic gene expression.
- Others
 - Emerging pathways of importance of fibrosis include contributions from
 - Adipokines (leptin)
 - Neuroendocrine signals (2-AG)
 - TLR signaling
 - Angiogenic signals (VEGF), among other
- SREBP-1, the sterol regulatory element binding protein-1c, CHREBP, the carbohydrate regulatory element

Abbreviations: NF κ B, nuclear factor kappa B; ROS, reactive oxygen species; RNS, reactive nitrogen species

Adapted from: Pellicoro A, and Faber KN. *Alim Pharm Ther* 2007; 26 (2): pg. 149-160 and Wood NJ. *Nat Rev Gastroenterol Hepatol* 2012; 9(3):123.

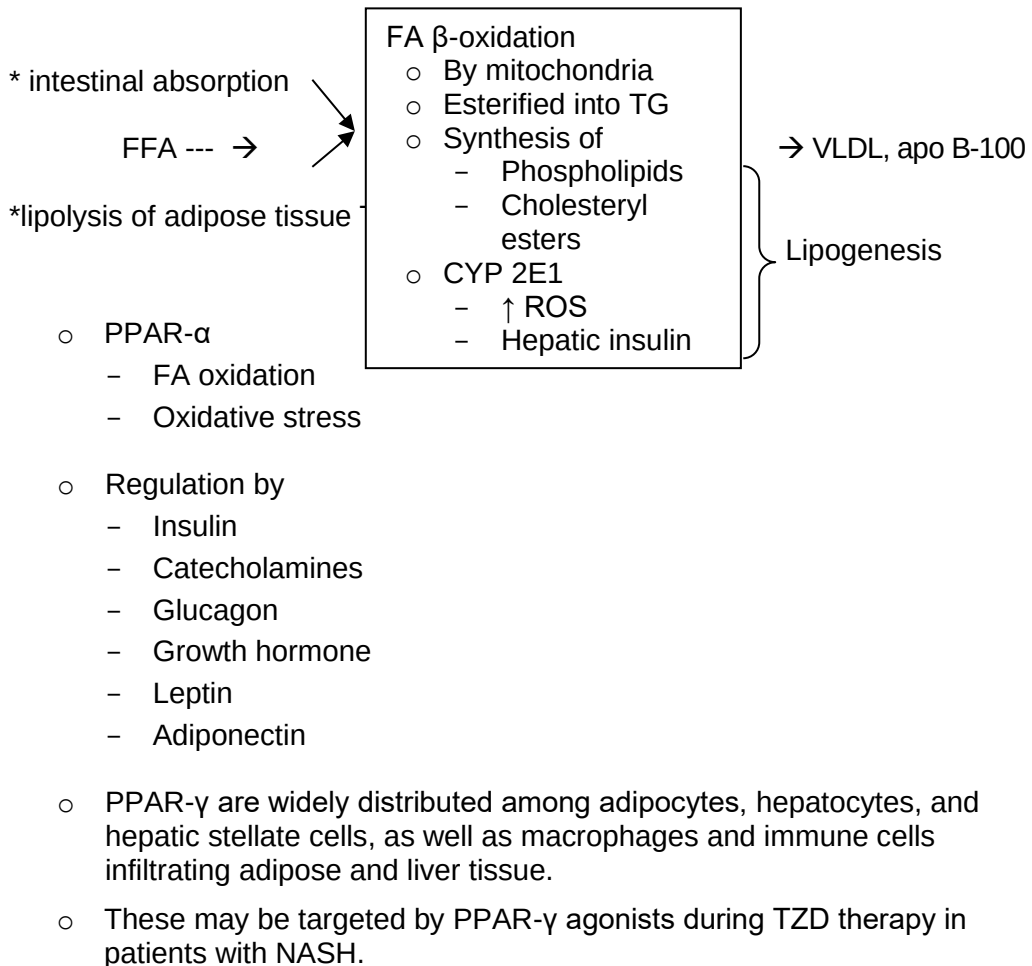
➤ Pro-inflammation

- Inflammasome-dependent processing of IL-1 β and IL-18 could be important in NAFLD / NASH.
- Inflammasomes – proinflammatory multiprotein complexes consisting of a Nod-like receptor (NLR) protein or a PYHIN protein – sense pathogen-associated molecular pattern (PAMPs) or damage-associated molecular patterns (DAMPs) and are key to the production of the proinflammatory cytokines IL-1 β IL-18.
- Reactive oxygen species (ROS) activate the NLRP3 inflammasome and their generation is triggered by many DAMPs.
- Increased ROS generation is a proinflammatory insult in the progression of NAFLD.
- Endo-/ exotoxin-mediated release of proinflammatory cytokines

Source: Wood NJ. Microbiota: Dysbiosis driven by inflammasome deficiency exacerbates hepatic steatosis and governs rate of NAFLD progression. *Nat Rev Gastroenterol Hepatol*. 2012 Feb 21;9(3):123. doi: 10.1038/nrgastro.2012.21.



➤ Balance of lipolysis / lipogenesis (↑ FFA, ↓ mitochondrial function)



➤ FFA (free fatty acids)

- Activated immune response
 - ↑ NFkB
 - ↑ IL-6
 - ↓ adiponectin
 - ↑ leptin, ↑ leptin resistance
 - Lysosomal destabilization (↑ TNF-α)
- ↑ ROS (reactive oxygen species), ↑ CYP 2E1
- Toxicity to mitochondrial membranes

➤ Mitochondrial dysfunction



- ↓ respiratory chain complexes
- ↑ ROS
 - ↑ TNF- α
- ↓ ATP
- Mitochondrial DNA damage

➤ Stellate cell

- Activation (initiation and perpetuation)
 - Pro-inflammatory cytokines
 - Angiotension
 - Oxidative stress
 - Growth factors
 - Extracellular matrix
 - PDGF (platelet-derived growth factor)
 - Connective tissue growth factor
 - Connective tissue growth factor
 - Leptin-associated production of TGF- β by kupffer cells
- Adipose tissue is composed of adipocytes and the stromal vascular fraction.
- This includes macrophages and other immune cells that have a relevant role in the autocrine-paracrine regulation of adipocytes. In obesity, activation of macrophages/immune system contributes to the development of dysfunctional, insulin-resistant adipocytes that release excessive amounts of FFA and cause insulin resistance and lipoapoptosis in distant tissues (liver, muscle, pancreatic beta cells, vascular bed, other).
- Accumulation of triglyceride-derived toxic lipid metabolites activates intracellular inflammatory pathways within hepatocytes and Kupffer and other immune cells, in resemblance to defects within adipocytes.
- Activation of hepatic stellate cells leads to collagen deposition and the potential for cirrhosis.
- Adipocyte
 - ↑ fat → insulin resistance
 - ↑ cytokines
 - Activated macrophages
- A signaling pathways regulating HSC activation



- PDGF signals partially through ERK activation and also through AKT via mTOR mediated protein synthesis regulation.
- PDGF activation also allows for influx of Ca²⁺ ions, which contributes to gene regulation
- In addition to PDGF, several other growth factors can activate tyrosine receptors which lead to Akt activation and then either mTOR or JNK activation.
- TGFβ recruits Smad 2/3, leading to their phosphorylation and stimulation of fibrogenic gene expression.
- Emerging pathways of importance of fibrosis include contributions from adipokines (leptin), neuroendocrine signals (2-AG), TLR signaling, and angiogenic signals (VEGF), among other.

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- Give 3 monogenic causes of chronic liver disease which are associated with fatty liver in children.
 - Fatty acid oxidation defects
 - Lysosomal storage diseases
 - Peroxisomal disorders

➤ Clinical

- NAFLD is often associated with metabolic syndrome (which is diagnosed as well as with laboratory measurements) as well as with insulin resistance.
- NAFLD, both simple steatosis as well as NASH (steatosis hepatitis with / without fibrosis) is a risk factor for HCC (hepatocellular cancer),
- About 1/3 of persons with NAFLD and simple steatosis will progress to NASH. patients with NASH will develop cirrhosis and portal (PHT). Preventing fatty liver disease is important, but the physician needs to be able to identify the person with simple steatosis who is at risk for progression to the more serious condition, NASH.



➤ Clinical Course

18. Give 5 patient-related and 5 laboratory-related **predictors of progression** of NAFLD (simple steatosis) to NASH.

○ Patient

- Age > 45 years
- Female
- Ethnicity (Hispanic, Asian >White >Black)
- Type II diabetes mellitus
- BMI > 35 (especially visceral obesity)
- Insulin resistance
- Hypertension
- Metabolic syndrome (insulin resistance), even in young, non-obese persons
- Stigmata of portal hypertension
- Comorby: alcohol, HCV infection

○ Laboratory

- ↑ ALT > 2x ULN
- ↑AST:ALT >1 [suggests fibrosis]
- ↑ Triglycerides >1.5
- ↑ INR
- ↑ Bilirubin
- ↓Platelets
- ↓Albumin
- Indexes of insulin resistance (HOMA [homeostatic model assessment, QUICKI, OGIS)
- ↑ Elevated ferritin levels
- ↑ Hyaluronic acid
- ↑ glucosaminoglycan
 - Produced in mesenchymal cells
 - Increased in cirrhosis because of sinusoidal capillarization
 - Fasting hyaluronan > 100 mg/L, performance characteristics for detection of cirrhosis
 - Sensitivity, 83%
 - Specificity, 78%
 - Useful if normal



- Anti-MDA antibodies
- Support the diagnosis of NAFLD
- US, CT, MRI do not predict severity: do not distinguish simple steatosis (SS) from NASH
- Diagnostic Imaging
 - Ultrasound (US) ↑ echogenicity
 - CT liver density = spleen
 - MRI bright T1 – weighted imaging of liver
 - Detection of > 33% fat in liver
 - Sensitivity
 - US, 100%
 - CT, 93%
 - MRI, 95%
 - PPV
 - US, 62%
 - CT, 76%

Curiosities of Investigation

- ~25% of NAFLD have
 - ANA (antinuclear antibodies, titre usually < 1:320)
 - ↑ serum ferritin

Abbreviations: PPV, positive predictive value; NASH, non-alcoholic steatohepatitis; SS, simple steatosis

- MRE (magnetic resonance elastography)
 - “....superior to TE for staging liver fibrosis in patients with a variety of chronic liver disease” (Feldman M., et al. Sleisenger and Fordtran’s Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier, Philadelphia, 2010, page 1235)
- Fibro Scan[®] (aka TE [transient elastography])
- Useful to identify advanced but not early cirrhosis from
 - HCV
 - PBC (primary biliary cirrhosis)
 - HH (hereditary hematomachrosis)
 - NAFLD
 - Recurrent chronic hepatitis after liver transplantation



➤ Pathology

19. Give the pros and cons of performing a percutaneous liver biopsy in a patient with NAFLD and abnormal liver enzymes.

Issues	Argument in favor of biopsy with acceptable risk	Reasons for not performing a biopsy.
➤ Abnormal hepatic biochemical tests and NAFLD		
○ Elevated ALT	- Confirm diagnosis	- Cause accurately identified clinically in > 90% cases without biopsy
○ Diagnosis of NAFLD	- Patients may not have classic NAFLD risk factors	- Accurate diagnosis of NAFLD generally possible without biopsy
○ Identify severity of NAFLD	- Only biopsy can distinguish simple steatosis from steatohepatitis	- Non-invasive markers may be developed to distinguish the two
○ Treatment of NAFLD	- Presence of steatohepatitis or fibrosis may motivate some to undertake risk factor modification	- There is no proven therapy for NAFLD. Absence of steatohepatitis or fibrosis may remove motivation for some to undertake risk factor modification

Printed with permission: Reddy K R. 2006 AGA Institute Postgraduate Course Syllabus: pg. 81.

20. Give 8 liver biopsy criteria for NASH.

➤ Present in all or most cases

- Diffuse or centrilobular steatosis, predominantly macrovesicular; degree may correlate with BMI
- Parenchymal (lobular and portal) inflammation (+/- focal necrosis), neutrophils, macronuclear cells
- Lobular necrosis

➤ Features observed with varying frequency

- Ballooning hepatocyte degeneration



- Pericellular fibrosis (“chicken wire fibrosis” on trichrome stain) – perivenular* (zone 3), perisinusoidal or periportal (37%-84%)
- Mallory bodies
- NAFLD Activity Score (see Useful background which follows)
- Cirrhosis (7%-16% on index biopsy)
- Glycogenated nuclei
- Lipogranulomas
- Stainable iron

Adapted from: Reid AE. *Sleisenger & Fordtran's Gastrointestinal and Liver Disease: Pathophysiology/Diagnosis/Management* 2006: pg. 1796; and 2010, pg 1407.

- Focal Fatty Liver (FFL)
 - Patchy process of fat accumulation which may look like a hepatic mass on diagnostic imaging
 - Typical appearance on CT scan which helps to distinguish FFL from metastatic lesion:
 - Density close to water
 - Not spherical in shape
 - No mass effect
 - The FFL may regress without treatment

21. Give 15 causes of **macrovesicular** steatosis.

- Liver – Wilson disease, alcohol, NAFLD/NASH, HCV-3 (acute fatty liver of pregnancy)
- Infection – HCV-3, bacterial overgrowth, fever, viral infections
- Drugs – corticosteroids, alcohol, estrogen, amiodarone, HAART (for HIV) tetracycline, vitamin A toxicity
- Metabolic – hyperlipidemia, TPN, tyrosinemia, galactosemia, glycogenoses, abetalipoproteinemia, diabetes
- Nutrition – rapid weight loss or gain, obesity, pancreatic insufficiency, Kwashiorkor, TPN, bariatric surgery, short bowel syndrome
- Pediatric conditions - Weber-Christian
- Idiopathic

Adapted from: Oh MK, et al. *Aliment Pharmacol Ther* 2008; 28:pg. 507.



22. Give 5 causes of **microvesicular** steatosis.

- Pregnancy—Acute fatty liver of pregnancy, HELLP syndrome
- Infection – HBV, HCV, HDV
- Drugs – Reye syndrome (salicylates), valproic acid, amiodarone, AZT, DDI, tetracycline
- Metabolic – Jamaican vomiting sickness, urea cycle and mitochondrial defects, carnitine deficiency, Wolfman disease
 - Aide de memoir: “A, B, C, D, E-J (**A**FLP; **H**BV; **H**CV; **D**rugs; **H**ELLP-Jamaican)

Adapted from: Oh, M.K. et al. *Aliment Pharmacol Ther* 2008; 28:pg. 507.
Genetic abnormalities may exist in some persons with alcoholic liver disease (ALD), cholelithiasis, primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC), alpha1 anti-trypsin deficiency (α 1-AT), and polycystic liver disease (PCLD)

Useful background: **Grading and staging** of the biopsy lesions of NASH

➤ Grade I. Mild

- Steatosis: predominantly macrovesicular, involves <33% or up to 66% of the lobules; increased BMI may correlate with BMI
- Ballooning: occasionally observed; zone 3 hepatocytes
- Lobular inflammation: scattered and mild acute (polymorphs) and chronic (mononuclear cells) inflammation
- Portal inflammation: none or mild

➤ Grade 2. Moderate

- Steatosis: any degree and usually mixed macrovesicular and microvesicular
- Ballooning: present in zone 3
- Lobular inflammation: polymorphs may be noted associated with ballooned hepatocytes, pericellular fibrosis; mild chronic inflammation may be seen
- Portal inflammation: Mild to moderate



➤ Grade 3. Severe

- Steatosis: typically >66% (panacinar): commonly mixed steatosis
- Lobular inflammation: scattered acute and chronic inflammation; polymorphs may appear concentrated in zone 3 areas of ballooning and perisinusoidal fibrosis
- Portal inflammation: Mild to moderate

➤ Staging (fibrosis)

- Stage 1: zone 3 perivenular perisinusoidal fibrosis, focal or extensive
- Stage 2: as above plus focal or extensive periportal fibrosis
- Stage 3: bridging fibrosis, focal or extensive
- Stage 4: cirrhosis
- Types 3 and 4 of NAFLD commonly occur together, and may be known as NASH, and types 1 and 2 of NAFLD are known as SS (simple steatosis) or non-NASH fatty liver (NNFL) (Matteoni CA, et al. *Gastroenterology* 1999;116:1413-9.)

23. Give the meaning of **Mallory bodies**, and with what hepatic conditions are they associated?

- Mallory bodies
 - Cytoplasmic inclusions in hepatocytes
 - Red colour from
 - Cytokeratin intermediate filaments, and
 - Ubiquitins
 - “twisted rope” appearance
- Associations
 - ALD (alcoholic liver disease) (~66%)
 - NAFLD (non-alcoholic liver disease)
 - PBC (primary biliary cirrhosis) (~25%)
 - WD (Wilson disease) (25% to 50%)
 - DILI
 - Amiodarone



24. Give 4 conditions other than obesity, DMT2, dyslipidemia or metabolic syndrome which may also predispose to NAFLD.

- Endocrine
 - Hypothyroidism
 - Hypopituitarism
 - Hypogonadism
 - Hyperuricemia
 - Vitamin D deficiency
- Ovary
 - Polycystic ovary syndrome (PCOS)
- Pulmonary
 - Obstructive sleep apnea
- GI
 - Pancreatico-duodenal resection
 - Total Parental Nutrition (TPN)

Diagnostic Tip

"In NAFLD-associated cirrhosis, the typical histological features of NAFLD may be minimal or absent, potentially to the misdiagnosis of cryptogenic cirrhosis" (Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier, Philadelphia, 2010, page 1407).

- Approximately 1/3 of NAFLD patients have the same histology (over 1 to 14 years), 1/3 improve and one third worsen; however
- There may be sampling error and misclassification of histological grade
- Because NAFLD is a diffuse process, it is not clear how important an effect this sampling error would be

Clinical Confusion – What the Experts Say About Liver Biopsy in NAFLD

"Liver biopsy is the standard means of diagnosis and the only test that can reliably differentiate simple steatosis from advanced NAFLD (i.e., non-alcoholic steatohepatitis), although non-invasive methods for assessing fibrosis are under study" (Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier, Philadelphia, 2010, page 1407).

"The correlation among clinical, laboratory, and histologic findings in NAFLD is poor, and patients with normal liver biochemical tests results can have significant liver injury on biopsy specimens" (Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier, Philadelphia, 2010, page 1407).

".....the risk of liver-related complications in NAFLD correlates, at least to some extent, with the degree of hepatocellular injury and fibrosis found on an index liver biopsy specimen" (Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier, Philadelphia, 2010, page 1408).



Detection of Hepatic Fibrosis

- Gold standard
 - Liver biopsy
 - Only “bronze standard” because of considerable sampling variation (patchy changes)
- A panel of blood tests
 - α 2-microglobulin
 - Apolipoproteins A-1
 - Haptoglobin
 - Total bilirubin
 - GGT
 - ALT
 - To estimate
 - Hepatic fibrosis
 - First 5 test
 - Necroinflammatory activity
 - All 6 tests
- Fibro test (aka Fibrosure)
 - Performance characteristics
 - Sensitivity, 90%
 - Specificity, 36%
 - PPV, 88%
 - NPV, 40%
 - Validated in HBV, HCV, ALD, methotrexate in psoriasis
 - Low cut-off (0.30)
 - NPV, 90%
 - 0.30 to 0.70, inaccurate (this range includes 1/3 of NAFLD patients tested with Fibro Test)
- FIBROSpect II
 - A score derived from variably weighted values of the following:
 - Hyaluronate
 - Tissue inhibitor of metalloproteinase I
 - α 2-macroglobulin



- Performance characteristics for advanced fibrosis in HCV
 - PPV, 88%
 - Sensitivity, 72%
 - Specificity, 74%
 - Severe steatosis (centrilobular, macrosteatosis)
 - ↑ Stainable iron
 - Signs of cirrhosis
 - Performance characteristics for fibrosis, cut-off value
 - High cut-off (0.70)
 - PPV, 73%
 - Specificity, 98%
- FibroScan®
- NAFLD Fibrosis Score
- Age
 - BMI
 - Blood sugar
 - AST / ALT
 - Platelet count
 - Albumin
 - High cut-off
 - PPV, 82% to 90%
 - Low cut-off
 - NPV, 88% to 93%

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; HOMA, homeostatic model assessment; MDA, malondialdehyde; NPV, negative predictive value; OGIS, oral glucose insulin sensitivity index; PPV, positive predictive value; QUICKI, quantitative insulin-sensitivity check index; ULN, upper limit of normal.

Adapted from: Pinzani, et al. *Nature Clinical Practice Gastroenterology & Hepatology* February 2008; 5(2): pg 102; and Reid AE. *Sleisenger and Fordtran's Gastrointestinal and Liver Disease: Pathophysiology/ Diagnosis/ Management* 2010, pg 1408.



➤ Management

25. Give a clinical approach to the patient with suspected NAFLD / NASH.

- Abnormal liver biochemistries and / or fatty liver on abdominal ultrasound
- Access for
 - ALD; obesity, T2DM, dyslipidemia, metabolic syndrome (treat appropriately)
 - Exclude HAV, HBV, HCV, HH, AIH, PBC, PSC
- Liver biopsy with / without Fiber Scan
- Lifestyle interventions
 - ↓ body weight by at least 3% to 5%
 - Exercise
 - Avoid heavy use of alcohol (drinkers per week: men > 14, women > 7)
- Insulin sensitizing agents
 - Metformin
 - Pioglitazone
- Vitamin E 800 IU / day
 - Controversial use; no longer recommended in some guidelines
 - “In patients with other types of liver disease who have co-existing NAFLD and NASH, there are no data to support the use of vitamin E or pioglitazone to improve the liver disease (Chalasani N, et al. Gastroenterology 2012; 142: 1592-1609).
 - Note: increases risk of prostatic cancer in healthy men by 1.6 per 100 person years of vitamin E use.
- Screening for
 - Cirrhosis
 - Esophageal varices
 - HCC (hepatocellular cancer)
- Consideration for liver transplantation (LT)
 - Primary graft non-function, as well as mortality (immediate, year 1 and 2) from LT are significantly increased with morbid obesity, which should be considered a contraindication to LT.



- Patients being assessed for LT may have ascites and / or peripheral edema, for which corrections must be made to estimate the potential LT patient's lean body mass (to exclude morbid obesity, and to thereby possibly remove this contraindication to LT).

26. Give the effects of corticosteroids, calcineurin inhibitors (CNI), anti-metabolites and mToRi (mammalian target of rapamycin inhibitors) on hepatic steatosis, weight gain, hypertension, dyslipidemia, and diabetes mellitus (DM).

Drug class	Hepatic steatosis	Weight gain	Systemic hypertension	Dyslipidemia	New onset DM
Corticosteroids	++	++	+	+	++
CNI	-	+	++	++	++
Antimetabolites	-	-	-	-	-
mToRi	-	-	-	+++	+/-

Source: Newsome PN, et al. Gut 2012; 61: 484-500.

27. Give the correction for fluid excess in body mass in liver patients with ascites and peripheral edema.

	Ascites	Ascites / kg	Peripheral edema / kg
○ Minimal		2.2	1
○ Moderate		6	5 (to knees)
○ Severe		≥ 14	10 (to thighs)

Source: Newsome PN, et al. Gut 2012; 61: 484-500.

Tacrolimus is preferred to cyclosporin as the CNI for LT, but it does have a major impact on new onset DM and renal dysfunction; even then blood levels remain in the range of 5 to 8 ng / mL. Mycophenolate permits the use of lower levels of tacrolimus.

mToRi may be used as first-line agent for HCC and as rescue therapy.



Alcoholic Liver Disease (ALD)

- Definition: ALD is a disorder associated with the intake of excessive amounts of alcohol over prolonged periods of time, leading to acute and / or chronic compensated / decompensated liver disease.
- Pathophysiology
 - Metabolizing enzymes
 - ADH (alcohol dehydrogenase)
 - Main enzyme at < 10 mM alcohol
 - CYP2E1 (cytochrome P450 2E1)
 - Main enzyme at > 10 mM alcohol self-inducible (alcohol increases CYP 2E1)
 - Catalase
 - ALDH (aldehyde dehydrogenase)

Alcohol $\xrightarrow{\text{ADH}}$ Acetaldehyde

Acetaldehyde $\xrightarrow{\text{ALDH}}$ Acetate

- Role of acetaldehyde
 - Acetaldehyde forms adduct with reactive residues (oxidatively modified proteins) on proteins or small molecules
 - Antibodies form against these adducts (e.g. MAA [malondialdehyde and acetaldehyde])
- Methionine metabolism
 - Methionine is related upon by MAT (methionine adenosyltransferase) to SAM (S-adenosyl-methionine)
 - SAM usually is acted upon in the transmethylation pathway, forming SAH (S-adenosyl homocysteine)
 - In ALD, there is ↓ MAT and ↓ SAM
 - With SAM and ↓ transmethylation
 - ↓ transmethylation - there is ↓ DNA RNA, histones, biogenic amines, phospholipids



- SAH (s-adenosyl histone)
 - ↑ SAH and ↓ SAM / SAH ratio --→ ↓ transmethylation reactions → ↓ SAM
 - ↓ SAM →
 - ↓ glutathione in mitochondria --→ mitochondria dysfunction
 - ↑ LPS (lipopolysaccharide)
 - Stimulated release of TNF
 - ↑ IL-10 from monocytic cells
 - ↑ homocysteine, ↑ SAH
 - ↑ SAH and ↑ homocysteine
 - ↑ hepatocyte sensitivity to TNF-mediated destruction
 - ↑ hepatocyte sensitization from
 - ↓ glutathione in mitochondria
 - ↑ SAH
 - ↓ proteasomes
 - ↓ THF, ↓ methionine
 - Alcohol ↓ folic acid absorption and metabolism, including
 - ↓ 5-mTHF (5-methyltetrahydrofolate [THF])
- Hypoxia
 - Alcohol
 - ↑ O₂ uptake by liver
 - ↑ lobular O₂ gradient
 - ↑ NADH / NAD⁺ --→ ↑ HIF (hypoxia-inducible factor) 1 and 2 genes
 - When alcohol ↓, HIF ↓
 - Reperfusion injury, especially in centrilobular area
- Mitochondria dysfunction
 - ↑ TNF impairs function of mitochondria
 - ↑ NADH/NAD⁺ ---→ ↑ generation of superoxide
 - In ALD, ↓ transport of glutathione into mitochondria
 - Glutathione-depleted mitochondria -→ ↑ sensitive to damage by TNF
 - ↑ depolarization leads to
 - ↑ membrane permeability
 - ↑ apoptosis of hepatocytes
- Redox state (oxidative-reduction state)
 - Alcohol --→ ↑ CYP 2E1 --→ leaking of electrons --→ ↑ oxidative stress
 - ↓ ATP



- ↓ metabolism of
 - Carbohydrate
 - Fat (e.g. steatosis)
 - ↑ oxidants: ↑ ROS (reactive oxygen species), ↑ RNS (reactive nitrogen species), ↑ oxidative stress
 - ↓ antioxidants
 - ↑ cell injury
 - ↑ membrane lipid peroxidation
 - ↑ protein and DNA oxidation
 - ↑ NF-κB (nuclear factor kappa B) → ↑ TNF
- Dysregulated proteasome system
 - ↓ removal of proteins damaged by oxidative stress
- Dysregulated cytokines production
 - Hepatocytes
 - IL-8, IL-18
 - Neutrophil chemotactic peptide
 - Angiogenesis factor
 - Kupffer cells
 - NF-κB → TNF-α
 - IL-10
 - Sinusoidal endothelial cells
 - Adhesion molecules
 - Stellate cells
 - TGF-β → fibrosis
 - ↑ intestinal permeability → ↑ LPS
 - ↑ apoptosis of hepatocytes → ↑ release of IL-8 (neutrophil chemoattractant), IL-18 (primes TNFα release, and type 1 helper T cell response)
 - ↑ TNF-α inducible IL-6, IL-8, IL-18, MCP-1 (monocyte chemoattractant protein 1)
 - As well as ↑ pro-inflammatory cytokines, there is ↓ anti-inflammatory cytokines
- Apoptosis

“hepatocyte apoptosis may sustain proinflammatory cytokine production and cell injury or death” (Feldman M., et al. Sleisenger and Fordtran’s Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier, Philadelphia, 2010, page 1387).



- Autoimmune changes
 - Mutation in CTLA-4G (cytotoxic T lymphocyte-associated antigen 4G) allele activates T cell function
 - Hydroxyethyl radical from breakdown of alcohol modifies CYP 2E1
 - Modifies CYP2E1 plus CTLA-4G mutation → ↑ anti-CYP2E1 autoantibodies
 - Activation of HSC and Hepatic Fibrosis

SO YOU WANT TO BE A HEPATOLOGIST!

Women are at greater risk than men in developing alcohol-related liver injury, and for this injury to progress faster to more severe forms of ALD. “Although rates of metabolism and elimination of alcohol have been reported to be more rapid in women than men, when adjusted for liver volume, elimination rates are similar between genders” (Feldman M., et al. Sleisenger and Fordtran’s Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier, Philadelphia, 2010, page 1388).

- Give 4 factors which are increased in women as compared to men may explain the greater risk of ALD in women than in men.
 - LPS (endotoxemia)
 - Lipid peroxidation
 - Monocyte chemotactic protein mRNA
 - NF-kB activation
 - Polymorphism in the promoter regions of TNF- α and IL-10

➤ Pathology

- Steatosis
 - Centrilobular
 - Perivenular
 - Microvesicular
 - If combination of macro- plus microvesicular, then there is an ↑ risk of cirrhosis
- Ballooning degeneration
- Mallory bodies in damaged hepatocytes
- Necroinflammatory reaction around damaged
 - Polymorphonuclear leukocytes



- Central vein
 - Sclerosing hyaline necrosis
- Micronodular fibrosis, perisinusoidal
 - Macronodular cirrhosis
- Hepatic siderosis occurs in ~20% of ALD patients
- Conditions which may mimic ALD
 - NAFLD (non-alcoholic fatty liver disease)
 - HH (hereditary hemochromatosis)
 - BCS (Budd-Chiari syndrome)
 - Amiodarone hepatotoxicity

28. Compare and contrast viral hepatitis and alcoholic hepatitis based on histology and physical, 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, florid stigmata
○ Laboratory tests	AST variable	AST < 300
○ 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 -

“Try not to become a man of success but a man of value.”

Albert Einstein



➤ Clinical Prognosis

29. Give the 5 year survival rates of alcoholic liver disease.

5 year survival rates	
Overall	50%
Steatosis	75%
Hepatitis	50%
Cirrhosis plus hepatitis	35%

Alcohol hepatitis	One-month MR
- Alcohol hepatitis plus HE	50%
- Alcohol hepatitis plus HRS	75%

Abbreviations: HE, hepatic encephalopathy; HRS, hepatorenal syndrome; MR, mortality rate

Alcoholic cirrhosis	CTP score	5 year survival rate
- Compensated	5-7	60%
- Decompensated	Ascites	
	Variceal bleeding	
	HE	~20%
	SBP	~50%
	HRS	Median, < 2 weeks

○ Abstinence

After hospital admission for ALD	2 year survival rate
- Abstinence	~ 75%
- No abstinence	~25%

Abbreviations: Child / Child-Pugh Classification; Child-Turcotte-Pugh (CTP) score



30. Give 3 **prognostic scoring systems** used for patients with alcoholic hepatitis (AH), the components used to calculate the scores, and the value of the score which reflects a poor prognosis.

Name of prognostic test	Components		Poor prognosis score
MADDREY Score MDF, modified Maddrey discriminant function	MDF = 4.6 (patients PT – control PT) + total bilirubin (mg / dL)		≥ 32
MELD score*	MELD score = 3.8 log _e (bilirubin (mg / dL) + 11.2 log _e (INR) + 9.6 log _e (creatinine) mg / dL		> 18
	1	2	3
Age	< 50	≥ 50	-
WBC	< 15	≥ 15	
Urea (mmol / L)	< 15	≥ 5	-
PT ratio	< 15	1.5 – 2.0	> 2
Bilirubin	< 7.3	7.3 – 14.6	> 14.6

> 8 (day 1 or 7)

*MELD, Model for End-Stage Liver Disease, available online calculator: www.mayoclinic.org/meld/mayomodel7.html

Source: O'Shea RS, et al. Alcoholic liver disease. Hepatology. 2010;51(1):307-28

- Conditions which may accelerate progression of ALD
 - HCV
 - Look for focal lymphoid aggregates
 - Portal inflammation
 - Periportal or bridging fibrosis
 - HCV + ALD have 10x ↑ risk of cirrhosis, and ↑ risk of HCC
 - Obesity
 - Smoking



SO YOU WANT TO BE A HEPATOLOGIST!

A male alcoholic with cirrhosis develops feminization.

- Give the mechanisms responsible for the shift of sex hormones from androgens to estrogens.
 - ↑ SHBG (sex hormone binding globulin) →
 - ↑ bound testosterone (T) ↓ free T
 - ↓ bound estrogen (E), ↑ free E
 - ↓ production of dehydroepiandrosterone → ↓ production of testosterone
 - Alcohol toxicity
 - On Leydig cells
 - On hypothalamic-pituitary-gonadal axis
 - ↓ LH (luteinizing hormone)
 - ↓ responsiveness to GRH (gonadotropin-releasing hormone)

On the basis of your knowledge of disordered coagulation and the balance between pro- and anticoagulant factors which develop in patients with cirrhosis.

- Give possible criticisms to the inclusion of the INR in the calculation of the MELD score.
 - Interlaboratory variability
 - The substantial interlaboratory variability with use of the standard international sensitivity index (ISI) to normalize varying sensitivities of thromboplastin reagents
 - This variability may result in as much as 25% difference in mean INR for a single patient sample assayed with different reagents”

➤ Laboratory

31. Give 8 laboratory abnormalities commonly seen in persons with alcoholic hepatitis.

➤ Hematology

- Macrocytic anemia (increased MCV)
- ↑ WBC
- ↓ platelets



➤ General chemistry

- ↑ blood sugar
- ↑ uric acid
- ↑ triglycerides
- Ketosis

➤ Tests of liver function and injury

- ↓albumin
- ↑ bilirubin
- ↑ INR
- ↑ AST/ALT (ratio of 1.5 to 2.5 and total increase <10-fold)
- ↑ GGT
- ↑ alkaline phosphatase (mild)

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ -glutamyltransferase; MCV, mean corpuscular volume.

Printed with permission: Shah VH. *Mayo Clinic Gastroenterology and Hepatology Board Review* 2008: pg. 331.

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- Give the performance characteristics of other laboratory blood tests used to assess the risk of alcohol abuse.

Test	Sensitivity	Specificity
ALT	50%	87%
AST	47%	95%
CDT	63%	98%
GGT	58%	99%
GGT + CDT	90%	98%
MCV	45%	94%

Abbreviation: CDT, carbohydrate-deficient transferrin



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The most sensitive and specific tests for recent alcohol use in the concentration of alcohol in the blood, urine, or breath.

- Give the disadvantage of using these measurements to prove recent alcohol take, and indicate how this has been addressed.
 - The concentration of alcohol in blood, urine or breath is influenced by the short half-life of alcohol in this body pools.
 - Biomarkers of recent alcohol abuse may have a longer $T_{1/2}$, and thereby overcome the short half-life of alcohol
 - The most specific of these markers is CDT (carbohydrate-deficient transferrin)
 - The specificity of CDT increases markedly when CDT is combined with the measurement of GGTP.

➤ Treatment

32. Give 8 treatments for ALD (not specifically acute alcoholic hepatitis) which have proven to be of benefit.
- Risk assessment
 - MDF score
 - MELD score
 - Alcoholism itself, when treated by abstinence, improves survival
 - Abstinence
 - Baclofen (GABA [gamma aminobutyric acid] agonist), naloxone
 - Smoking cessation
 - Obesity reduction
 - Malnutrition (protein / calorie)
 - Aggressive nutritional support
 - Enteral nutrition
 - Glucocorticosteroids for DF > 32, and with no
 - GI bleeding needing blood transfusion
 - Active infection
 - Hepatorenal syndrome



- Pentoxifylline
 - Non-selective phosphodiesterase inhibitor
 - ↑ cAMP and ↑ cGMP
 - ↓ TNF production
 - May be used when renal function is poor, and steroids cannot be used
- Anti-TNF therapy
- SAM (s-adenosylmethionine)
 - Antioxidant
 - ↓ TNF
 - Methyl donor
 - ↑ glutathione
 - Maintains mitochondrial function
- Liver transplantation
 - Some centres report lower rates, especially in those who continue to drink or smoke (↑ risk of post-operative cancer of pharynx, esophagus, stomach)
- RCT's and meta-analyses support the utility of steroids in patients with alcoholic hepatitis and discriminant function (DF)>32, or in those with hepatic encephalopathy; one study has shown a benefit at one year, but patients with infection or GI bleeding should be excluded (Shah V. Alcoholic hepatitis: are we back to prednisone? *ACG Annual Scientific Meeting Symposia Sessions* 2009:64-66.)
- Preventative care
 - Screening for HCC and for ; non-liver cancers
 - Vaccination
 - Standard nutritional guidelines

Autoimmune Hepatitis (AIH)

- Definition: "AIH is a disorder of unknown cause characterized by unresolving inflammation of the liver and by the presence of interface [limiting plate of the portal tract is disrupted by a lymphoplasmacytic infiltrate] on histologic examination, ... hypergammaglobulinemia" (Feldman M., et al. *Sleisenger and Fordtran's Gastrointestinal and Liver Disease*. 9th Edition. Saunders/Elsevier, Philadelphia, 2010, page 1461), and autoantibodies".
- Demography
 - Varies world-wide
 - In North America, incidence ~ 2/10⁵ / year; prevalence ~ 17/10⁵



SO YOU WANT TO BE A HEPATOLOGIST!

- Give the comparison of non-hereditary versus hereditary AIH (aka APECED*)

Feature	Non-hereditary	Hereditary
➤ Gender effect	F > M	F = M
➤ Gene mutation	No	Single-gene mutation of AIRE (autoimmune regulator), autosomal recessive, complete gene penetrance
➤ HLA predisposition	HLA-DR3 (DRB1*0304)	No
➤ Response to therapy	65% achieve remission within 3 years; therapy improves 10-year survival rate to 93%	Poor

Abbreviation: APECED, autoimmune polyendocrinopathycandidiasis – ectodermal dystrophy

➤ Pathophysiology

33. Give the pathophysiology of primary / idiopathic AIH.

- Unknown and possible environment antigenic peptide (molecular mimicry) --> inciting antigen fits in the antigen-binding groove of the class II DR molecule of the MHC antigen presenting cells (in USA / Canada, DRB1 gene, susceptibility alleles DRB1*0301 and DRB1*0401)
- The DR molecule-antigen complex of the APC (antigen-presenting cell) interacts with the antigen receptor of CD4+ T-helper cells (1st signal).
- The CD28 molecule on the surface of CD4+ t-helper cell binds to the B7 ligand on the surface of the APC” (2nd signal) (Feldman M., et al. Sleisenger and Fordtran’s Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier, Philadelphia, 2010, page 1464).
- CD4+ T-helper cells differentiate into Th1 or Th2 T-cells



- The cytokine milieu of Th1 and Th2 cytokines is regulated
- This balance between Th1 and Th2 may be disturbed by
 - ↓ NKT (intrahepatic natural killer T cells)
 - ↓ regulation of CD8+ T cell proliferation by
 - T-reg (T-regulatory CD4+ CD25+) cells
- Hepatocyte damage is caused by
 - Cell-mediated cytotoxicity (regulated by type 1 cytokines), or
 - Antibody-dependent cell-mediated cytotoxicity (regulated by type 2 cytokines), or by
 - Both mechanisms
- Th1 (type 1 cytokine) pathway of activated CD4+ t-helper cells is stimulated by polymorphism of
 - TNF A*2 (TNF gene)
 - TNF receptor superfamily gene (FAS)
 - CTLA4 (the cytotoxic T lymphocyte antigen 4 gene)
 - TNFRSF6 (FAS gene phenotype at position – 670)
- These polymorphisms and Th1 T-cells
 - Sensitize cytotoxic T cells
 - ↑ cell-mediated cytotoxicity
 - ↑ apoptosis of hepatocytes
- The cytokine pathways are increase by ↓ activity of T-reg (T-regulatory) cells
- Th2 (type 2 cytokine) pathway of activated CD4+ T-helper cells causes differentiation of B cells into plasma cells
 - Plasma cells → ↑ production of immunoglobulin
 - Immunoglobulins → antibody-mediated cellular toxicity

“An alcoholic is a person who drinks more than his
physician!”

Don't believe it: TRUST, BUT VERIFY.

Grandad



SO YOU WANT TO BE A HEPATOLOGIST!

Persons with drug-associated AIH (autoimmune hepatitis) closely resembles non-drug associated AIH, including the presence of antinuclear anti-smooth muscle antibodies.

- Apart from the historical aspects of time-associated clinical or laboratory changes, give the clues in an individual patient that the AIH is drug-associated.
 - Drug-associated AIH is not associated with
 - History of other autoimmune diseases
 - HLA-B8 and HLA-DR ws alleles

SO, IF YOU HAVEN'T GIVEN UP AND THROWN IN THE TOWEL, AND YOU STILL WANT TO BE A SUPER-STAR HEPATOLOGIST!

- Give the 3 infectious agents which have homology with epitopes of CYP2D6, and are recognized by anti-LKM1.

Organisms showing molecular mimicry / molecular footprint / share motif with anti-LKM1 include

- HCV
- CMV
- HSV

This is outrageous; why would any sober person in their right mind need to know these molecular mimicries?

What does “Das Book” (Feldman M., et al. Sleisenger and Fordtran’s Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier, Philadelphia, 2010) say? – “these molecular mimicries may result in cross-reactivity antibodies and support the hypothesis that repeated viral infections may break self-tolerance and cause disease”.

34. List 5 prescription **medications**, OTC preparations or herbs which may induce or unmask an AIH-like syndrome.

- Antibiotics
 - Minocycline
 - Nitrofurantoin



- Rifampin
- Interferon
- INH
- Metabolic
 - Orlistat
 - Statins
 - Propyl thiouracil
- Antihypertensives
 - Alpha methyldopa
- Herbs
 - St. John's Wort
 - Chaparral leaf
 - Black cohosh
- Immune
 - Anti-TNF therapy

Abbreviation: OTC, over-the-counter

Printed with permission: Heathcote EJ. *2007 AGA Institute Spring Postgraduate Course Syllabus*: 96.

➤ Clinical

- I (F, 50) ANA+ ASM+ IgG↑
- II (children) ALKMI+

➤ Types/ laboratory

35. Give a classification of autoimmune hepatitis (AIH) based on autoantibody profiles of patients

- Type 1 AIH
 - Sudden onset of symptoms in 40%, including fulminant hepatic failure



- 38% have associate “autoimmune” disorders
- F:M ratio of 3.6:1
- Usual age of presentation, 50 years
- Serum antibodies
 - ANA (anti-nuclear antibody)
 - SMA (smooth muscle antibodies)
 - ANA plus SMA
 - Anti-actin
 - PANCA (perinuclear anti-neutrophil cytoplasmic antibodies; aka ANNA, anti-neutrophil nuclear antigens)
 - ↑ IgG
- Type 2 AIH
 - Usually diagnosed in children aged 2 to 4 years positive for anti-LKM1 (liver-kidney microsome) 1 expression of anti-LKM1 is associated with DB1*07 anti-LKM1 reduce the activity of CYP2D6
- Type 3 (M, 30) ASLA/LP+
- Overlap syndrome AMA-neg. PBC, PSC, AMA-

Adapted from: Czaja AJ. *Sleisenger and Fordtran’s Gastrointestinal and Liver Disease* 2006. pg. 1872-1875; and 2010, pg. 1467.

In Germany, 20% of AIH type 2 occur in adults. Please see Feldman M., et al. *Sleisenger and Fordtran’s Gastrointestinal and Liver Disease*. 9th Edition. Saunders/Elsevier, Philadelphia, 2010, Table 88.3, page 1464, “Classification of Autoimmune Hepatitis Based on Autoantibodies”.

Feature	Type 1 AIH	Type 2 AIH
○ Characteristic autoantibodies	ANA ASMA Anti-actin antibody Anti-SLA/LP antibodies 25% of patients ANA negative	Anti-LKM-1 antibody Anti-LC-1 antibody
○ Geographical	Worldwide	Worldwide



Feature	Type 1 AIH	Type 2 AIH
variation		
○ Age at presentation	All ages	Usually childhood and young adulthood
○ Sex (F:M)	3:1	10:1
○ Clinical phenotype	Variable	Generally severe
○ Histopathological features at presentation	Broad range: mild disease to cirrhosis	Generally advanced, ↑ inflammation/cirrhosis common
○ Treatment failure	Rare	Common
○ Relapse after drug withdrawal	Variable	Common
○ Need for long-term maintenance	Variable	Approximately 100%
○ Note: Although immunofluorescence is the traditional method for measuring the repertoire of conventional autoantibodies in AIH, many laboratories (especially those in the USA) are increasingly using ELISA-based methods, especially for anti-LKM antibodies.		
– In relation to anti-LKM-1 antibodies, these may be erroneously reported as detectable anti-mitochondrial antibodies.		

Abbreviations: ANA, antinuclear antibody; ASMA, anti-smooth muscle antibody; anti-LC, anti-liver cytosol; anti-LKM, liver kidney microsomal antibody; anti-SLA/LP, soluble liver antigen/liver pancreas antigen.

Printed with permission: Gleeson D, Heneghan MA; British Society of Gastroenterology. British Society of Gastroenterology (BSG) guidelines for management of autoimmune hepatitis. Gut. 2011;60(12):1611-29, Table2.

Please see: Swan MG. Chapter 58. In: Therapeutic Choices. Grey J, Ed. 6th Edition, Canadian Pharmacists Association: Ottawa, ON, 2011, Table 5: Autoimmune Hepatitis, page 778.

➤ Clinical Course

- Asymptomatic ~ 40% (70% later become symptomatic)
- Spontaneous resolution ~ 15%



- Compensated cirrhosis ~ 40%
- Esophageal varices (EV) ~ 55%

36. Give 5 **clinical presentations** of AIH.

- Acute hepatitis
- Fulminant hepatitis
- Asymptomatic chronic hepatitis +/- cirrhosis
- Symptomatic chronic hepatitis +/- cirrhosis
- “Burned out” decompensated cirrhosis +/-
- *De novo* or recurrent AIH after liver transplantation (alloimmune)
- AIH with overlapping PBC/PSC/AMA-neg PBC
- Suspected from liver disease associated with other conditions
- HCC

37. Give 15 **immune diseases/disorders** which are associated with AIH.

○ Skin, eye	– Iritis – Gingivitis – Dermatitis herpetiformis – Erythema nodosum – Lichen planus – Pyoderma gangrenosum
○ CNS/PNS	– Peripheral neuropathy – Myasthenia gravis
○ Thyroid	– Autoimmune thyroiditis – Graves’ disease*
○ Heart, lung	– Pleuritis – Fibrosing alveolitis – Pericarditis
○ Pancreas	– Insulin-dependent diabetes – Autoimmune pancreatitis
○ Gut, liver	– Celiac disease – Ulcerative colitis – Autoimmune sclerosing cholangitis – Pernicious anemia (PA) – Autoimmune cholangitis (PSC)



- Kidney
 - Glomerulonephritis (immune complex)
- Blood
 - Coombs- positive hemolytic anemia
 - Cryoglobulinemia
 - Idiopathic thrombocytopenic purpura (ITP)
 - Pernicious anemia + ITP (Evan syndrome)
 - Neutropenia
- MSK
 - Rheumatoid arthritis
 - Sjögren's syndrome
 - Synovitis
 - Systemic lupus erythematosus
 - Focal myositis

Printed with permission: Czaja AJ. *Mayo Clinic Gastroenterology and Hepatology Board Review* 2008: pg. 398.

Clinical Cautions

- The presence of symptoms of AIH does not reflect the hepatic histology – “histological findings, including the frequency of cirrhosis, are similar in asymptomatic and symptomatic patients.....”
- “the asymptomatic state does not preclude the need for glucocorticoid therapy if other objective manifestations of disease activity are present or emerge, and close surveillance of these patients for worsening inflammation is justified”.
- Untreated asymptomatic mild AIH still progress, and there are no clinical indices that predict the course of the disease”.

(Feldman M., et al. *Sleisenger and Fordtran's Gastrointestinal and Liver Disease*. 9th Edition. Saunders/Elsevier, Philadelphia, 2010, page 1471).

➤ Diagnosis

- The diagnosis of AIH is based on exclusion and probabilities expressed through the use of scoring systems.
- Other causes of chronic liver disease with similar features need to be excluded, including conditions which overlap with AIH (PBC, PSC, AIH with cholestatic features, autoantibody-negative AIH).
- There are scoring systems which may be used to assist in making a definite or a probable diagnosis: please see Feldman M., et al. *Sleisenger and Fordtran's Gastrointestinal and Liver Disease*. 9th Edition. Saunders/Elsevier, Philadelphia, 2010, Table 88.1, page 1463,

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“Revised Original Scoring system for the Diagnosis of Autoimmune Hepatitis”, and Table 88.2, “Simplified Scoring System for Diagnosis of Autoimmune Hepatitis”

38. Give the **definite and probable criteria** for the diagnosis of AIH

Definite AIH	Probable AIH
➤ Exclude other causes of chronic liver disease ○ Normal AAT phenotype ○ Normal ceruloplasmin level ○ Normal iron and ferritin levels ○ No active hepatitis A, B, or C infection ○ Daily alcohol <25 g ○ No recent hepatotoxic drugs ○ Predominant serum aminotransferase abnormality ➤ Suggestive lab' tests ○ Globulin, γ-globulin, or IgG level ≥ 1.5 times normal ○ ANA, SMA, or anti-LKM1 $\geq 1:80$ in adults and $\geq 1:20$ in children; no AMA ➤ Liver biopsy ○ Interface hepatitis—moderate to severe ○ No biliary lesions, granulomas, or prominent changes suggestive of another liver disease	○ Partial AAT deficiency ○ Abnormal copper or ceruloplasmin level but Wilson disease excluded ○ Nonspecific iron or ferritin abnormalities ○ No active hepatitis A, B, or C infection ○ Daily alcohol <50 g ○ No recent hepatotoxic drugs ○ Predominant serum aminotransferase abnormality ○ Hypergammaglobulinemia of any degree ○ ANA, SMA, or anti-LKM1 $\geq 1:40$ in adults; other autoantibodies ○ Interface hepatitis—moderate to severe ○ No biliary lesions, granulomas, or prominent changes suggestive of another disease

Printed with permission: Czaja AJ. *Mayo Clinic Gastroenterology and Hepatology Board Review* 2008: pg. 392.

- **Simplified scoring system** for diagnosis of autoimmune hepatitis



Category	Variable	Score
➤ Autoantibodies		
○ Antinuclear antibodies (ANA)	- 1:40	+1
	- >1:80	+2
○ Smooth muscle antibodies	- >1:40	+2
○ Antibodies to liver kidney microsome type 1		
○ Antibodies to soluble liver antigen	- Positive	+2
➤ Immunoglobulin level		
○ Immunoglobulin G	- >Upper limit of normal	+1
	- >1.1 times upper limit of normal	+2
➤ Histologic findings		
○ Morphologic features	- Compatible with autoimmune hepatitis	+1
	- Typical of autoimmune hepatitis	+2
➤ Viral disease		
○ Absence of viral hepatitis	- No viral markers	+2
➤ Pre-treatment aggregate score		
○ Definite diagnosis		>7
○ Probable diagnosis		6

Adapted from: Hennes EM, Zeniya M, Czaja AJ, et al. Simplified diagnostic criteria for autoimmune hepatitis. *Hepatology* 2008;48:169-76.

"It's not your perfection that makes you an angel;
it's your intention."

Alberto Agraso and Mony Dojeiji



Clinical Words of Wisdom – the need for liver biopsies in AIH

- “evaluation of liver tissue [doing a liver biopsy] before drug withdrawal is essential to establish remission because histologic activity may be present in 55% of patients who satisfy other requirements for remission”.
- “...histological improvement lags behind clinical and histologic resolution by three to eight months.....”
- “.....complete resolution of the clinical and histological manifestations of the disease [AIH] does not preclude relapse after drug withdrawal”
(Feldman M., et al. Sleisenger and Fordtran’s Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier, Philadelphia, 2010, page 1473).

- Revised original scoring system for the diagnosis of autoimmune hepatitis

Category	Variable	Score
➤ Gender	○ Female	+2
➤ AP/AST	○ >3	-2
	○ <1.5	+2
➤ Gamma globulin or IgG level above normal	○ >2.0	+3
	○ 1.5-2.0	+2
	○ 1.0-1.5	+1
	○ >1.0	0
➤ ANA, SMA, or anti-LKM1 titer	○ >1:80	+3
	○ 1:80	+2
	○ 1:40	+1
	○ <1:40	0
➤ AMA	○ Positive	-4
➤ Viral markers	○ Positive	-3
	○ Negative	+3
➤ Drug history	○ Yes	-4
	○ No	+1
➤ Alcohol	○ <25 g/day	+2
	○ >60 g/day	-2
➤ HLA	○ DR3 or DR4	+1



Category	Variable	Score
➤ Immune disease	○ Thyroiditis, ulcerative colitis, synovitis, others	+2
➤ Other liver define autoantibodies	○ Anti SLA, anti actin, anti LC1, Panca	+2
➤ Histologic features	○ Interface hepatitis	+3
	○ Plasmacytic infiltrate	+1
	○ Rosettes	+1
	○ None of above	-5
	○ Biliary changes	-3
	○ Other features	-3
➤ Treatment response	○ Complete	+2
	○ Relapse	+3
➤ Pre-treatment score		
○ Definite diagnosis	>15	
○ Probable diagnosis	10-15	
➤ Post treatment score		
○ Definite diagnosis	>17	
○ Probable diagnosis	12-17	

Adapted from: Alvarez F, Berg PA, Bianchi FB, et al. International Autoimmune Hepatitis Group report: Review of criteria for diagnosis of autoimmune hepatitis. *J Hepatol* 1999; 31: 929-38.

➤ Prognosis

Factors associated with clinically significant **endpoints** in autoimmune hepatitis (AIH)

Endpoint	Relapse (off treatment)	Progressive fibrosis or development of cirrhosis	Liver-related death or transplantation
○ Frequency	50–90%	10–50%	10–20%
○ Factors			
- At presentation	Long symptom duration	Low serum albumin and coagulopathy	Females
	High serum globulin	Confluent necrosis on biopsy	African-American men
	LKM antibody positive		Type 2 AIH and SLA positive AIH
	SLA/LP positive or no immune markers		Cirrhosis



Endpoint	Relapse (off treatment)	Progressive fibrosis or development of cirrhosis	Liver-related death or transplantation
○ Frequency	50–90%	10–50%	10–20% Confluent necrosis
○ On treatment	Short treatment duration Long time to remission	Persistent AST elevation (failure of AST to halve in 6 months) Failure to achieve remission over 2 years Persistent inflammation on liver biopsy	Poor response, long time to achieve remission, persistent serum AST elevation
○ Pretreatment withdrawal	Raised serum ALT or AST Raised serum globulin IgG Liver biopsy with any inflammation, or with portal tract plasma cells		
○ Subsequently		Multiple relapses	Multiple relapses Development of cirrhosis

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; LKM-1, liver kidney microsomal-1 antibody; SLA/LP, soluble liver antigen/liver pancreas antigen.

Printed with permission: Gleeson D, Heneghan MA; British Society of Gastroenterology. British Society of Gastroenterology (BSG) guidelines for management of autoimmune hepatitis. Gut. 2011;60(12):1611-29, Table 6.

➤ Treatment

Tricks or Treats

In patients with AIH (autoimmune hepatitis), if they are HLA-Dr3 positive, their therapeutic response may be lower.



Useful background: New predictors of response to treat in autoimmune hepatitis type 1

- Low levels of anti- α -actinin at baseline are independent predictors of response.
- Autoantibodies against filamentous-actin and α -actinin.
- Can be used as predictors of response to treatment in patients with AIH 1

Please see Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier, Philadelphia, 2010, Table 88.4, page 1467, for a summary of the 4 "Variant Forms of Autoimmune Hepatitis".

Useful background: The Mayo Clinic **treatment schedules** for adults with severe autoimmune hepatitis

Treatment duration (weeks)	Combination therapy		Prednisone monotherapy (mg daily)
	Prednisone (mg daily)	Azathioprine (mg daily)	
1	30	50	60
1	20	50	40
2	15	50	30
Maintenance until end point	10	50	20

Printed with permission: Loza AJM, and Czaja AJ. *Nature Clinical Practice Gastroenterology & Hepatology* 2007; 4(4): pg. 204.

Useful background: For patients with AIH, the first and second choice conventional and empiric treatments, as well as the third and fourth choice possible empiric treatments for suboptimal responses to firstline treatment

Clinical event	Conventional treatments		Possible empiric treatments	
	<u>1st choice</u>	<u>2nd choice</u>	<u>3rd choice</u>	<u>4th choice</u>
○ Treatment failure	Prednisone (30 mg daily) and Azathioprine (150 mg daily), or prednisone alone (60 mg daily)	Prednisone (30 mg daily) Plus Mercaptopurine (1.5 mg/kg body weight daily)	Cyclosporin (5-6 mg/kg body weight daily) or prednisone (30 mg daily) plus Mycophenolate mofetil (2 g daily)	Tacrolimus (4 mg twice daily)



	<u>1st choice</u>	<u>2nd choice</u>	<u>3rd choice</u>	<u>4th choice</u>
○ Drug toxicity	Azathioprine (2 mg/kg body weight daily) if prednisone intolerant	Prednisone (20 mg daily) if Azathioprine intolerant	Budesonide (3 mg twice daily)	UDCA (13-15 mg/kg body weight daily)
○ Incomplete response	Prednisone maintenance ($\leq$ 10 mg daily) if serum AST level < three times normal value	Azathioprine maintenance (2 mg/kg body weight daily) if serum AST level < threetimes normal value)	Budesonide Maintenance (3 mg twice daily)	UDCA Maintenance (13-15 mg/kg body weight daily)
○ Relapse	Azathioprine maintenance (2 mg/kg body weight daily) if serum AST level <three times normal value	Prednisone Maintenance reduced to ($\leq$ 10 mg daily) if serum AST level <three times normal value	Mycophenolate mofetil maintenance (2 g daily)	Cyclosporin Maintenance (5-6 mg/kg body weight daily)

Abbreviations: AST, aspartate aminotransferase; UDCA, ursodeoxycholic acid

Printed with permission: Loza A, et al. *Nature Clinical Practice Gastroenterology & Hepatology* 2007; 4(4): pg. 206.

➤ Therapy: continue steroids until

- Remission
 - “.....absence of symptoms, resolution of all laboratory indices of active inflammation and histologic improvement of normal liver tissue or inactive cirrhosis” ((Feldman M., et al. *Sleisenger and Fordtran’s Gastrointestinal and Liver Disease*. 9th Edition. Saunders/Elsevier, Philadelphia, 2010, page 1473).
- Treatment failure
 - “worsening of the serum AST or bilirubin levels by at least 67% of previous values, progressive histological activity, or onset of ascites or encephalopathy”
- Incomplete response: “...improvement that is insufficient to satisfy remission criteria” (Feldman M., et al. *Sleisenger and Fordtran’s*



Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier, Philadelphia, 2010, page 1474).

- Drug toxicity
 - Relapse
 - Occurs in 50% in 6 months
 - ~ 75% in 3 years
 - Defined as “... the reappearance of histologic disease after discontinuation of drug therapy” after previous achieved remission
 - Rational for maintenance therapy: repeated relapse and re-treatment leads to
 - ↑ cirrhosis
 - ↑ hepatic failure
 - ↑ need for liver transplantation
 - ↑ drug adverse effects
 - ↑ mortality
39. Give the difference in the treatment of AMA-positive and –negative AIH (autoimmune hepatitis)
- AIH  PBC in 10% to 15%, causing 2 overlap syndromes
 - AMA-positive AIH steroids, azathioprine (treat as per guideline for AIH, type I; may also be ANA-positive)
 - AMA- negative PBC steroids, UDCA (ursodeoxycholic acid) (aka autoimmune cholangiopathy)

Please see: Swan MG. Chapter 58. In: Therapeutic Choices. Grey J, Ed. 6th Edition, Canadian Pharmacists Association: Ottawa, ON, 2011, Table 3: Hepatic Encephalopathy, page 775.

- Liver transplantation

Clinical Tip – Early Failure of Treatment and Need for Liver Transplantation.

- Profile of patient with needs to be considered early for liver transplantation include:
 - Decompensated patients with biopsy evidence of multilobular necrosis, in whom
 - Hyperbilirubinemia does not improve, and
 - At least one other lab test does not return to normal



➤ **AIH overlap (variant) syndromes**

- About 10% of persons with AIH also have HCV infection, and about half of HCV patients have features suggestive of AIH, such as
 - Autoantibodies
 - Other immune diseases, or
 - Both of above
- The treatment of AIH will affect the HCV, and vice versa. Treatment is usually focused on the predominant component, AIH or HCV.
- It is often best to first treat the AIH, because the interferon used in the treatment of HCV would worsen the AIH.
- AIH plus PBC
 - Low titres of PBC-specific M2 mitochondrial antigens
 - AMA may come and go in 18% of persons with AIH
- AIH plus PSC / PSC in adults, 41% of AIH who have
 - Cholestatic 'la' findings
 - Associated IBD (especially UC)
 - Failure to respond to steroids
 - Have cholangiographic changes of PSC
 - 54% of persons with PSC have features supporting a diagnosis of AIH (definite, or probable)
 - The duct changes in AIH plus PSC may be only in the small ducts ("small duct PSC")
 - In children with AIH
 - Large duct small duct PSC
 - AMI-positive PBC
 - AMA-negative PBC
 - Autoimmune cholangitis
- Autoantibody negative AIH
 - No antibodies, but
 - Usually abnormal
 - HLA (HLA-D3 or DR4)
 - Interface hepatitis



40. Give the features which help to distinguish between autoimmune predominant AIH, or AIH plus HCV (HCV predominant).

Feature	AIH predominant	HCV predominant
○ Associated diseases	- “autoimmune” disorders in 38%	“immune complex”
○ Autoantibodies	- Multiple	One
○ Symptomatic cryoglobulinemia	- Rare	Common
○ AST, IgG	↑↑	↑
○ Histology**	- Panacinar hepatitis - Interface hepatitis - Portal plasma cells	- Steatosis - Portal lymphoid aggregates
○ Immune complex disorders	- Vasculitis - Glomerulonephritis	

41. Give the treatments of the **variant syndromes** of AIH.

Variant syndrome	Salient features	Empiric treatment strategies
➤ AIH and primary biliary cirrhosis (PBC)	○ AMA positivity ○ Cholestatic and hepatitic tests ○ Increased serum IgM and IgG levels	○ Corticosteroids if serum ALP is $\leq$ twice ULN ○ Add ursodeoxycholic acid (UDCA) if serum ALP is $>$ twice ULN and/or florid duct lesions in liver tissue
➤ AIH and primary sclerosing cholangitis (PSC)	○ Ulcerative colitis ○ Pruritus ○ Cholestatic and hepatic tests ○ ALP:AST$>$1.5	○ Corticosteroids



Variant syndrome	Salient features	Empiric treatment strategies
➤ AIH and cholangitis (possibly AMA-negative biliary sclerosis)	○ Abnormal cholangiogram ○ Fatigue ○ Pruritus ○ Cholestatic and hepatitic tests ○ AMA negative ○ ANA and/or SMA positive ○ Normal cholangiogram	○ Prednisone, ursodeoxycholic acid, or both, depending on hepatic and cholestatic components

Abbreviations: ALP, Alkaline phosphatase; AMA, antimitochondrial antibodies; ANA, antinuclear antibodies; AST, aspartate aminotransferase; SMA, smooth muscle antibodies; ULN, upper limit of normal.

Adapted from: Czaja AJ. *Sleisenger & Fordtran's Gastrointestinal and Liver Disease: Pathophysiology/Diagnosis/Management* 2006 pg. 1874.

42. Give 10 **preventative measures** about which to advise patients with AIH treated with prednisone +/- azathioprine.

➤ General

- Monitor for weight gain
- Supplement with calcium, vitamin D, +/- bisphosphonates
- Monitor blood sugar, lipids, fat soluble vitamins
- Monitor CBC, ALT (if on Azathioprine)
- Annual checks for BP, cataract, glaucoma, BMD, Pap' smear, esophageal varices
- Check stools for ova/parasites after foreign travel
- "Stop" order on Rx
- Screening mammography, colonoscopy
- Access for depression
- Stress high doses of steroids, if necessary
- Wear medical alert bracelet.



- Avoid stopping steroids suddenly (Addisonian crisis, recurrence of AIH)
- Avoid unplanned pregnancy; consider avoiding pregnancy if portal hypertension is marked; contraception
- Drug interactions
- Immunizations (see below)

➤ Specific

- If cirrhotic: avoid sedation, NSAIDs, anesthesia, interferon
- If cirrhotic, screen for HCC
- Avoid vaccination with varicella, MMR, yellow fever
- Vaccination for H. influenza, HAV, HBV, pneumococcus (hyposplenism)
- Assess for esophageal varices for primary prevention with banding or beta blockers (avoid use in pregnancy – fetal hypoglycemia)
- Assess for Ascites and spontaneous bacterial peritonitis (SBP)

Adapted from: Heathcote J. *Am J Gastroenterol* 2006;101:S630–S632.

➤ Prognosis

- Death from bleeding EV (esophageal varices) ~ 20%
- Relapse may occur after drug withdrawal
- The clinical course is influenced by the level of ALT and gamma globulins, serology (anti-soluble liver antigen (SLA), anti-asialoglycoprotein receptor (ASGPR), anti-chromatin), liver biopsy (bridging or multilobular necrosis, or cirrhosis), HLA status, and response to treatment. Each of the above is associated with an adverse outcome.
- The MELD (model for end-stage liver disease) score predicts survival
 - Based on degree of impaired liver function, not affected by cause or presence of cirrhosis
 - MELD $\geq$ 12 (at presentation), 97% of these persons will fail steroid therapy

For the details of these prognostic factors and outcome, please see Feldman M., et al. *Sleisenger and Fordtran's Gastrointestinal and Liver Disease*. 9th Edition. Saunders/Elsevier, Philadelphia, 2010, Table 88.5, page 1469, "Prognostic Factors and Associated Reported Outcomes in Autoimmune Hepatitis".



43. Give the complications of **liver transplantation** (LT) which are more common for AIH than compared with non-autoimmune liver disease.

- Acute rejection
- Chronic rejection
- Steroid-resistant rejection
- Difficult in stopping steroids

Patients with NASH cirrhosis may come to liver transplantation (LT). Lifelong immunosuppression will be required, but the immunosuppression agents may worsen the hepatic steatosis, or worsen components of the metabolic syndrome.

Total Trivia

- Autoimmune polyendocrinopathy
 - Candidiasis
 - Ectodermal dystrophy APECED
- Polyendocrinopathy
 - Failure of
Parathyroids
Adrenals
- Candidiasis
 - Mucocutaneous
- Ectodermal dysplasia
 - AIH (autoimmune hepatitis)
- Give the usual features of hereditary autoimmune hepatitis (AIH, aka APECED).
 - Autosomal recessive with complete penetrance
 - Females = males frequency
 - Single gene mutation on chromosome 21q22.3, altering AIRE (autoimmune regulator)
 - AIH is usually severe, and responds poorly to usual effective therapy



Primary Biliary Cirrhosis (PBC)

- Definition: PBC is an autoimmune liver disease characterized by specific antibodies, a characteristic liver biopsy (inflammatory destruction of the intralobular bile ducts), and progressing to chronic cholestasis, biliary cirrhosis, and complications related to portal hypertension and liver failure.
- Demography
 - F >> M, 9:1
 - Age of diagnosis
 - Usually 30 to 60 years
 - Incidence
 - 3/10⁵
 - Prevalence
 - 40 / 10⁵
- Pathogenesis

44. Give the **pathoimmunology** of PBC (primary biliary cirrhosis).

- Immune-mediated response to an unknown antigen (molecular mimicry)
- Activation of CD4+ and CD8+ T lymphocytes, B cells, and NK cells
- Aberrant polyclonal activation of B cells (↑ IgG, IgM)
- Breakdown of tolerance against mitochondrial antigens → production of autoantibodies against proteins on the inner membrane of mitochondria
 - AMA (anti-mitochondrial antibody, in 95% of PBC patients) directed against the E2 component of
 - PDC E2 (pyruvate dehydrogenase complex)
 - PDC E1a subunit of PDC
 - E3 BP subunit of PDC
 - BCO-ADC-E2 (branched-chain of 2-oxo-acid dehydrogenase complex)
 - Molecular target is gene gp120 or nucleoprotein p62



- Anti-gp 210
 - AMA+PBC, 25%
 - Sensitivity AMA-PBC, 50%
 - Specificity, AMA+PBC, 99%, AMA-PBC, 25%
 - Gp 210 and p62 associated with poor prognosis
 - Gp 201 protein and AMA persist in serum after liver transplantation for PBC
 - Clinically for AMA, immunoblotting and ELISA (enzyme-linked immunosorbent) assays have excellent performance characteristics for AMA: > 90% for both sensitivity and specificity.
 - These methods may detect AMA in persons who were negative by direct immunofluorescence testing
 - PDC-E2-specific CD4+ lymphocytes interact with duct cells in the small intrahepatic bile ducts
 - This interaction of CD4+ and CD8+ T cells is facilitated by ICAM-1 (intracellular adhesion molecule 1)
 - Other antibodies:
 - ANA (antinuclear antibodies)
 - In 50% of AMA+PBC, and 85% of AMA-PSC
 - Anti-MNA (anti-multiple nuclear dot)antibodies
 - Molecular target, sp 100 (soluble protein)
 - Anti-centromere antibodies
 - Antinuclear envelop antibodies
 - Other autoantibodies
 - Rheumatoid factor, 70%
 - Anti-smooth muscle, 16%
 - Anti-thyroid, 41%
 - HLA class II molecular phenotype may be associated with PBC
- Clinical
- Time course from no symptoms (asymptomatic) to symptoms
 - 40% in 5 to 7 years
 - 95% in 20 years
 - Development of esophageal varices (EV) ~ 30%
 - Bleeding of EV in 3 years ~ 12%



Metabolic Bone Disease

- Osteoporosis (OP)
 - Defective bone formation
- Osteomalacia
 - Defective bone mineralization
- At diagnosis, 20% of PBC patients already have osteoporosis
- Cumulative risk of fragility fractures – 10% to 20%
- Presence and severity of OP increased with progression from stage 1 and 2 to stages 3 and 4 PBC
- After liver transplantation (LT), for PBC
 - 50% develop a pathologic fracture within 1 month

45. Give the factors that increase the risk of bone disease in patients with chronic cholestatic liver disease.

➤ General

- Reduced physical activity
- Low body mass index
- Increasing age
- Smoking
- Female sex
- Reduced sunlight exposure
- Family history

➤ ↓ Intake

➤ ↓ Absorption - Cholestasis

- Vitamin D and K deficiency
- Reduced calcium availability (steatorrhea)
- Increased serum bilirubin
- Genetically abnormal vitamin D receptor genotype

➤ ↑ Requirements

- Menopause/hypogonadism



46. Give the reason why patients with PBC but no cirrhosis may develop portal hypertension.
- NRH (nodular regenerative hyperplasia) may be associated with PBC, and causes presinusoidal portal hypertension
47. Give the reason why PBC patients with hypercholesterolemia do not have early onset of atherosclerotic disease.
- The hypercholesterolemia in PBC is from HDL and not from LDL-cholesterol, so the risk of atherosclerosis is not increased.

Clinical Curiosities in PBC

- The commonly observed symptom of fatigue is an independent predictor of mortality, especially mortality from cardiac death.
- Gallstones occur in about 1/3 of persons with PBC.
- Recurrence of PBC after liver transplantation “does not seem to decrease survival” (Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier, Philadelphia, 2010, page 1487).

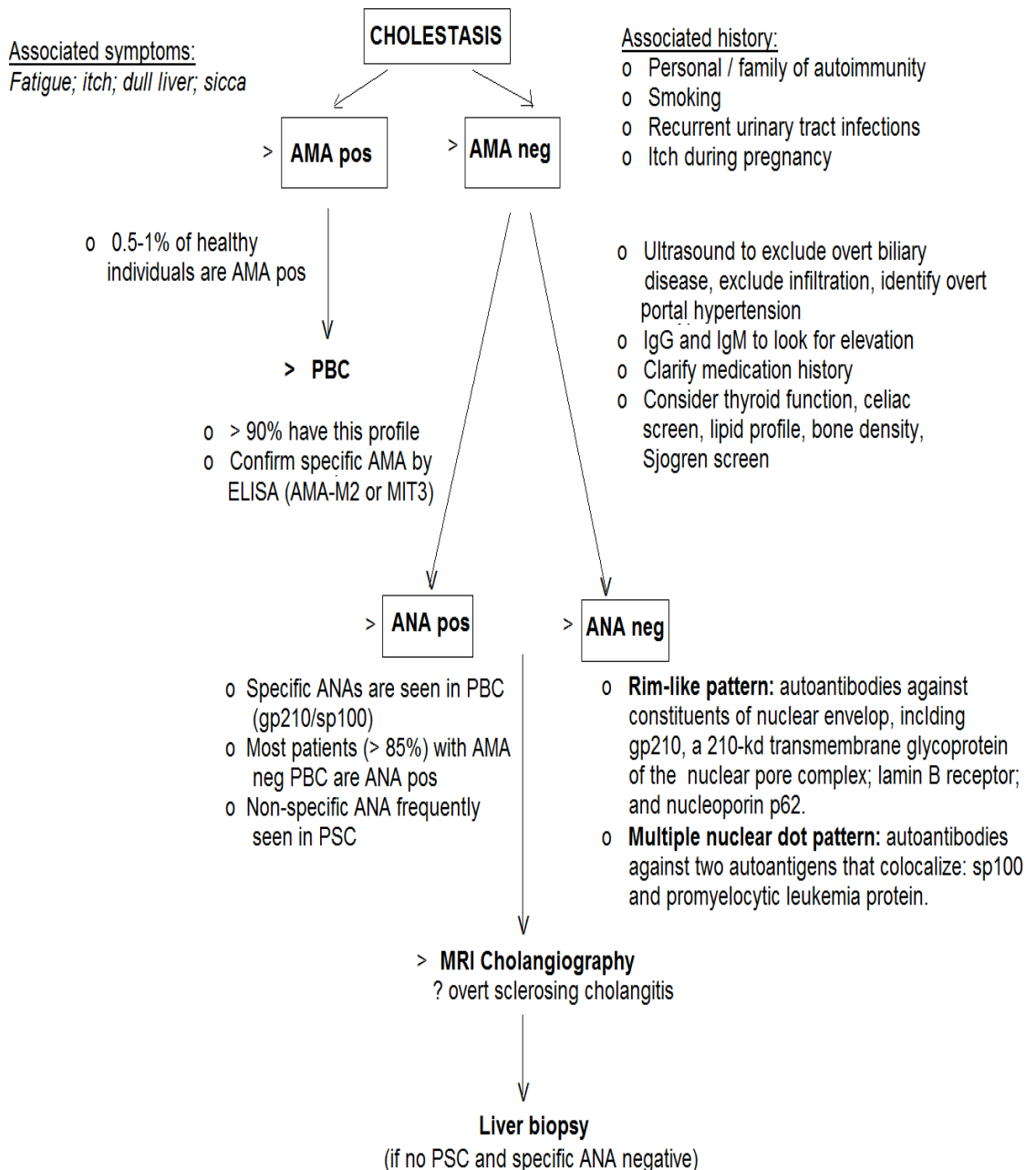
“Your greatest invention lies in your hands, it is
your future.”

Apoorve Dubey



➤ Laboratory

○ Suggested flow chart for **investigating cholestatic patients**



Printed with permission: Hirschfield GM, et al. BPRCG 2011; 25: 701-712.



➤ Pathology

48. Give the histopathology used to determine Ludwig's 4 stage classification of PBC.

- Stage I
 - Focal areas of inflammation (lymphocytes) confined to the portal space
 - Florid duct lesion
 - Inflammatory destruction of the small ($< 100 \mu\text{m}$ diameter) intrahepatic interlobular and septal bile ducts
 - Development of ductopenia
 - Reactive proliferative of bile ductules
- Stage II
 - Interface hepatitis (aka piecemeal necrosis):
 - Inflammation extends from portal tract into hepatic parenchyma
 - Some destruction of the limiting plate
- Stage III
 - Fibrosis, with no regenerating modules
- Stage IV
 - Fibrosis
 - With regenerating nodules (cirrhosis)
 - Fibrous septa

Clinical Tip: Liver Biopsy in PBC

- "In a patient with AMA in serum, the combination of a serum alkaline phosphatase [AP] level greater than 1.5 times the upper limit of normal [ULN] plus a serum AST level less than 5 times the upper limit of normal yields a 98.2% positive predictive value for a diagnosis of PBC".
- 98% PPV for PBC: AMA+, $\uparrow \text{AP} > 1.5 \times \text{ULN} + \uparrow \text{AST} < 5 \times \text{ULN}$
- "...a liver biopsy is not necessary to confirm the diagnosis in most patients with PBC and should be performed in only the mimicry of AMA-positive patients with a serum alkaline phosphatase level less than 1.5 times normal or a serum AST level greater than 5 times normal" (Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier, Philadelphia, 2010, page 1481).



MCQ Alert

You are asked a multiple choice question about which has the higher “mortality rate”, those PBC patients who have symptoms at the time of diagnosis, or those who are asymptomatic. Watch carefully the wording, whether mortality is liver-related or non-liver related:

Symptoms at diagnosis	Cause of higher mortality
○ None	– Non-liver related
○ Fatigue, pruritis, jaundice	– Liver-related
○ For PBC patients who are symptomatic (fatigue, pruritus, jaundice) at the time of diagnosis, the liver-related mortality rate (MR) is higher than in the PBC patients who were asymptomatic at the time of diagnosis.	
○ However, the initially asymptomatic PBC patients have a high MR from non-liver related conditions, than do the initially symptomatic PBC patients.	
○ The trick is whether the question addresses liver-related mortality rates in a- / symptomatic PBC patients.	

➤ Differential diagnosis

49. Give 12 examples of chronic benign biliary disorders involving the intrahepatic, extrahepatic, and combined intra- and extrahepatic ducts (big duct abnormalities), which may **mimic PBC**.

- Congenital
 - Alagille syndrome (and nonsyndromatic)
 - Cystic fibrosis
 - Duct plate abnormalities
 - Choledochal cysts
- Infectious
 - Cytomegalovirus
 - Biliary sepsis
 - Parasites
 - HIV (intrahepatic), AIDS cholangiopathy (extrahepatic)



- Infiltrative
 - Cholangiocarcinoma
 - Histiocytosis X
 - Lymphoma
 - Mastocytosis
- Ischemic
 - Thrombosis of hepatic artery
 - Paroxysmal nocturnal hemoglobinuria (PNH)
 - Vasculitis
 - Henoch-Schönlein
 - Ischemic strictures (post liver transplantation)
- Immune
 - PSC, secondary sclerosing cholangitis
 - Sarcoid autoimmune cholangiopathy
 - Graft vs host disease
 - Allograft rejection
- Drugs and toxins
 - Drugs
 - Floxuridine
 - TPN-associated cholestasis
- Idiopathic
 - Caroli syndrome

Abbreviation: PNH, paroxysmal nocturnal hemoglobinuria; TPN, total parenteral nutrition

➤ **AMA-Negative PBC**

- Symptoms, biochemistry, liver histology, clinical course, therapy and indications for liver transplantation are similar to AMA + PBC
- Human leukocyte antigen (HLA) alleles may be different in AMA- versus AMA + PBC, with possible loss of protective allele
- No difference in Treg (regulatory T cells / or t cell subgroups)
- Serology
 - Most have ANA or anti-smooth muscle antibodies
 - 50% have anti-gp 210



50. Compare and contrast PBC and AIH under the following headings.

Finding	PBC	AIH
○ Gender	F>M	F>M
○ Prominent symptoms	Pruritus	Fatigue
○ Laboratory	AMA+, ↑ IgM (if associated autoimmune syndromes)	AMA-, ↑ IgG, ASA+, Anti-DNA+
○ Pathology		
- Ducts	Florid duct damage	Minimal duct damage
- Hepatocytes	Intact lobules	Interface hepatitis (zone 1)
- Infiltration	Lymphoid aggregates	Lymphocytes and plasma cells

Abbreviation: ASA, anti-smooth muscle antibody

➤ Prognosis

51. Give the **predictors for survival** in PBC.

- Patient
 - Older age
 - Symptoms
 - Complications
 - Hepatomegaly
 - Ascites, edema
 - GE variceal bleeding
- Laboratory
 - ↑ AP, bilirubin, PT
 - ↓ albumin
- Histopathology
 - Cholestasis
 - Mallory hyaline
 - Fibrosis
 - Cirrhosis

Abbreviations: AP, alkaline phosphatase; PT, prothrombin time (aka, INR)



Please refer to Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier, Philadelphia, 2010, Table 89.4, page 1482, for "Independent Predictors of Survival in Patients with Primary Biliary Cirrhosis in Various Clinical Trials".

- Prognosis (useful to select optimal timing for liver transplantation)
 - Simple: total serum bilirubin > 10 mg/mL
 - Life expectancy then is only 2 years
 - Sophisticated: Mayo Risk score for PBC: Please see <http://www.mayoclinic.org/gi-risk/mayomodel2.html>
- Treatment
 - UDCA (ursodeoxycholic acid)
 - Used routinely in patients with stage 1 to 3 PBC
 - 7-β epimer of chenodeoxycholic acid
 - 13-15 mg / kg per day, with meals, taken od, or divided into bid
 - Take 2 hr before or after bile acid binding agents, e.g. cholestyramine
 - Budesonide
 - Non-systemic steroid
 - 6 mg po od
 - Used in stages 1 to 3 PBC
 - Alone, or with UDC (requires more clinical data)
 - Avoid use in stage 4 (↓ metabolism of budesonide → ↑adverse effects)
 - Nutrition
 - Fat soluble vitamins
 - Treat associated
 - Pruritis
 - Steatorrhea
 - Proximal renal tubular disease (type II)

Adapted from: Angulo P, and Lindor KD. *Sleisenger & Fordtran's Gastrointestinal and Liver Disease: Pathophysiology/ Diagnosis/ Management* 2006; pg.1894.; and Glasova H, and Beuers U. *J Gastroenterol Hepatol* 2002; 17(9): 938-48.

- Pruritus
 - The mechanism of the development of pruritus in PBC is unknown; the pruritic factor is not bile acids themselves,



- However, binding bile acids with cholestyramine and increasing their fecal excretion by diluting the bile acid pool with more hydrophobic UDCA may improve the pruritus.
- The antibiotic Rifampin induces CYP, and this presumably reduce itching by acting on the release of endogenous opiates. It is not clear what is the mechanism of the known anti-pruritic effect of
 - Antihistamines, 5-HT3 antagonists, serotonin reuptake inhibitors, or phenobarbital

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- Give the explanation why opioids must be used cautiously in cholestasis (**opiate-withdrawal syndrome** in persons with cholestasis treated with opiates which are suddenly discontinued).
 - In cholestasis, the endogenous opioids are not secreted, their levels in the blood are increased, and sudden withdrawal of even most doses of exogenous opioids represents sufficient to lead to opioid withdrawal syndrome.

52. Give 7 beneficial outcomes for the use of UDCA in PBC.

Probability of Developing Cirrhosis When UDCA used for PBC

	Stages at diagnosis of PBC		
	1	2	3
After 5 years	4	12	59
After 10 years	17	27	76

	UDCA
○ Mayo risk score	↓
○ Biochemistry	↓
○ Liver biopsy progression	↓
○ Cirrhosis development	↓
○ Gastroesophageal varices	↓
○ Ascites	↓
○ Liver transplantation	↓
○ HCC risk	↓
○ Death	↓



➤ Liver transplantation (LT)

SO YOU WANT TO BE A GENIUS HEPATOLOGIST!

PBC recurs after liver transplantation (LT). There are several risk factors for post-LT PPC (age, males, use of tacrolimus).

- Give the likely mechanism for the recurrence of PBC post-LT.
 - AMA and other autoantibodies (e.g. ANA, anti-MND, anti-gb 210) are immunological makers for PBC, and they persist in the serum post-LT. These autoantibodies do not cause the disease, but reflect continuing activity of B- and T-lymphocytes, as well as NK cells.
 - The basic abnormality in the humoral and cellular response to an unknown antigen presumably continues
 - Defects in immunological regulation lead to bile duct obstruction in the allograft.
- The number of LT performed for PBC is falling, not because of a ↓ incidence or prevalence, but instead because of the favourable outcomes with UDCA
- Survival rates for LT for PBC
 - 1 year > 90%
 - 5 year > 80%
- Organ allocation in PBC is established by risk stratification with the MELD (Model for End-stage Liver Disease) score
- See: <http://mayoclini.org/meld/mayomodel6.html>
- Risk of recurrence of PBC after LT
 - Median time ~ 4 years
 - ↑ with time: ~ 40% in 10 years post LT
 - ↑ risk of recurrence with
 - ↑ age
 - Males
 - Use of tacrolimus



53. Give the diagnostic criteria for recurrent PBC after liver transplantation (LT) for PBC, as well as the important differential diagnostic considerations.

Diagnostic Criteria for Recurrent PBC	Differential Diagnostic Considerations
○ LT for confirmed diagnosis of PBC ○ Persistence of serum AMA ○ Compatible Histopathology - Portal inflammation - Lymphocytic inflammatory infiltrates - Lymphocytic cholangitis - Epithelioid granulomas	▪ HCV infection with lymphocytic cholangitis ▪ Drug-induced liver injury (DILI) ▪ Acute cellular rejection ▪ Biliary obstruction ▪ Graft-vs.-Host Disease (GVHD)

➤ Exclusion of differential diagnostic considerations

Interpretation: 2 of 4 diagnostic criteria = probable; 3 of 4 = definite

Printed with permission: Ilyas JA, et al. Liver transplantation in autoimmune liver diseases. Best Pract Res Clin Gastroenterol. 2011;25(6):765-82.

Primary Sclerosing Cholangitis (PSC)

➤ Definition

- PSC is a chronic cholestatic liver disease characterized by inflammation and fibrosis of the extrahepatic and intrahepatic bile ducts than can progress to cirrhosis.

➤ Demography

- Incidence – $1/10^5$ per year
- Prevalence – $10/10^5$
- The prevalence of PSC is 20.9 and 6.3 per 100,000 men and women, respectively.



➤ Laboratory

54. Give 5 serum autoantibodies which are most prevalent in PSC.

Antibody	Prevalence
Anti-neutrophil cytoplasmic antibody	50%–80%
Anti-nuclear antibody	7%–77%
Anti-cardiolipin antibody	4%–66%
Anti-endothelial cell antibody	35%
Anti-smooth muscle antibody	13%-20%
Thyroperoxidase	7%–16%
Thyroglobulin	4%
Rheumatoid factor	15%

➤ Diagnostic Imaging

55. Give the features on diagnostic imaging that distinguish between the cholestatic conditions PSC and PBC (primary biliary cirrhosis).

PSC	PBC
○ Usually intra- and extrahepatic ducts tapered and narrow ○ Diffuse segmental strictures ○ Dominant strictures ○ Intrahepatic duct “pruning” (↓ arborisation) → “beading”	- Intrahepatic ducts smoothly tapered and narrow ● Lymphocytic interface may be hard to distinguish from AIH (autoimmune hepatitis) ● Diffusely thickened, fibrotic wall ● Inflammation of duct epithelium and glands ● Hyperplasia of biliary glands ● Neural proliferation ● Atrophy of biliary epithelium

Abbreviations: AMA, antimitochondrial antibodies; anti-BEC, anti-(human) biliary epithelial cells; ANA, antinuclear antibodies; pANCA, perinuclear antineutrophil cytoplasmic antibodies



➤ Pathology

○ Types

- Large-duct PSC (95%) 80% are associated with IBD.
 - If large-duct PSC not associated with IBD, test for ↑ IgG4 to diagnose autoimmune cholangitis.
 - Diagnosis may be made by ERCP / MRCP.
- Small-duct PSC (5%)
 - Small-duct PSC is a variant in which only the intrahepatic ducts are involved.
 - Liver biopsy necessary to make diagnosis because ERCP likely normal
 - “onion-skin” fibrosis
 - Destruction of the bile duct
 - Replacement of destroyed duct with fibrous tissue

▪ Small-duct PSC $\xrightarrow{20\%}$ large-duct PSC $\xrightarrow{10\%}$ cholangiocarcinoma

- PSC + gallbladder polyps → elective cholecystectomy for high risk of malignant degeneration of even small gallbladder polyps

○ Findings

- Medium-sized bile ducts:
 - “onion skin” lesion: (fibro-obliterative process)
 - Small interlobular / septal bile duct branches: fibro-obliterative cholangitis
- Periductular inflammation
- Obliteration of bile duct by fibrosis
- Atrophy
- Duct openia
- Proliferation

➤ Stages

- Stage I (portal stage)
 - Portal tracts



- Inflammation
 - Fibrosis
 - Cholangitis
 - Stage II (periportal stage)
 - ↑ inflammation interface hepatitis
 - ↑ fibrosis
 - Piecemeal necrosis
 - Ductular proliferation
 - Cholangitis
 - Stage III (septal stage)
 - Fibrosis which bridges from one portal tract to the next
 - Stage IV (cirrhosis)
 - Differential diagnosis
56. Give a classification of the secondary causes/ associations of secondary sclerosing cholangitis (SSC), and provide 15 examples.
- GI disease associations
 - Colon
 - Ulcerative Colitis
 - Crohn colitis or ileocolitis
 - Liver
 - Hepatic allograft rejection
 - Hepatic graft-versus-host disease (after bone marrow transplantation)
 - Cystic fibrosis
 - Overlap with PBC
 - May be difficult to distinguish from AIH (PSC may have lymphocytic interface hepatitis)
 - Bile ducts
 - Cholangiocarcinoma
 - Choledocholithiasis
 - Stricture
 - Biliary parasites



- Recurrent pyogenic cholangitis
 - Fungal infection
 - Cholangitis
- Pancreas
 - Chronic pancreatitis
 - IgG4-associated cholangitis (IAC), with or without IgG4-associated pancreatitis
- Post-liver transplantation (fibro-intimal hyperplasia)
- Systemic diseases with fibrosis
 - Retroperitoneal fibrosis
 - Riedel's thyroiditis
 - Mediastinal Fibrosis
 - Pseudotumour of the orbit
 - Inflammatory pseudotumour
 - Peyronie's disease
 - Chronic sclerosing sialadenitis
- Autoimmune or collagen vascular disorders
 - Systemic lupus erythematosus
 - Systemic sclerosis
 - Type I diabetes mellitus
 - Rheumatoid arthritis
 - Sjögren's syndrome
 - Autoimmune hemolytic anemia
- Kidney
 - Membranous nephropathy
 - Rapidly progressive glomerulonephritis
- Infections
 - Biliary TB
 - HIV (CD4+ T lymphocytes < 100 / mm³)
 - AIDS cholangiopathy
 - Cryptosporidium
 - Microsporidium
 - CMV



- Inflammation
 - Sarcoidosis
 - Hypereosinophilic syndrome
- Immunodeficiency diseases
 - Congenital immunodeficiency
 - Combined immunodeficiency
 - Dysgammaglobulinemia
 - X-linked agammaglobulinemia
 - Acquired immunodeficiency
 - Selective immunoglobulin A deficiency
 - Acquired immunodeficiency syndrome (HIV/AIDS)
 - Angioimmunoblastic lymphadenopathy
- Congenital abnormalities
 - Caroli's disease
 - Choledochal cyst
- Iatrogenic (drugs)
 - Hepatic arterial infusion of chemotherapy, intraductal formaldehyde or hypertonic saline (used for echinococcal cyst removal)
 - Intra-arterial floxuridine (FUDR, causing ischemia and toxic vasculitis)
 - Formaldehyde (for hydratid cyst)
 - Intra-arterial floxuridine
- Ischemic
 - Vascular injury from liver surgery
 - Hepatic allograft arterial occlusion
 - Paroxysmal nocturnal hemoglobinuria
 - Prolonged circulatory failure (shock)
 - Systemic vasculitis
- Infiltration
 - Benign
 - Mastocytosis



- Histiocytosis X
- Biliary papillomatosis
- Malignant
 - Cholangiocarcinoma
 - Hepatocellular carcinoma (HCC)
 - Metastatic cancer
 - Lymphoma

Adapted from: Tung BY, and Kowdley KV. *Sleisenger & Fordtran's Gastrointestinal and Liver Disease: Pathophysiology/Diagnosis/Management* 2006 pg. 1462.

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An Asian Canadian with no previous biliary tract surgery, presents with recurrent episodes of fever, RUQ pain and jaundice (Charcot triad). He is negative for AMA, ANA, ASMA, pANCA and HIV, and ERCP shows multiple filling defects and a stricture / dilation of the left hepatic duct.

- Give the likely diagnosis.
 - RPC (recurrent pyogenic cholangitis) may be confused with PSC, but the demography, negative serology, , and the findings of ERCP defects in the left rather than the right hepatic duct make this diagnosis likely.
- In the context of investigating a person with PSC and possible cholangiocarcinoma, give reasons for false-negative and false-positive CA 19-9 elevations, an false-positive PET scans.
 - CA 19-9
 - False negative
 - Negative Lewis antigen status
 - False positive
 - Choledocholithiasis
 - Bacterial cholangitis
 - PET scan
 - False positive
 - Bacterial tract inflammation



PSC and Inflammatory Bowel Disease (IBD)

➤ Demography

- 80% of PSC have IBD
- 3% of IBD have PSC
- Associated with ulcerative colitis (UC) and Crohn colitis, but not Crohn disease of just the small bowel

57. Give 10 characteristics of inflammatory bowel disease (IBD) associated with primary sclerosing cholangitis (PSC).

- More R-sided colitis and rectal sparing
- More CRC, pouchitis, backwash ileitis
- Rectal sparing
- Extensive colitis
- Right-sided predominance of inflammatory activity
- Often mild or quiescent course
- Clinical course of PSC + IBD
 - Independent
 - Colectomy does not affect PSC
- ↑ risk of colorectal neoplasia
- ↑ risk of pouchitis in patients undergoing proctocolectomy with IPAA
- Backwash ileitis
- ↑ risk of peristomal varices in patients undergoing proctocolectomy with ileostomy
- After liver transplantation for PSC
 - UC may still develop
 - HGD / CRC may develop
 - HGD may already have been present
 - HGD may develop following diagnosis of UC
- UC → panproctocolectomy → PSC may develop de novo



- PSC → liver transplantation → UC may develop de novo, or PSC may recur
 - Note: That's why annual colonoscopies may still be needed in PSC patients who do not (yet) have UC.
- Perform annual colonoscopy in UC + PSC

Abbreviations: CRC, colorectal cancer; HGD, high grade dysplasia

Adapted from: Chapman R, Fevery J, Kalloo A, Nagorney DM, Boberg KM, Shneider B, Gores GJ; American Association for the Study of Liver Diseases. Diagnosis and management of primary sclerosing cholangitis. *Hepatology*. 2010;51(2):660-78.

- The high mortality in PSC (median survival time after diagnosis, 10-12 years) can be attributed to complications from cirrhosis as well as the high incidence of malignancies associated with PSC (e.g. colon, gallbladder).

58. Give 8 **biliary tract complications** in PSC.

- Gallbladder tumors (in 41%)
 - Current guidelines recommend an annual screening ultrasound for gallbladder cancer in patients with PSC, and a cholecystectomy once a gallbladder polyp is detected regardless of size.
- Gallbladder polyps → cancer
 - Gallbladder polyps < 8 mm on ultrasound have a low likelihood of being malignant in non-PSC persons.
- Cholelithiasis (in ~ 25%)
- Choledocholithiasis in ~25%)
- Cholangitis
- Multiple strictures
- Single / strictures
- “dominant” stricture (> 1.5 cm)
 - Intrahepatic > 10 mm in length
 - Extrahepatic, > 15 mm)
- Cholangiocarcinoma (in ~ 10%)



- Cirrhosis, and its complications
- Cholecystectomy
 - Use the Child-Pugh score to risk-stratify patients with PSC who undergo a cholecystectomy.
 - Primary sclerosis cholangitis (PSC) with or without cirrhosis have a high morbidity rate following a cholecystectomy that is comparable to patients with cirrhosis from other causes.

Adapted from: Eaton JE, et al. Am J Gastroenterol 2012; 107: 431-439.

➤ Prognosis

- This high mortality in PBC (median survival time after diagnosis, 10-12 years) can be attributed to complications from cirrhosis as well as the high incidence of malignancies associated with PSC.

	Years		
	1	2	5
○ % progression beyond Stage			
– II → III / IV	42%	66%	93%
– II → IV	14%	25%	52
○ Asymptomatic PSC			
– Median survival free of liver failure, 71%			
○ Symptomatic PSC			
– 6 years survival rate, 60%			
– "...may facilitate selection for timing of liver transplantation (Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9 th Edition. Saunders/Elsevier, Philadelphia, 2010, page 1159).			
○ Prognostic models (multivariant)			
– See Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9 th Edition. Saunders/Elsevier, Philadelphia, 2010, Table 68.2, page 1159 for "Independent Predictors of Survival and Prognostic Sclerosing Cholangitis".			
○ After development of cholangiocarcinoma			
– Median survival, 5 months (in ~10%)			
– With appropriate indication and surgical resection by hepatic segmentectomy or lobectomy, 5 year survival rate ~25%.			

Please see Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier, Philadelphia, 2010, Table 69.5, page 1176 for "Exclusion Criteria for Resection of Hilar Cholangiocarcinoma.



➤ Treatment

- Supportive for complications
- UDCA **no** longer used in PSC, unless for overlap syndrome (PSC plus PBC)
- Endoscopic stenting of strictures
- Gallbladder screening for polyps, cancer
- Colon cancer surveillance if PSC plus IBD
- Liver transplantation

Clinical Gem

.....endoscopic management of a dominant stricture may alter the course of PSC [for the better]" (Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier, Philadelphia, 2010, page 1166)

59. Give the clinical scenarios and diagnostic considerations > 90 days after OLT (orthoptic liver transplantation) for recurrent primary sclerosing cholangitis (PSC).

Clinical Scenario	Diagnostic Considerations
○ OLT for confirmed diagnosis of PSC	▪ Hepatic artery thrombosis or stenosis
○ Cholangiographic evidence of: – Intrahepatic and/or extrahepatic strictures* – Beading and irregularity of bile ducts	▪ Solitary anastomotic stricture ▪ Ischemic strictures ▪ Bacterial or fungal cholangitis with strictures
○ Compatible Histopathology – Fibrous cholangitis and/or – Fibro-obliterative lesions with or without ductopenia, fibrosis or cirrhosis – Interface hepatitis	▪ Chronic ductopenic rejection ▪ ABO incompatibility between donor and recipient ▪ CMV infection ▪ Cryptosporidium

Printed with permission: Ilyas JA, et al. Liver transplantation in autoimmune liver diseases. Best Pract Res Clin Gastroenterol. 2011;25(6):765-82; and Eaton JE, et al. Am J Gastroenterol 2012; 10: 431-439.



Infectious Hepatitis

Bacterial Hepatitis

There are certain “buzz words” which are meant to signal a likely diagnosis.

60. Give 3 buzz words which when applied to the patient with acute hepatitis, suggest typhal fever from infection with either *Salmonella typhi* or *Salmonella paratyphi*.

- Hepatitis plus
 - “Stepwise fever”
 - Stepwise increase temperature
 - “Temperature-pulse dissociation”
 - Pulse rate does not increase as much as expected for the temperature (i.e. relative bradycardia)
 - “Rose spots on skin”
 - Salmon-pink macules on skin of trunks
- Other clues that acute hepatitis might represent typhoid fever.
 - RLQ tenderness (ileitis / cecitis)
 - ALT / LDH < 4 ($\uparrow$ ALT, $\uparrow\uparrow$ LDH)
 - $\uparrow$ AP (AP increased more than in most patients with hepatitis)
 - $\uparrow\uparrow$ WBC, with “left shift”
- Treatment
 - Fluoroquinolone

A young woman presents with RUQ pain and tenderness, fever and abnormal liver enzymes. The CT of the upper abdomen shows only non-specific hepatic changes.

61. In this context, give the meaning of the “**Fitz-Hugh Curtis (FHC) syndrome**” and “violin string”. perihepatic adhesions on laparoscopy.

- Fitz Hugh Curtis syndrome is a gonococcal or chlamydial infection of the female pelvic organs which involves the surface of peritoneum, causing the perihepatic fibrinous exudate (violin string adhesions).
- In diagnosis would be suspected in a sexually active women with a painful pelvic examination.



Viral Hepatitis

62. Give the name of common viral infections of the liver.

- The “viral alphabet soup” (HAV, HBV, HCV, HDV, HEV*)
- EBV (Epstein-Barr virus)
- CMV (cytomegalovirus)
- HSV* (herpes simplex virus)

63. Give a comparison of viral hepatitis (A, B, C, D, E) under the headings - virus type, mode of transmission, incubation period, serological diagnosis, risk of fulminant hepatitis and risk of chronicity.

	Virus type	Trans- mission	Incuba- tion (days)	Serologic diagnosis	Fulminant hepatitis	Risk of chronicity
➤ Fecal/oral						
○ HAV	RNA		20-35	HAV-IgM	0.1-2.0%	No
○ HEV	RNA		10-50	Anti-HEV	1-2% 15-20% Pregnant	No
➤ Percutaneous						
○ HBV*	DNA	-IVDU	60-110	HBsAg	0.1-0.5%	Adults < 5% Preschool ers 25% Neonates >90%
○ HCV**	RNA	-Sexual (MSM, prostitute services, promiscuity)	35-70	Anti-HCV	<1%	> 80%
○ HDV	RNA	-IVDU (IV drug use) (even once), pre-1990 blood transfusions -Sexual promiscuity	60-110	Anti-HDV		Usual in a superinfe ction with HBV; rare by itself

* Also perinatal

** Pre-1990 blood transfusion

Abbreviation: MSM, men who have sex with men



64. Give which two of the viral causes of hepatitis have a higher mortality during pregnancy.
- HEV
 - HSV
65. Give the prevention, vaccination, post-exposure prophylaxis and treatment which is recommended for exposure to HAV, HBV and HCV.
- Prevention
 - Good sanitation and hygiene
 - Avoid high risk behavior
 - For HBV condoms advised for multiple sex partners, anal intercourse, and intercourse during menses
 - Vaccination
 - HAV
 - HBV
 - HCV
 - No vaccine
 - Post-exposure prophylaxis)
 - HAV
 - Children ≥ 2 years of age in communities with high rates of Hep A
 - Chronic liver disease
 - All household and sexual contacts
 - Immune serum globulin 0.02 mL/kg IM if within 2 weeks of exposure
 - Vaccinate
 - No treatment for casual school or work contacts
 - HBV
 - When HBC reactivation (“flare”, decompensation) may occur – use of chemotherapy, prednisone, anti-TNF therapy
 - HCV
 - Needlestick injury:
 - Test for HCV-RNA, AST, bilirubin at baseline, then at 4 and 12 weeks—of positive, treat with PEG-IFN and Ribavirin
 - Perinatal: Rare transmission—more likely of mother is immunosuppressed



➤ Treatment when infected

- Supportive care. Most cases resolve spontaneously. Hospitalization rarely needed. Prophylaxis and prevention of secondary spread is perhaps the most important aspect of treatment.
- Activity—symptom guided return to work: no activity limitations.
- Diet—fatty foods poorly tolerated, exclude ETOH, no other dietary restrictions.
- Drugs—no role of corticosteroids—may increase the risk of a chronic carrier state, avoid sedatives, tranquilizers.

Adapted from: Grover PT, and Ma M. *First Principles of Gastroenterology* 2005: 547-552.

Please see: Peltekian KM, Hirsch G. Chapter 59. In: Therapeutic Choices. Grey J, Ed. 6th Edition, Canadian Pharmacists Association: Ottawa, ON, 2011, Table 6: HDV, HBV Immunization, page 797-798.

Hepatitis A Virus (HAV)

Useful background

➤ Demography

- Transmission is by fecal-oral route
 - Person-to-person
 - Contaminated food or water
- Males >> females
 - Injection illicit drugs
 - Non-injection illicit drugs
 - MSM (men who have sex with men)

➤ Modes of clinical presentation

- Acute hepatitis
- Fulminant hepatitis failure (FHF)
 - Week 1 of HAV, 55%
 - Week 4 of HAV, 90%
- Clinical alert
- Relapsing or “prolonged” but not chronic course
- HAV may trigger onset of AIH (autoimmune hepatitis)



➤ Diagnosis

- About one third of adults with acute HAV will have hyperbilirubinemia
- Relapse of ↑ ALT may occur weeks after the acute symptoms have reduced, if glucocorticosteroids were inappropriately given.
- IgM-anti HAV
 - Once symptoms occur, IgM-anti HAV is positive in serum
 - Usually becomes negative by 4 months
 - Sometimes becomes negative after 12 months
- IgG-anti-HAV
 - Marker of previous HAV infection

➤ Prognosis

- HAV has one serotype, and four genotypes (I, II, III, and IV).
- Hospitalization, 25%
- Death
 - Overall, 0.3%
 - > 49 years, 1.8%
 - Also high in patients with chronic liver disease

Clinical Alert: IgM anti-HAV and low HAV RNA

“.... Detection of IgM anti-HAV coupled with non-detection or finding of low-titer HAV RNA in patients with severe acute hepatitis [HAV] may signal an ominous prognosis and the need for early referral for liver transplantation” (Feldman M., et al. Sleisenger and Fordtran’s Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier, Philadelphia, 2010, page 1283).

➤ Prevention

- Sanitation
- Life-style considerations
- HAV vaccine
 - Comparable to SIG for post-exposure protection against HAV
- Serum immune globulin (SIG)
 - Lasts ~ 20 year
 - Reduced response when HIV > 400 copies/mL, and CD4+ < 25 / mm³
- For persons with chronic liver disease
 - Pre-exposure prophylaxis

For Groups at High Risk of Hepatitis a virus Infection, please see Feldman M., et al. Sleisenger and Fordtran’s Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier, Philadelphia, 2010, Table 77.2, page 1283).



Hepatitis B Virus (HBV)

➤ Demography

66. Give the geographic site for the most common distribution of Hepatitis B genotypes A-H .

- A. Northwestern Europe, North America, Central Africa
- B,C. Southeast Asia, including China, Japan, and Taiwan (prevalence is increasing in North America)
- D. Southern Europe, Middle East, India
- E. West Africa
- F. Central and South America, United States (Native Americans), Polynesia
- G. United States, France
- H. Central and South America

Source: *Sleisenger and Fordtran's Gastrointestinal and Liver Disease: Pathophysiology/ Diagnosis/ Management*. 2010, Table 78-1.

○ HBV progression

Acute HBV → chronic HBV:

- Neonate 90 asymptomatic enteric disease
- Children 50
- Adults 10 symptoms

Source: *Clin Liver Disease* 10; 14: 75-91; *Hepatology* 07; 45:1056-75

"Management is doing things right; leadership is doing the right things."

Peter F. Drucker



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- Give the rate of vertical transmission of HBV from (HBsAg)-positive mothers.
 - HBeAg
 - Positive, transmission in 60% to 90%
 - Negative transmission in 15% to 20%
 - Give the risk of PCR-detectable HBV DNA in persons who are positive for anti-HBc.
 - 0% to 30%
 - Give the clinical importance of the 0% to 30% of anti-HBc positive persons having HBV DNA in their serum.
 - Blood that is HBsAg negative but anti-HBV positive has up to a 30% risk of having HBV DNA, and therefore of being infectious.
 - Give the explanation for the high rate of transmission of HBV from HBsAg-negative but HBe-positive blood donors.
 - HBV may replicate in many body tissues other than liver
 - These extrahepatic tissues act as reservoirs for HBV DNA
-
- Spontaneous HBeAg seroconversion, ~10%
 - 5-year cumulation risk of progression of HBeAg – positive chronic hepatitis B to cirrhosis, ~10%
 - HBV-associated compensated cirrhosis progressing to decompensation, 16%
 - 5-year cumulative risk of developing HCC, 14%

➤ Molecular biology

67. Give the **molecular biology** of HBV infection.

- HBV is a DNA virus which goes through an RNA intermediate, and requires an active viral reverse transcriptase / polymerase enzyme.
- High daily point mutation rate, low replication fidelity
- The 5 gene encodes HBsAg, a viral surface, envelop protein



- The core gene has
 - Precore region → HbeAg
 - Core region → core proteins
- HBV DNA polymerase reverse transcriptase pregenomic RNA into a negative-strand HBV DNA ("needed for encapsidation of viral RNA into a negative strand of viral DNA (reverse transcription) and conversion of this first HBV DNA strand into a second DNA strand of positive polarity (Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier, Philadelphia, 2010, page 1291).
- The negative-strand HBV DNA is a template for the synthesis of a positive-strand.
- The positive strand is incorporated into the maturing nucleocapsid.
- The nucleocapsids are coated with the surface protein (HBsAg) in the ER.
- From the ER, the enveloped nucleocapsid bud off from the hepatocyte membrane, and enter the circulation.

➤ Pathogenesis

68. Give the mode of transmission and the approximate lifetime risk of HBV infection in persons who reside in different geographical areas

Geographical Area	Mode of Transmission	Lifetime Risk of HBV Infection
➤ NA, WE, SA, Au	○ Horizontal person-to-person, young adults ○ Sexual	< 20%
➤ SE, EE, ME, IS fUSSR, NAFR	○ Infancy ○ Early childhood	20% to 40%
➤ SEA, CHINA, AFRICA	○ Perinatal ○ Horizontal, young children	60% to 80%

Abbreviations: Au, Australia; EE, Eastern Europe; fUSSR, former USSR; IS, Indian Subcontinent; ME, Middle East; NAFR, Northern Africa; NA, North America; SEA, South East Asia; SA, South America; SE, Southern Europe; WE, Western Europe



- Liver damage from HBV is immune-mediated (not a direct hepatocyte cytopathic effect of HBV).
 - Cellular immune response – innate and adaptive
 - Viral clearance by CTLs (cytotoxic T lymphocytes)
 - CD4+ T cells produce antiviral cytokines which reduce the production of neutralizing antibody.
- Clinical
- Stages (based on serology)
 - Immune tolerant
 - Normal ALT level
 - Minimal or no inflammation or fibrosis
 - High levels of HBV DNA
 - Presence of HBeAg
 - Immune tolerant
 - May be high levels of HBV DNA, but HBeAg may cause an immune tolerant phase, initially with little inflammation to the liver
 - ALT normal or near normal
 - When HBV is acquired early in life such as from vertical transmission, and who have a high-normal ALT, may already have entered the immune clearance phase.
 - Liver biopsy “....can be a useful tool to distinguish persons in the immune clearance phase despite normal or near-normal ALT levels but with active liver disease from active liver disease”. (Feldman M et al., Sleisenger and Fordtran’s Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier, Philadelphia, 2010, page 1294).
 - Immune active
 - Liver inflammation and fibrosis
 - HBV DNA elevated, but lower than in immune tolerant
 - HBeAg + or –
 - Elevated ALT
 - Active T cell response to virus



- Inactive
 - Normal ALT
 - Healing liver histology
 - Resolving liver fibrosis
 - Low or absent HBV DNA
 - Strong T cell response to virus
- Recovery
 - Lower risk of develop of HCC
 - Loss of HBsAg

Adapted from: McMahon BJ, et al. Clin Gastro Hep 2012; 10: 218-219.

➤ Clinical presentations

- Active hepatitis
 - Circulating HBsAg – anti-HBs complexes activate complement
 - HBsAg – anti-HBs complexes are deposited in wall of the blood vessels of the skin synovium
 - Serum sickness-like prodrome, with 1/3 of patients developing jaundice
 - Low levels of HBV may persist in the serum
- Fulminant hepatitis
 - Survival
 - Spontaneous, 20%
 - Liver transplant, 50%
- Fulminant HBV
 - Due to “massive immune-mediated lysis of infected hepatocytes”
 - Usual-onset
 - Within 4 weeks of symptoms of HBV
 - Untreated mortality rate, > 80%
 - Late-onset liver failure after several months of onset of HBV symptoms



- May be associated with “flares” (exacerbations of disease)
 - ↑ ALT (2x the baseline value)
 - IgM anti-HBe
 - Associated with histological progression of disease
- Chronic inactive HBV (inactive HBsAg carrier)
 - HBsAg positive for more than 6 mon
 - HBeAg negative, anti-HBe positive
 - HBV-DNA <10⁵ copies/mL (<20,000 Iu, low risk of HCC)
 - Persistently normal ALT/AST (low risk of progression)
 - Liver biopsy showing no inflammation
 - No evidence of on-going replication (inactive chronic HBV infection)
- Active HbsAg (chronic active HBV) carrier
 - HBV replication
 - PCR-based, +
 - Non-PCR-based, +
 - AST, ALT
 - Intermittent or persistent increases
 - Liver biopsy
 - Chronic hepatitis
- Progression
 - Infection
 - Vertical, 95%
 - Horizontal, < 5%
 - HBV infection becoming carriers, < 5%
 - Carriers developing cirrhosis, %
 - Cirrhosis, 5 year survival rate
 - Compensated, 84%
 - Decompensated, 14%



➤ Resolved hepatitis B

- Previous known history of acute or chronic hepatitis B
- HBsAg negative
- HBeAg negative
- HBcAb positive/HBsAb positive
- Undetectable HBV-DNA
- Normal ALT

Adapted from: Keeffe EB, et al. *Clin Gastroenterol Hepatol* 2006;4(8):936-62.

- Reactivation
 - A proportion of these with inactive carrier state undergo spontaneous or immunosuppression-mediated reactivation of replication of HBV DNA
 - ↑ HBV DNA in serum
 - ↑ ALT
 - Necroinflammation recurs
 - Seroconversion of HBeAg^{+/-}
 - During or after HBeAg seroconversion (anti-HBe → HBeAg⁺), precore or core promoter mutants appear
 - Precore or core promoter mutants ↓ HBeAg production
 - Optimal time for treatment
- Immune clearance
 - ↓ HBV DNA
 - ↑ ALT
 - HBeAg⁺
 - Hepatic necroinflammation (immune-mediated lysis of HBV-infected hepatocytes)
 - Optimal time for treatment
- Associations with HBV
 - Fibrosing cholestatic hepatitis
 - Reactivation of HBV from immunosuppressants given for organ transplantation ↑↑↑ HBsAg and HBeAg in liver tissue
 - Infection with other hepatotropic viruses (A, C, D)



- Extrahepatic manifestations
 - Fever, arthralgias (proximal interphalangeal joints), angioneurotic edema
 - PAN (polyarteritis nodosa)
 - HBV-associated renal disease
 - Glomerulonephropathy
 - Membranous glomerulonephritis
 - Membranoproliferative glomerulonephritis
 - Immune-complex glomerulonephritis
 - Nephrotic syndrome
 - Renal failure
 - Cryoglobulinemia

➤ Laboratory

69. Give the laboratory assessment prior to therapy of HBV, and explain why.

- HBsAg – if positive, measure
- HBeAg and anti-HBe
- Measure HBV DNA if ALT elevated
- ALT, ALP, bilirubin, albumin, PT INR, CBC, HIV, anti-HCV

Printed with permission: Grover PT, and Bain V. *First Principles of Gastroenterology* 2005:547-556.

70. List 5 markers of HBV infection, and what they signify.

- HBsAg – appears first and if persists for > 6 months, the patient is chronically infected (exposed, chronic infection)
- HBsAb – implies recovery or immunity to HBV, either naturally occurring or after vaccination
- HBcAb-IgM – past or present HBV infection (newer and more sensitive assays may also be positive during reactivation of chronic infections)
- HBeAg – indicates active infection/replication of HBV, but absence cannot be taken as absence of viral replication (i.e., precore mutant, e.g. eAg negative)



- Anti-HBe – presence indicates seroconversion but can also be found in active disease in patients with HBeAg negative chronic hepatitis. (not replicating – precore mutant)
- HBV-DNA – detectable in serum, it is a measure of the level of viral replication. (infected) (reflects risk of HCC)

Printed with permission: Balart LA. 2007 ACG Annual Postgraduate Course: 198.

- The CDC now recommends HBV diagnostic testing in all persons going on immunosuppressants or undergoing cancer chemotherapy
- Natural clearance of HBV occurs in 5% of neonates and 95% of adults infected with HBV
- Baseline HBV DNA levels in patients aged 30-65 years are directly related to the likelihood of developing HCC 10 years later

71. Give the **laboratory features** which suggest each of the 5 stages of HBV.

Stage	HBeAg	HBV DNA	ALT / AST	progression to fibrosis
○ Immune tolerant	+	↑↑	N / low	Very low
○ Immunoreactive (HBeAg - positive netcroinflammation)	+	↑	↑ / fluctuating	low
○ Inactive HBV carrier state	Negative (zero conversion to anti-HBe antibody)	< 2000 IU / mL Low / undetectable	N	Low
○ HBe antigen negative CHB (later immune reactive face)	After seroconversion or after years of immune reactive phase	↑ / ↓	↑ / ↓	High
○ HBs antigen negative	Negative	HBV DNA in liver but not detectable in blood	N	Low

Abbreviation: CHB, chronic hepatitis B



72. Give the clinical laboratory and histopathology characteristics of the **different stages** of chronic hepatitis B infection.

Features	Immune tolerant	Immune reactive	Low replicative stage	e- Ag negative reactivation
➤ <u>ALT</u>	○ <u>Normal</u>	○ Elevated	○ Normal	○ Fluctuates (fluctuating viremia)
➤ HBV-DNA by PCR	○ >20,000 IU/ml	○ >20,000 IU/ml	○ <2,000 IU/ml	○ >2,000 IU/ml
➤ e-antigen	○ (+)	○ (+)	○ (-)	○ (-)
➤ e-antibody	○ (-)	○ (-)	○ (+)	○ (+)
➤ Liver biopsy recommended	○ No progression of disease for about 3-6 months	○ HBeAg seroconversion with treatment		○ 8-10% develops cirrhosis each year, compared with 2-6% of HBeAg positive patients
➤ Liver biopsy	○ Inactive	○ Active/+ fibrosis	○ Inactive	○ Active/+ fibrosis
➤ Treatment	○ Not recommended	○ Recommended	○ Not recommended	○ Recommended

Adapted from: Herrera JL. 2009 ACG Annual Postgraduate Course:161- 166.

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In acute HBV, HBsAg disappears and several weeks later anti-HBs appears.

- Give the serological test used during this “**window period**” to prove acute HBV infection.
 - During the window period when HBsAg disappears and anti-HBs appears, the presence of serum IgM-anti-Hbe confirms a recent HBV infection.

In both acute and in chronic HBV infection, there may be both HBsAg as well as anti-HBs in the serum.

- Give the explanation for this possibly surprising finding.
 - There may be two subtypes of HBsAg, one which causes the liver disease, and one minor HBsAg against which the low concentration of anti-HBs is formed.



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In non-endemic areas for HBV, there may be isolated anti-HBe in the serum of the health general population.

- Give 7 reasons for anti-HBe being in the serum.

There are many reasons for anti-HBe being in the serum of healthy persons

- Acute HBV – IgM anti-HBe
- Recovery from acute HBV
- Exacerbations of HBV in chronic carrier
- Progression of acute HBV
- Chronic HBV → HBsAg is undetectable
- Acute HBV window period, IgM anti-HBe (HBsAg⁺ → HbsAg⁻, and development of anti-HBs)
- Long interval after recovery from acute HBV (small amounts of HBV DNA in serum, liver and peripheral mononuclear cells; anti-HBs undetectable)
- Technical factors relating to sensitivity of HBsAg assay
- Coinfection of HBV plus HCV (60%)
- False-positive test
- HBV DNA in serum

➤ Pathology

73. Give the hepatic histopathological features of HBV infection.

- Ground-glass hepatocytes
 - HBsAg in the ER of infected hepatocytes
 - Cystine in HBsAg stained by orcein, Victoria blue, aldehyde fuchsin indicate viral replication
 - Also there may be core antigen in cytoplasm and hepatocyte nuclei
 - After treatment cytoplasmic core antigen disappears, but persistence of nuclear core antigen indicates presence of HBV cccDNA template



- Peripheral infiltration with mononuclear cells
- Interface hepatitis (disruption of hepatocytes of the limiting plate)
- Fibrous tissue extending from peripheral areas
- Active septa mononuclear cells between fibrous extensions from portal tracts and hepatocyte parenchyma

➤ Prevention

Useful background: HBV vaccination

- Neutralizing antibody anti-HBs is produced against the “a” epitope of HBsAg by HBsAg-specific helper T cells and by T cell-dependent B cells.
- Protective levels of anti-HBs occur in > 90% of persons who are vaccinated with HBsAg.
- If a person who has been anti-HBc has had a mild.
- Subclinical HBV infection, either because
- After HBV vaccination, subclinical HBV infection may occur, either because
 - Over time the titre of anti-HBs may have fallen to levels which are no longer protective (25% to 50% of vaccinated persons develop non-protective levels of anti-HBs over 5 to 10 years)
 - Initial hyporesponders, with the development of low and non-protective concentrations of anti-HBS
- Booster doses of vaccine are needed
 - In hemodialysis patients
 - In persons who are immunocompetent
- Some persons with low or no anti-HBS after vaccination appear to be protected

For reference purpose, please see Feldman M et al., Sleisenger and Fordtran's Gastrointestinal and Liver Disease, 9th Edition. Saunders / Elsevier, Philadelphia, 2010.

Table 78.7, “Recommended Dosing for the Currently Available Hepatitis B Vaccines”, page 1309.

Table 78.8, “Hepatitis B Prophylaxis of Infants Born to Hepatitis B Surface-Antigen-Positive Mothers”, page 1309.

Table 78.9, “Post exposure Prophylaxis of Hepatitis B if the Source is HBsAg Positive”, page 1309.



- HBV anti-core⁺ can reactivate with Prednisone, azathioprine, anti-TNF therapy
- Patients on infliximab are at risk for vaccine-preventable disease, including hepatitis B virus (HBV).
- Older age, lower albumin levels, and the presence of pancolitis were risk factors for the absence of protective antibodies against HBV.
- A significant minority of previously vaccinated patients did not respond to an HBV booster, indicated that they are not at risk for HBV infection.

Source: Mosses J, et al. Am J Gastroenterol 2012; 107: 133-138.

74. Give 10 **high-risk groups** for whom hepatitis B virus (HBV) vaccination should be considered.

- Health care workers
- Hemodialysis patients
- Household contacts and sexual partners of HBV carriers or patients with acute hepatitis B
- Injection drug users
- Inmates of correctional facilities: International travellers to areas endemic for HBV who may have intimate contact with the local population or take part in medical activities
- Men who have sex with men
- Patients who are likely to require multiple transfusions with blood or blood products
- Patients with chronic liver disease (other than chronic hepatitis B)
- Potential organ transplant recipients
- Public safety workers with likelihood of exposure to blood
- Sexually active heterosexual men and women, if they have more than one partner
- Staff and clients of institutions for developmentally disabled

Printed with permission: *Sleisenger and Fordtran's Gastrointestinal and Liver Disease: Pathophysiology/ Diagnosis/ Management*. 9th edition, 2010, page 1308.



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- Give 10 reasons why a person immunized with HBs-Ag vaccine may not develop an adequate anti-HBs response.
 - Persons
 - Very young, or old (> 50 yrs)
 - Obese
 - Smoking
 - Chronic liver disease
 - Immunosuppressed
 - Transplantation
 - Chemotherapy
 - Immunodeficient HIV positive
 - Co-infection
 - HIV
 - HCV
 - Administration of vaccine into buttock muscles
 - Genetic factors
 - HLA
 - Alleles DR3, DR7, DQ2
 - No HLA-A2
 - Vaccine-frozen
 - Wrong dose or timing of vaccine
 - Virus
 - Mutant HBV virus strains (mutation of “a” determinant of HBV, are not neutralized by vaccination with HBsAg, so are called HBV escapes mutants)

“There are three constants in life... change, choice and principles.”

Stephen Covey



75. Give the **immunoprophylaxis** for HBV in adults accidentally exposed to possibly infectious blood (within the last 7 days), or sexual contacts (within the past 14 days).

- Check donor blood for HBsAg; check victim's blood for HBsAg and HBcAb
- Give at once 0.06 ml/kg HBIG plus first dose of hepatitis B vaccine

	HBsAg	HBcAb	Further action to victim
Victim	-ve	+ve	None: Immune
"Donor" (source)	+ve	-ve	Continue vaccine course
	-ve	-ve	None, or continue vaccine course if victim is at risk of further hepatitis B exposure

Adapted from: Sherlock S, and Dolley J. *Diseases of the Liver and Biliary System* (Eleventh Edition) 2002. pg. 285-303.

Please see *Sleisenger and Fordtran's Gastrointestinal and Liver Disease: Pathophysiology/ Diagnosis/ Management*. Ninth edition, 2010, for the following additional information: Table 78.6, "High-Risk Groups for Whom Hepatitis B Virus (HBV) Vaccination Should be Considered", page 1308.

➤ Treatment

76. Give 6 **goals of treatment** of HBeAg⁺ and HBeAg⁻ HB.

E-antigen (+) HB E-antigen (-) (+)

- Loss of E-antigen
- Appearance of anti-E
- Conversion to inactive status
- Normalization in serum liver aminotransferase
- Loss of detectable HBV DNA
- Improvement in liver histology



- Reduce the risk of hepatocellular carcinoma
- Loss HBs Ag

Printed with permission: Shiffman ML. 2008 AGA Annual Postgraduate Course Syllabus: pg. 166.

The importance of HBeAg status

➤ HBeAg

- Represents
 - ↑ viral replication
 - Active liver disease
 - Need for antiviral therapy

77. Give the comparisons of HBeAg positive and HBeAg negative HBV, under the headings epidemiology, natural history, treatment response, monitoring of treatment response.

Comparisons	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 (10-20% /yr) (immune tolerance)	▪ Higher rate of progression to cirrhosis
○ Treatment response	- Higher sustained response rate to IFN- α therapy	▪ Lower sustained response rate to IFN- α therapy



Comparisons	HBeAg positive	HBeAg negative
○ Monitoring of treatment response	– HBeAg seroconversion to anti-HBV positive (also, possibly seroconversion to HBs Ag negative) – Normalization of liver enzymes and marked reduction in HBV DNA	▪ Normalization of liver enzymes and marked reduction in HBV DNA

➤ Treatment Definitions

- Virological response - HBV DNA < 2000 IU / mL at 0, 6 and 12 months after the end of therapy
- Sustained virological response - HBV DNA < 2000 IU / mL at 12 months after the end of therapy
- Virological break through
 - ↑ HBV DNA 1 log₁₀ IU/mL compared to lowest previous level of HBV DNA on Rx
 - Characterized by ↑ ALT
 - Due to
 - Poor adherence to therapy, or
 - HBV resistance (due to therapy associated selection of HBV resistant variants)
- Of course the long-term goal of HBV is to improve the patient's quality of life, and the prevention of progression of the disease to cirrhosis, HCC, decompensation.
- With the currently available treatments, the importance of therapy of biological markers which serve as surrogates for the benefit of HBV therapy on the host of the infection, the patient.

78. Give 3 **virological responses** which represent acceptable **end points** for HBV therapy.

- Sustained off- therapy loss of HBsAg
- Sustained off therapy loss of HBeAg (anti-HBe antibody positive)



- Sustained off therapy HBe antigen negative patient who was HBe antigen negative at baseline
- Undetectable HBV DNA (by sensitive PCR assay) while on anti-HBV therapy
- Does not completely eliminate HBV infection, since the HBV (a DNA virus) becomes integrated within the hepatocyte genome as CCC, (covalently closed circular) DNA
- The **goals of therapy** in HBV infection:
 - Reduce viral load as much as possible to control the disease
 - Normalize liver enzyme levels
 - Advance resolution of hepatic necroinflammation
 - Achieve e-Ag seroconversion (note that e-Ag seroconversion is not possible if the patient is infected with the e-Ag mutant of the HB virus)
 - HBsAg seroconversion (occurs in < 10%, and is often not seen for 4-5 years after therapy has been completed and e-Ag has occurred)
- Lamivudine has high resistance rates; because telbivudine develops resistance mutations at the same site as for lamivudine, telbivudine is not effective in persons who have lamivudine resistance
- Entecavir has low rates of resistance (1.2% after 5 years), and 20% rate of eAg seroconversion after 48 weeks
- The diagnosis of chronic HBV infection in an HIV patient is an indication to start tenofovir-based HAAR therapy
- Tenofovir is a potent selective inhibitor of HBV-DNA polymerase, and is active in HBV
- A roadmap to treatment of HBV has been updated
 - HBe-Ag positive and negative persons.
 - After 48 weeks of therapy, HBV-DNA becomes negative in 76% of HBeAg positive and 91% of HBeAg-negative persons

Abbreviation: HBV, Hepatitis B

79. Give the reason why it is important to distinguish between inactive HBV carrier state (stage III) from HBe-Ag negative CHB.

	Prognosis	Risk of complications
○ Inactive HBV carrier	Good	Low
○ HBe-Ag negative CHB	Poor	High



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Adults who are HBeAg-positive usually have active HBV, whereas children who are HBeAg-positive do not.

- Give the explanation why HBeAg⁺ in children is not usually associated with active hepatitis.
 - The secretion of HBeAg may be reduced by
 - Precore or core promoter mutations
 - Low levels of wild-type HBV

80. Give the **indications** for initiation of HBV therapy.

- ↑ HBV DNA (> 2000 IU / mL)
- ↑ ALT (> ULN)
- Moderate / severe necroinflammation, and / or
- ≥ moderate fibrosis
- When to start HBV therapy without liver biopsy
 - HBeAg-negative, ↑ ALT (2x ULN), HBV DNA > 2000 IU / mL; or
 - HBeAg-positive
- When to start HBV therapy with normal ALT.
 - ↑ HBV DNA, necroinflammation changes and fibrosis on a liver biopsy
 - Compensated cirrhosis, even if HBV DNA undetectable
 - Decompensated cirrhosis plus detectable HBV DNA
- Chronic HBV
 - HBeAg⁺
 - 90% have HBV DNA > 105 copies/mL
 - HBeAg⁻
 - Lower serum HBV DNA levels, especially if ALT is normal
 - Higher HBV DNA in HBeAg⁻ with ↑ ALT
- Seroconversion (HBeAg⁺ → HBeAg⁻, anti-HBe) usually associated with ↓ HBV DNA



81. Give the pre-treatment **baseline evaluation** of the patient with HBV infection.

- Laboratory
 - Revised normal ALT levels (30 IU/L for men, and 19 IU/L for women) should be used as criteria for treatment
 - Baseline evaluation should include HBV genotype, particularly if peginterferon therapy considered
 - Preferred first line treatment options: adefovir, entecavir, peginterferon alfa-2a, and possibly telbivudine (Lamivudine not first-line choice secondary to high rate of resistance to Interferon alfa-2b)
 - Liver biopsy should be considered for patients with normal ALT levels, especially if age >35-40 years
- Assessment of risk (risk to develop fibrosis progression, cirrhosis and those at greatest risk for development of HCC)
 - Active HBV:
 - HBeAg (+), HBV DNA >500,000 copies/mL (20,000 I μ /ml), and elevated ALT > 2 X ULN
 - Active hepatitis with variable degrees of fibrosis on liver biopsy
 - Pre-core mutations of HBV:
 - Includes patients with all features above, except eAg(-)
 - Inactive HBV:
 - Patients with inactive HBV, and HBV DNA < 500,000 copies/mL are NOT currently considered candidates for HBV therapy, unless they have evidence of cirrhosis on liver biopsy. These patients are at low risk to develop fibrosis progression or HCC.

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- Give when anti-HBV therapy should be given for acute HBV.
 - HBV acute infection, when HBeAg lasts beyond 12 wks
 - HBV therapy may reduce the 5% risk of development of chronic HBV
 - Fulminant HBV
 - INR > 1.5 plus clinically deep jaundice
 - Anti-HBV useful since patient may need a liver transplantation



- Principles – Keep the HBV DNA levels as low as possible
 - ↑ immunological response to HBV
 - ↓ HLA class I antigen expression on surface of hepatocytes
 - ↑ CD8+ CTL activity
 - ↓ HBV ccc DNA (“the genomic template for viral transcription)
 - No drug resistance
 - Associated with seroconversion (HBeAg+ → HBeAg-)
 - Genotype A ~ 50%
 - B, C, D ~ 25%

82. Give the **general management strategy** of the person with HBV.

- Treatment strategies
 - PEG-IFN or NA monotherapy for finite duration
 - NA for long-term duration
- PEG-IFN or NA monotherapy used for finite duration
 - PEG-IFN (in the absence of contraindications) for HBeAg- positive and -negative patients for 48 weeks

Caution: do not combine PEG-IFN with lamivudine or telbivudine (development of severe neuropathy)

- Entecavir or tenofovir for 12 months after seroconversion in about 2/3 of these initially HBeAg-positive HBV patients
- NA for long-term duration
- Entecavir or tenofovir monotherapy for
 - HBeAg-positive patients who failed to seroconvert or HBeAg-negative patients
 - All HBV cirrhosis
- Monitoring and stopping



83. Give the potential management strategies for HBV by on-treatment virologic response categories.

Category	Strategy*
○ Primary treatment failure at week 12	- If noncompliant, counsel patient on importance of adherence to prescribed drug regimen - If compliant, change therapy to more potent drug or possibly a drug combination
○ Complete virologic response at week 24	- Continue therapy with same drug; monitoring may be extended to 6-month intervals
○ Partial virologic response at week 24	- If drug has a low genetic barrier to resistance, add a second drug that is not cross-resistant - If drug has a high genetic barrier to resistance, repeat monitoring at 3-month intervals and continue beyond 48 weeks - If drug has a delayed antiviral effect e.g. adefovir, repeat monitoring at 3-month intervals and if response becomes complete at 48 weeks, continue therapy; but if response remains partial or becomes inadequate at 48 weeks, add a more potent drug
○ Inadequate virologic response at week 24	- Add another drug (preferably one that is more efficacious, or if such a drug is not available, then add one that is not cross-resistant) - Repeat monitoring at 3-month intervals - Monitoring after 48 weeks may be extended from 3 to 6 months if response becomes complete

*patients with advanced disease should be monitored at 3-month intervals while on treatment, regardless of virologic response

Printed with permission: Keeffe EB. 2007 AGA Institute Postgraduate Course: pg. 77.



84. Give the recommendations regarding monitoring and stopping HBV treatment.

- **Monitoring rules**

- PEG-IFN

- HBeAg-positive
 - On treatment
 - Every 6 and 12 months: anti-HBe antibodies, serum HBV DNA, ALT, HBsAg at 12 months
 - Off treatment
 - Every 12 months: HBeAg, anti-HBe antibodies, serum HBV DNA, ALT, HBsAg
 - HBeAg seroconversion (HBeAg-positive → negative)
 - Test HBsAg every 12 months (seroreversion)
 - No HBeAg seroconversion (serum HBsAg > 20,000 IU/mL, or no ↓ HBsAg at 3 months)
 - Stop PEG-IFN
- HBeAg-negative
 - On treatment, at month 3 if ↓ HBV DNA $\geq 2 \log_{10}$ IU / mL, and no ↓ HBsAg
 - Stop PEG-IFN (especially genotype D)

- NA (nucleos[t]ide

- On treatment every 6 months HBeAg, anti-HBe, HBV DNA, serum creatinine
 - Measure HBsAg every 12 months after HBe seroconversion
 - Stop NA 12 months after anti-HBe seroconversion, or
 - Stop NA until loss of HBsAg (with or without antibodies to HBsAg), especially if there is severe fibrosis or cirrhosis.

- NA resistance and switching

- Stopping



85. Give when HBV therapy should be reassessed or stopped.

- HBeAg+: HBeAg seroconversion and – HBV DNA
- HBeAg-: ? Long term therapy
- Inadequate VR (<2,000 IU/mL) at week 24
- Development of antiviral drug resistance

Abbreviation: VR, viral response

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86. Give 5 factors that are **predictive of a viral response** (VR) to treatment of HBV infection.

- Patient
 - Immunocompetent
- HBV
 - Adult-acquired infection
 - Low HBV-DNA level
 - Absence of HDV or HIV co-infection
 - HBeAg +ve
- Biopsy
 - Active liver disease—ALT > 5x upper limit of normal (ULN), active hepatitis on biopsy
- Specific treatment algorithms
 - HBeAg+
 - HBeAg-
- Select optimal agent
- Reassess therapy
- Screen for HCC

Adapted from: Keefe EB, et al. *Clin Gastroenterol Hepatol* 2006;4(8):936-62.

Useful background: HBV DNA

- When HBV DNA is high, the response rate to interferon is lower.
- HBV DNA is negative correlated with response to interferon.
- The higher the HBV DNA, the higher the risk of HBV recurrence with liver transplantation



- If HBV DNA reappears during treatment of HBV, resistance to the drug has likely occurred.
- In fulminant HBV, the HBs Ag may have disappeared, but the diagnosis can be made by finding HBV.

➤ **Drug choices**

- The menu of therapies in HBV
 - IFN (interferon)
 - PEG-IFN (pegylated IFN)
 - Nucleosides
 - Lamivudine
 - Telbivudine
 - Emtricitabine
 - Entecavir
 - Nucleotides
 - Adefovir
 - Tenofovir

87. Give the advantages and disadvantages of current therapies for chronic HBV hepatitis.

Agent	Advantages	Disadvantages
○ Interferon	- HBsAg loss - Short treatment duration - No drug resistance	● Parenteral administration ● Frequent side effects
○ Peg-IFN	- HBsAg loss - Fixed duration of treatment - No drug resistance	● Parenteral administration ● Frequent side effects but less than interferon



Agent	Advantages	Disadvantages
○ Lamivudine	- Oral administration - Excellent tolerance - Use in ESLD - Use in adefovir failures	● Drug resistance: common (~20%/year, and up to 70% with 4-5 years of therapy)
○ Adefovir	- Oral administration - Excellent tolerance - Use in ESLD - Use in lamivudine failures	● Less potent, with suboptimal responses not uncommon ● Drug resistance: delayed and less common (0% at year 1, 2% at year 2, 7% at year 3, 15% at year 4, and 29% at year 5 of therapy)
○ Entecavir	- Oral administration - Excellent tolerance - High potency in lowering HBV DNA levels - Use in adefovir failures	● Drug resistance: rare in nucleoside naïve patients (0.1% at year 1, 0.4% at year 2 and 1.1% at year 3), but common in patients with lamivudine resistance (6% at year 1, 14% at year 2, and 32% at year 3)
○ Telbivudine	- Oral administration - Excellent tolerance - High potency in lowering HBV DNA levels	● Drug resistance: intermediate rates (5% at year 1, and 21.6% at year 2 in HBeAg-positive patients, and 8.6% in HBeAg-negative patients)

Abbreviation: ESLD, end-stage liver disease

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“What lies behind us and what lies before us are
tiny matters compared to what lies within us.”

Henry Stanley Haskins



Results of main studies for the treatment of chronic hepatitis B at 6 months following 48 all 52 weeks of pegylated interferon alpha (PEG-IFN α), and at 48 all 52 weeks of nucleos(t)ide analog (NA) therapy.

HBeAg positive	PEG-IFN		Nucleoside analogs			Nucleotide analog	
	PEG-IFN-2a	PEG-IFN-2b	LAM	TEL	ENT	ADE	TEN
Dose	180 μ g	180 μ g	100 μ g	600 mg	0.5 mg	10 mg	245 mg
Anti-HBe seroconversion (%)	32	29	16-18	22	21	12-18	21
HBV DNA < 60-80 IU / mL (%)	14	7	36-44	60	67	13-21	76
HBeAg negative	PEG-IFN		Nucleoside analogs			Nucleotide analog	
			LAM	TEL	ENT	ADE	TEN
ALT normalisation (%)	41	32	41-72	77	68	48-54	68
HBsAg loss (%)	3	7	0-1	0.5	2	0	3
Dose	180 μ g		100 μ g	600 mg	0.5 mg	10 mg	245 mg
HBV DNA < 60-80 IU / mL (%)	19		72-73	88	90	51-63	93
ALT normalisation (%)	59		71-79	74	78	72-77	76
HBsAg loss (%)	4		0	0	0	0	0
Drug resistance 1 / 5 years	0 / 0		24 / 70	41	0.2 / 1.2	0 / 29	0 / 0

Abbreviations: ADE, adefovir; ENT, entecavir; LAM, lamivudine; TEL, telbivudine; TEN, tenofovir

Printed with permission: European Association for the Study of the Liver. EASL clinical practice guidelines: Management of chronic hepatitis B virus infection. J Hepatol. 2012;57(1):167-85.



Useful background: Comparisons among current nucleos (t)ide analogues in treatment-naïve patients with chronic hepatitis B , in terms of (by reduction and undetectable) HBV-DNA (PCR) and HBeAg seroconversion and drug resistance

	Lamivudine		Adefovir		Entetavir		Telbivudine		Tenotovir	
HBV-DNA (PCR)	e(+)	e (-)	e(+)	e (-)	e(+)	e (-)	e(+)	e (-)	e(+)	e (-)
Log reduction:										
Year 1	5.4	4.5	3.6	3.7	6.9	5.0	5.7	4.4	6.5	4.5
Undetectable:										
Year 1	40%	7.3%	21%	61%	6.7%	9%	60%	88%	76%	93%
Year 2	39%	52%	NA	71%	74%	NA	5.6%	82%	78%	99%
Year 3	20%	40%	NA	77%	NA	NA	NA	NA	NA	NA
Year 4	NA	34%	NA	73%	NA	NA	NA	NA	NA	NA
HBeAg Serocon- version										
Year 1	20%	NP	13% ^a	NP	21%	NP	23%	NP	23%	NP
Year 2	26%	NP	29% ^a	NP	31%	NP	30%	NP	26%	NP
Year 3	40%	NP	37% ^a	NP	NA	NP	NA	NP	NA	NP
Year 4	47%	NP	35% ^a	NP	47%	NP	NA	NP	NA	NP
Drug resistance										
Year 1	11-	6-27%	0%	0%	0%	0%	5%	2%	0%	0%
Year 2	14%	26-	NA	3%	0%	NP	25%	11%	0%	0%
Year 3	40%	54%	NA	11%	1.2%	NP	NA	NA	NA	NA
Year 4	56%		20%	29%	1.2%	NP	NA	NA	NA	NA

Abbreviations: HBV, hepatitis B virus; PCR, polymerase chain reaction; E, hepatitis B e antigen; NA, not available; NP, not applicable

^aCumulative incidence

Printed with permission: Chien RN and Liaw YF. *Best Practise Res Clin Gastroenterol* 2008;22:1081-1092.



Note:

- The dose of NAs (NTs and NSs) must be reduced if creatinine clearance < 50 mL / min.
- All HBV positive patients must be screened for HIV before starting their HBV treatment with lamivudine, entecavir or tenofovir, since these drugs have activity against HIV and should not be used as more therapy for HBV for fear of causing HIV resistance.
 - PEG-IFN, adefovir and telbivudine are not active against HIV.
- PEG-IFN has advantages over nucleos(t)ide (NA) because of
 - The absence of resistance
 - The possibility of seroconversion (HBsAg-positive → negative) in about 25% of patients
 - The ~4% change of loss of HBsAg in persons who achieve and maintain undetectable HBV DNA (by sensitive testing).
 - IFN therapy responders enjoy a ~ 50% reduction in cirrhotic complications and 80% reduction in liver- related mortality.

Useful background: Overview of **response rates** in HBeAg positive and HBeAg negative patients with currently available antiviral drugs.

Antiviral therapy	HBeAg positive		HBeAg negative	
	End of therapy	Post treatment	Undetectable HBV DNA End of therapy	Post treatment
○ Alpha interferon	35%	30%	60%	35%
○ Peginterferon	40%	35%	63%	19%
○ Lamivudine	19%	12%	65%	10%
○ Adefovir	12%	NA	51%	NA
○ Adefovir in lamivudine resistance	20%	NA	19%	NA
○ Entecavir	21%	NA	90%	NA
○ Entecavir in lamivudine resistance	8%	NA	26%	NA
○ Telbivudine	22%	NA	88%	NA
○ Tenofovir	21%	NA	92%	NA

Abbreviation: NA, not applicable

Printed with permission: Buster, et al. *Best Practise Res Clin Gastroenterol* 2008;22:1093-1108.



88. Give the recommendations for treatment strategy (treatment algorithm) of HBeAg-positive compensated patients, based on their HBV DNA and ALT.

HBV DNA	ALT	Treatment Strategy
○ <20,000 I μ /ml	Normal	- No treatment - Monitor every 6-12 months - Consider therapy in patients with known significant histological disease even if low-level replication
○ $\geq$ 20,000 I μ /ml	Normal	- Low rate of HBeAg seroconversion for all treatments - Monitor every 3-12 months - Younger patients often immune tolerant - Consider biopsy; particularly if older than age 35-40 years; treat if significant disease. In the absence of biopsy, observe for rise in ALT levels. - If treated, adefovir, entecavir, peginterferon alfa-2a, or possibly telbivudine preferred.
○ $\geq$ 20,000 I μ /ml	Elevated	- Adefovir, entecavir, peginterferon alfa-2a, or possibly telbivudine are preferred - If "high" HBV DNA: adefovir, entecavir or telbivudine preferred over peginterferon alfa-2a.
○ HBV disease		- "acute" > 20,000 HBV DNA IU/ml - "inactive" < 20,000 HBV DNA IU/ml

"Great thoughts speak only to the thoughtful mind,
but great actions speak to all mankind."

Emily P. Bissell



89. Give the recommendations for treatment strategy of HBeAg-negative compensated patients, based on their HBV DNA and ALT.

HBV DNA	ALT	Treatment strategy
○ <2,000 I μ /ml	Normal	- No treatment: majority inactive HBsAg carriers - Monitor every 6-12 months
○ $\geq$ 2,000 I μ /ml	Normal	- Consider biopsy; treat long term if disease present. In the absence of biopsy, observe for rise in serum ALT levels (ALT often fluctuates). - If treated, adefovir, entecavir, peginterferon alfa-2a, or possibly telbivudine preferred.
○ $\geq$ 2,000 I μ /ml	Elevated	- Adefovir, entecavir, peginterferon alfa-2a, or possibly telbivudine are preferred - Long term treatment required for oral agents

Printed with permission: Keeffe EB, et al. *Clin Gastroenterol Hepatol* 2006;4(8):936-62.

INTERFERON

90. Give the early and late **adverse effects** of interferon.

➤ Early

- Flu-like illness; headaches, nausea
- Tenderness at site of infection

➤ Late

- General
 - Fatigue
 - Irritability Anxiety and depression
- Eyes
 - ↑ retinopathy DM
 - Optic tract neuropathy



- CNS
 - CNS (neuropsychiatric)
- MSK
 - Muscle aches
- Skin
 - Alopecia
 - Lichen planus worsens
- GI
 - Weight loss
 - Diarrhea
 - Anorexia
 - IBD worsens
- Endocrine
 - Autoimmune autoantibodies
 - Worsening thyroid disease
 - Autoimmune diseases worsen
- Pregnancy class C
- Bone marrow suppression
 - Bacterial Infections

Adapted from: Grover PT, and Bain V. *First Principles of Gastroenterology* 2005: 547-563.

91. Give 4 **contraindications** to the use of IFN / PEG-IFN.

- Decompensated HBV cirrhosis (↑ risk of bacteremia and ↑ decompensation further)
- Autoimmune disease
- Uncontrolled severe depression / psychosis
- Pregnancy
- Renal transplant patients (↑ risk of rejection)



92. Give 8 pros and cons of Lamivudine versus interferon (IFN) for the treatment of HBV.

Favoring lamivudine

- Needle phobia
- HIV co-infection
- Other immunosuppression (e.g. transplantation)
- Patients with depression
- Low WBC count
- Low platelet count
- Autoimmune disease
- Decompensated cirrhosis
- Vertical transmission
- Cost concerns
- Pregnancy, may be used
- Has 70% resistance rate at 5 years. It acts as an immunomodulatory agent resulting in loss of circulating HBeAg and HBV DNA in 30-40% of cases, and to a lesser extent as an antiviral agent resulting in loss of HBsAg in less than 5% of cases.
- Cross resistance with tenofovir

Favoring IFN

- Young Asian
- Genotype A
- Recent infection
- AST > 100
- Low serum HBV-DNA
- Active liver biopsy
- eAg+
- Possibility of seroconversion (eAg+→eAb+)
- Marginal benefit to baby
- Contraindicated with depression, renal failure

Adapted from: Grover PT, and Bain V. *First Principles of Gastroenterology* 2005:547-552.



➤ **Nucleoside (NS) / nucleotide (NT) analogs (NA)**

- “Competitive inhibitors of reverse transcriptase and DNA polymerase”.
- “Replace natural nucleoside during the synthesis of the first or second strand (or both) of HBV DNA”.
- Lamivudine
 - High rate of viral mutation and viral resistance
- ~40% at 2 years, 65% at 5 year
- Higher rate of resistance with treatment of co-infection with treatment of co-infection with HIV.
- HBV viral suppression
 - Lam < adefovir (Ade) < entecavir < telbivudine (Tel) < tenofovir (Ten)
- HBV resistance
 - Ten > Tel > Ent > Ade
 - Rate of resistance
 - Lam 69% / 5 yrs
 - Ade 30% / 4 yrs
 - Ten rare
- Adefovir dipivoxil
 - Acyclic phosphate nucleotide analog of adenosine monophosphate
 - ↓ HBV polymerase and reverse transcriptase
- Entecavir
 - Deoxyguanine nucleotide analog which selectively inhibits replication of HBV
 - ↓ priming of HBV DNA polymerase
 - ↓ synthesis of 192 nd strand of HBV DNA
- Development of resistance is associated with flares.
- Telbivudine
 - L. nucleoside analog of thymidine
- Tenofovir disoproxil fumarate
 - Chemically similar to adefovir mechanism of action similar to adefovir (a cyclic nucleotide inhibitor of HBV polymerase and reverse transcriptase)
 - Resistance does not occur



93. Give the management of nucleoside and nucleotide resistance.

- Nucleoside resistance
 - Lamivudine, telbivudine, entecavir → tenofovir or adefovir (nucleotide analogues);
 - Note: nephrogenic potential is adefovir > tenofovir; in fact, tenofovir may actually improve renal function)
- Nucleotide resistance
 - Adefovir
 - Naïve → tenofovir or entecavir (preferred for ↑↑ HBV DNA levels)
 - Prior lamivudine resistance → tenofovir plus telbivudine or entecavir (nucleoside analogues)
 - Tenofovir
 - Naïve → lamivudine, telbivudine, entecavir
 - Prior lamivudine resistance → entecavir

Abbreviations: NS-R, nucleoside resistance; NT, nucleotide; NT-R nucleotide resistance

94. Give the recommendations for treatment of HBV-associated cirrhotic patients (HBeAg positive or negative).

HBV DNA	Cirrhosis	Treatment strategy
○ <2,000	Compensated	○ May choose to treat or observe ○ Adefovir or entecavir preferred
○ ≥2,000	Compensated	○ Adefovir or entecavir are first-line options ○ Long-term treatment required, and combination therapy may be preferred
○ <200 or ≥200	Decompensated	○ Combination with lamivudine, or possibly entecavir, plus adefovir preferred ○ Long-term treatment required, and combination therapy may be preferred ○ Wait list for liver transplantation



95. Give the management options of **rescue therapy** for HBV when there is resistance to lamivudine, adefovir, entecavir or telbivudine.

Resistant drug	Rescue therapy
○ Lamivudine	-Continue lamivudine and add adefovir or tenofovir -Switch to emtricitabine/tenofovir
○ Adefovir	-Continue Adefovir and add lamivudine -Switch to or add entecavir (if no prior LAM-R) -Switch to emtricitabine/tenofovir
○ Entecavir	-Switch to or add adefovir or tenofovir
○ Telbivudine	-Continue telbivudine and add adefovir or tenofovir -Switch to emtricitabine/tenofovir

Abbreviation: LAM-R, resistance to LAM

Printed with permission: Keeffe EB, et al. *A Clin Gastroenterol Hepatol* 2008;6(12):1315-41.

- HBsAg mutants
 - Vaccine escape
 - In persons for whom HBIG does not prevent HBV, about half of these “escapes” are due to alterations in the “a” determinants of the HBsAg, leading to immune escape.
 - May influence HBV recurrence after liver transplantation.
- **Mutations in the Precore, Basal Core Promoter and Core Genes**
 - More common in HBe-Ag-negative persons
 - Stop the synthesis of HbeAg
 - ↑ development of fulminant HBV
 - ↑ risk of HCC
 - ↓ response to interferon
- **Mutations in HBV DNA polymerase**
 - “HBV reverse transcriptase function of the polymerase gene is highly preserved....” (Feldman M., et al. Sleisenger and Fordtran’s Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier, Philadelphia, 2010, page 1291).



96. Give the treatment of anti-viral resistant HBV.

- Lamivudine or telbivudine resistance
 - Add adefovir (or tenofovir)
 - (stop lamivudine, switch to Truvada)
 - (Switch to entecavir- pre-existing lamivudine resistant mutations predispose to entecavir resistance)
- Adefovir resistance
 - Add lamivudine
 - (stop adefovir, switch to Truvada)
 - Switch to or add entecavir
- Entecavir resistance
 - Switch to or add tenofovir

*Truvada-combination of emtricitabine and tenofovir

****Emtricitabine, tenofovir, and Truvada**

SO YOU WANT TO BE A HEPATOLOGIST!

- Viral resistance may occur weeks to months before a virologic breakthrough
- In the context of HBV, define “**virologic breakthrough**”.
 - Virologic breakthrough
 - “> 1 log₁₀ (10-fold) increase in serum HBV DNA levels above the previous nadir” (Feldman M., et al. Sleisenger and Fordtran’s Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier, Philadelphia, 2010, Table 78.3, page 1304).
- Virologic rebound may follow virologic breakthrough; define “virologic rebound”.
 - Virologic rebound HBV DNA > 10⁵ (20,000 IU/mL)

- **Special conditions in treating HBV infection**

97. Give the treatment in 7 special considerations of HBV infection.

- **Chronic renal failure, dialysis and renal transplantation**
 - The dose of NAs (NTs and NSs) must be reduced if creatinine clearance < 50 mL / min.
 - Vaccinate HBV surrogate patients with renal transplant, requiring renal dialysis, or end-stage renal disease



- HBV positive, renal impairment
 - NA dose reduction, except for tenofovir
 - Avoid PEG-IFN renal transplant patient (↑ risk of rejection)
 - Monitor creatinine clearance
 - Treat co-existing hypertension and diabetes mellitus
- **HIV co-infection**
 - All HBV positive patients must be screened for HIV before starting their HBV treatment with lamivudine, entecavir or tenofovir, since these drugs have activity against HIV and should not be used as more therapy for HBV for fear of causing HIV resistance.
 - PEG-IFN, adefovir and telbivudine are not active against HIV.
 - Tenofovir, emtricitabine or lamivudine, plus a third drug which is active against HIV
- **HCV co-infection**
 - Treat HCV, monitor HBV DNA and treat HBV activation with NAs (activity of HBV is often suppressed in presence of HCV).
- **Post-LT (liver transplantation)**
 - Entecavir monotherapy prophylaxis, or
 - Tenofovir plus emtricitabine with or without HBIG (hepatitis B immunoglobulin)
 - Lamivudine plus adefovir plus HBIG
- **Acute liver failure (ALF)** for severe acute HBV infection
 - Start entecavir or tenofovir
 - Assess for possible need for liver transplantation
 - Continue entecavir or tenofovir for at least
 - 3 months after seroconversion of HBsAg (HBsAg → anti-HBs)
 - 12 months after seroconversion of HBeAg (HBeAg > anti-HBe)
- **Pregnancy**
 - FDA category
 - B tenofovir (preferred), telbivudine
 - C lamivudine, adefovir, entecavir
 - **X PEG-IFN** – Do not use



- Woman with cirrhosis / advanced fibrosis, “planned pregnancy” (2-month contraception, PEG-IFN for 12 months)
 - If couple not cooperative with 2-month contraception, or IFN otherwise contraindicated, use NA with FDA B category drug
- Unexpected pregnancy
 - If on PEG-IFN → telbivudine or tenofovir (FDA X → B class Rx)
 - If on lamivudine, adefovir or entecavir → tenofovir or telbivudine (FDA C → B class Rx)
 - If HBV infection newly diagnosed, use the usual (non-pregnant) indications for HBV Rx for possible hepatic flare, during or after pregnancy
- To prevent vertical transmission to newborn child
 - NA to reduce viral loads (especially for mothers HBeAg-positive, and / or serum HBV DNA > 10⁷ IU / mL
 - HBIG plus HBV vaccination
- Safety of NA for mother who wishes to breast feed is unknown

Flares

98. Give 5 causes of “flares” of acute hepatitis (reactivation, decompensation) in persons with chronic HBV.

Cause of flares	Comment
○ Spontaneous	- Seroconversion HBeAg+ → HBeAg- - Reappearance of IgM anti-HBc
○ Drugs	
- Immunosuppressive therapy	- Flares are often observed during withdrawal of immunosuppressants; requires preemptive antiviral therapy
- Steroids, Interferon (systemic interferon, common; oral agents, rare)	- Flares are often observed during the second to third month: may herald virologic response
- Antiviral therapy, Lamivudine	
○ During treatment	- Flares are no more common than with placebo
○ YMDD mutant	- Can have severe consequences in patients with advanced liver disease



Cause of flares	Comment
○ Adefovir, entecavir	- On withdrawal, flares are caused by rapid reemergence of wild-type HBV; can have severe consequences in patients with advanced liver disease
○ HIV treatment	- Flares also can occur with immune reconstitution or secondary to antiretroviral drug hepatotoxicity
○ Genotypic variation - Precore and core promoter mutants	- Fluctuations in serum ALT levels are common with precore and core promoter mutants
○ Superimposed infection with	- HAV, HCV, HDV may be associated with suppression of
○ Other hepatitis viruses	- HBV replication
○ Alcohol use	
○ Reactivation of HBV infection - ↑ HBV-DNA - ↑ IgM anti-HBe - ↑ ALT, AST - Acute lobular hepatitis, plus anti-HBe - Acute lobular hepatitis, plus previous histological changes of chronic hepatitis	
○ Anti-HBe → HBeAg (seroconversion) - Type II polyclonal IgG, plus monoclonal IgM - Type III polyclonal IgG, plus rheumatoid factor	
○ Withdrawal of immunosuppression - Extrahepatic manifestations - Active state of immune clearance with anti-HBs or anti-HBe → HBsAg - Immunosuppressants - Biologicals - Chemotherapy	

Adapted from: Poterucha JJ. *Mayo Clinic Gastroenterology and Hepatology Board Review* 2008: pg.298.



SO YOU WANT TO BE A HEPATOLOGIST!

- A flare of HBV may occur with a superinfection with a hepatotropic virus, such as HAV, HCV, HDV.
- The prognosis for this superinfection is poor
- For example, acute HCV on top of chronic HBV is associated with a 34% risk of liver failure and a 10 mortality rate.
- In the presence of hepatotropic viral superinfection in chronic HBV, the non-PCR tests for HBV DNA and for HBeAg may be negative.
- Give the explanation for this surprising finding.
 - Negative HBV DNA and HBeAg with viral superinfection in chronic HBV, due to viral interference.

SO YOU WANT TO BE A HEPATOLOGIST!

- Give the reason why anti-HBV therapy during pregnancy is not usually indicated.
 - When “newborn child of an HBV-positive mother is given HBV vaccination plus injection of HBIG, breakthrough HBV infection in the child occurs in < 5%
 - Lamivudine may be discontinued during pregnancy
 - HBC, FDA category B
 - HBC plus HIV, FDA category C

- **Before starting immunosuppressive therapy or chemotherapy**
 - HBe-Ag-positive
 - NA before, during and for 12 months after immunosuppressive therapy or (preferable entecavir or tenofonir) chemotherapy, regardless of serum HBV DNA level
 - HBeAg-negative patients with detectable HBV DNA –treat as per above
 - HBeAg-negative, anti-HBe antibody positive, detectable serum HBV DNA – treat as per above,



- HBeAg-negative, anti-HBe antibody positive, undetectable serum, HBV DNA – monthly monitoring of ALT and HBV DNA, with NA for resection.
- Anti-HBe positive patients receiving bone marrow or stem cell transplantation – NA prophylaxis
- HbsAg negative recipient of liver graft from anti-HBe-positive donor – indefinite lamivudine prophylaxis
- Polyarteritis nodosa (PAN) – think of HBV / HCV infection

○ **Steroid withdrawal**

99. Give the reason why ALF may occur during steroid withdrawal for treatment of polyarthritis nodosa (PAN) in HBV, but not in HCV.

- Hepatic damage in HBV (but not in HCV) is immune-mediated, and would cause aggressive necrosis upon immune reconstitution resulting from withdrawal of steroids for treatment of PAN.

Please see: Peltekian KM, Hirsch G. Chapter 59. In: Therapeutic Choices. Grey J, Ed. 6th Edition, Canadian Pharmacists Association: Ottawa, ON, 2011, Table 3: Hepatitis B, page 789.

○ **Immune Rebound**

A short course of glucocorticosteroids (“steroids”) is no longer used to increase virologic response rates, because of the immune rebound when steroids are stopped.

100. Give the explanation for this immune rebound which occurs when the patient with HBV infection is placed on corticosteroids which are then stopped.

- When steroids are stopped, there is ↑ activation of T lymphocytes that promote the Th1 cytokine responses.
- The ↑ Th1 cytokine response occurs at the time when there is ↑ expression of HBV.
- The combination of ↑ HBV antigen plus ↑ Th1 cytokine response causes hepatic decompensation.
- Precore mutant HBV (aka HBe Ag-negative HBV) flares due to a change in the ratio of precore HBV / wild-type HBV.
- Mutations in basal core promoter region (with or without precore mutants)
 - ↑ HbeAg
 - ↑ HBV replication
 - ↑ necroinflammation



- HBe Ag-negative HBV plus both precore and core mutations
 - ↑ risk of flare with chemotherapy
- **Immune tolerant**
 - When immune tolerant, then no liver damage and no treatment needed
 - In HBV, “Be patient and wait”

Peginterferon 180 µg/wk	- 35%	E ⁺ → E ⁻ seroconversion
Genotype A	50%	
B, C, D	30%	

HBV Infection and Hepatocellular Cancer (HCC)

101. Give 5 characteristics of healthy HBV carriers (no cirrhosis) who are candidates for HCC screening.

- African males/ females > 20 years
- Asian male >40 years
- Asian female >50 years
- Caucasian
 - Inactive or active disease with cirrhosis*
- Family history of HCC
- Co-infection with HCV, HIV

*Caucasians with inactive disease and no cirrhosis have a low risk of HCC development, and HCC screening is generally not recommended, but may be considered if there is a family history of HCC, or co-infection with HCV.

Adapted from: Sherman M. *Best Practice & Research Clinical Gastroenterology* 2005;19(1): 105.

“Play a crucial and critical role in finding
your own humility and humanity.”

Grandad



102. Give 5 factors associated with ↑ risk of HCC in HBV infection.

- Patient
 - Male
 - > 45 years
 - 1^o relative with HCC
 - Race (African > Asian men > Asia women)
- Serology
 - HbsAg-positive
 - HBeAg-positive
 - Reversion of anti-HBe to HBeAg⁺
 - HBV DNA > 10⁵
 - Cirrhosis

Clinical Alert ! HBeAg and HCC

- HCC may develop in HBV
 - In the absence of cirrhosis
 - Even after seroconversion (HBeAg⁺ → HBeAg⁻, anti-HBe-positive)
 - Even after loss of HBsAg
 - This is why screening is so important
- A normal ALT is not a good marker for disease activity
 - ~25% of HBV carriers with normal ALT and serum HBV DNA > 10⁴ copies per mL have stage 2 or greater inflammatory or fibrosis on liver biopsy
- HBV and risk of HCC and cirrhosis
 - The level of HBV DNA correlates with the relative risk of HCC and cirrhosis
 - Lowering of HBV DNA is associated with ↓ risk of HCC and cirrhosis
 - Even HBV DNA of 200 IU/mL or 10,000 copies/mL may be associated with ↑ risk of HCC and cirrhosis
 - An argument can be made to use maintenance HBV therapy to suppress HBV and ↓ risk of long-term complications



Clinical Alert! Clearance of HBsAg and HCC

- Even HBsAg clearance, ... is not an absolute safeguard against the future development of HCC in persons who already have cirrhosis” (Feldman M., et al. Sleisenger and Fordtran’s Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier, Philadelphia, 2010, page 1289).
- HBV carriers (without cirrhosis) are also at risk of developing HCC, and should be appropriately screened.
- Because of vaccine escape mutants in the “a” determinant of the HBsAg, about 2% of vaccinated persons do not mount a protective response.

For more detail regarding treatment of chronic hepatitis B: definitions of response to antiviral therapy, see Feldman M., et al. Sleisenger and Fordtran’s Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier, Philadelphia, 2010, Table 78.3, page 1300.

For more details for guidelines and recommendations for treatment of chronic HBV, please see the attached guidelines from several professional organizations, as well as (Feldman M., et al. Sleisenger and Fordtran’s Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier, Philadelphia, 2010, Table 78.5, page 1301).

Hepatitis C Virus (HCV)

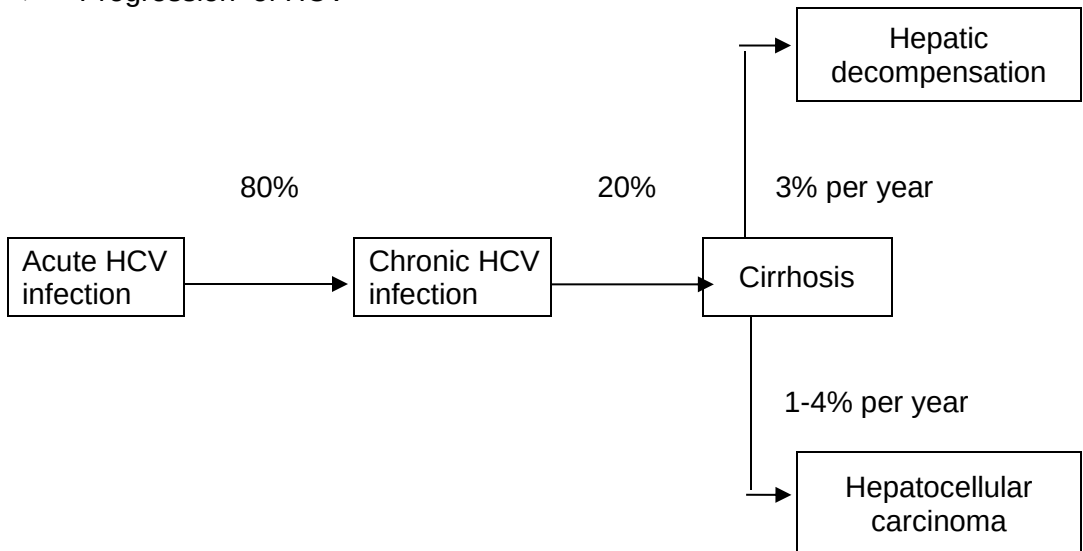
- Demography
 - Perinatal exposure
 - Transmission rate
 - HCV ~ 5%
 - HCV + HIV ~ 15%
 - Breastfeeding dangerous when HCV > 10⁸ copies/mL
 - Percutaneous
 - Blood products (1/2x10⁶)
 - IV drug use (60% to 90% HCV infected)
 - Nucleotide accidents
 - Hemodialysis
 - Non-percutaneous
 - Sexual contact
 - Intercourse
 - Per rectum
 - During menstruation



➤ Pathogenesis

- About 75% of persons with acute HBV develop chronic HCV because the HBV escapes the immune response to clear the infection.
- 75% of persons with acute HCV progress to chronic HCV infection because of ineffective immune against the HCV

➤ Progression of HCV



“Life is an opportunity for us to contribute something that outlasts us and makes the world a better place.”

Apoorve Dubey



➤ Risk factors and screening

103. Give six groups of persons at risk of hepatitis C virus (HCV) infection. Give the estimated **prevalence** of these persons who are infected with HCV in industrialized countries.

Groups at risk	Estimated prevalence (range %)
○ A blood transfusion received before 1990/91	- 5-10
○ Children born from HCV positive mothers	- 3-10
○ Health care workers	- Related to country of origin
○ Hemodialysis patients	
○ Hemophiliac treated before 1990/91	- 50-90
○ HIV infected persons	- 25-35
○ Incarcerated persons	- 30-80
○ Injection drug users	- 35-90
○ Migrants coming from endemic regions	- Related to country of origin
○ Persons with unexplained persistently elevated ALT	- 15
○ Thalassemics	- 42-83

Abbreviation: ALT, alanine aminotransferase

104. Give the 10 groups / types of persons who should be **screened** for HCV.

- Concurrent disease
 - Hemodialysis patients
 - Transplanted patients
 - Immunosuppressed patients
 - Hemophylics
 - Blood transfusion before approximately 1990 (depends on country)



- At risk occupations
 - Needle stick injury
 - Inmates
- At risk behaviour
 - HIV-positive patients
 - Men who have sex with men (MSM)
 - Sex trade workers (STWs)
 - Those with > 50 lifetime sexual partners
 - Those with a history of STD
 - STDs
 - IV drug users
- Regular folks
 - Those with unexplained elevated ALT
 - Immigrants

Printed with permission: Van Herck, et al. *Best Practice Res Clin Gastroenterol* 2008;22:6:1009-1029.

- The person pricked with an HCV-contaminated needle should be tested for HCV RNA within 4 weeks, then tested for anti-HCV and ALT at 12 and 24 weeks.
- Family members and sexual contacts of HCV-infected persons need to be tested for anti-HCV.
- Test the children of HCV-infected mothers for HCV RNA when 1 month old.

➤ Clinical

105. Give 10 non-dermatological **extrahepatic manifestations** of Hepatitis C (HCV) infections.

- Skin
 - Vitiligo
 - Lichen planus



- Lung
 - Idiopathic pulmonary fibrosis
- Endocrine
 - Diabetes mellitus
 - Autoimmune thyroiditis
 - Thyroid cancer

106. Give 10 **dermatological manifestations** in untreated or treated patients with patients with HCV infection.

- PCT (porphyria cutanea tarda)
 - Sporadic or autosomal dominant heredity
 - sun exposed areas, especially dorsal aspect of hands
- Mixed cryoglobulinemia
- Leukocytoclastic vasculitis (palpable purpura in legs)
- Reactions
 - At sites of injection of IFN (interferon)
 - Localize cellulitis / necrosis
 - Erythema multiforme major (Steven Johnson Syndrome)
 - Exfoliative dermatitis
 - Vesiculobullous reaction
 - Ribavirin (histamine like reaction)
 - Localized / confluent lashes
 - Vesicular lesions

107. A patient presents with abdominal pain, leucocytoclastic vasculitis, palpable purpura, and ↓ complement. Give the likely diagnosis.

- Young adult
 - HSP (Henoch-Schonlein purpura)
- Older adult
 - Mixed cryoglobulinemia (e.g. associated with HCV)



- Musculoskeletal disorders (MSK)
 - Chronic polyarthritis
 - Sicca syndrome
- Kidney
 - Cryoglobulinemic nephropathy
 - Non-cryoglobulinemic nephropathies
 - Renal cell carcinoma
 - Membranous nephropathy
 - MPEN (membranoproliferative) nephropathy
 - Glomerulonephritis
- Hematology
 - B cell non Hodgkin's lymphoma
 - Mixed cryoglobulinemia
 - Monoclonal gammopathies

Adapted from: *Sleisenger and Fordtran's Gastrointestinal and Liver Disease: Pathophysiology/ Diagnosis/ Management*. Ninth edition, 2010, Table 79.1, page 1320,

108. Give the clinical feature of acute HCV infection suggests that the patient will be in the lucky group and clear their HCV.

- Persons with acute HCV associated with jaundice have an increased chance of clearing in HCV.

109. Give 5 clinical findings in the patient with HCV which suggests associated **cryoglobulinemia**.

– Skin	– Purpuric leucocytoclastic vasculitis
– CNS / PNS	– Peripheral neuropathy
– GI	– Vasculitis → abdominal pain
– Kidney	– Acute / chronic renal failure
	– Nephrotic syndrome
	– Glomerulonephritis (membranoproliferative)
– Laboratory	– RF (rheumatoid factor) positive
	– ↓ complement



➤ Laboratory

Useful Reminders

- In acute HCV infection, HCV RNA appears before anti-HCV antibodies.
- The presence of HCV RNA plus anti-HCV antibodies may arise from acute HCV infection or a flare (exacerbation) of chronic hepatitis C.
- If hepatitis in the immunosuppressed patient, HCV RNA must be measured to make the diagnosis of anti-HCV antibodies.

110. Give the laboratory assessment prior to therapy of HCV, and explain why.

- Anti-HCV
- HCV RNA (qualitative +/- quantitative)
- HCV genotyping
- ALT, ALP, bilirubin, albumin, PT INR, HBsAg, HIV
- CBC, glucose, TSH, ANA, smooth muscle antibody (SMA), quantitative immunoglobulins, creatinine, B-HCG
- Abdominal Ultrasound, ECG (if age >50, cardiac disease history)
- Liver biopsy recommended but not mandatory

111. Give the **interpretation** of anti HCV results.

Anti HCV by ELISA	Anti HCV by RIBA	Interpretation
○ Positive	- Negative	False positive ELISA; patient does not have true antibody
○ Positive	- Positive	Patient has antibody ^a
○ Positive	- Indeterminate	Uncertain antibody status

Abbreviations: ELISA, enzyme linked immunosorbent assay; HCV, hepatitis C virus; RIBA, recombinant immunoblot assay

^aAnti- HCV does not necessarily indicate current hepatitis C infection



112. Give the reasons why the ALT or AST is not a useful marker for the progress of HCV.

- The transaminases
 - Fluctuate widely in HCV
 - A normal level may occur even though chronic HCV infection is present
 - Women with low levels of HCV RNA may more commonly have low ALT, less inflammation and less fibrosis.

113. Give 8 non-biopsy tests to predict the presence of fibrosis in HCV

➤ Blood tests

- ↑ AST and ↑ ALT, ALT > AST, AST-to-platelet index
- A2-macroglobulin
 - Haptoglobulin
 - Apolipoproteins A-1
 - GGT
 - Bilirubin
- FibroSure ®
 - Composite score of blood tests

➤ Transient elastography (Fibroscan®)

- AUC (area-under-the-curve) for predicting cirrhosis, 0.94

Note

- These tests do not accurately categorize
 - Lower grades of cirrhosis
 - Amount of inflammation

➤ Pathology

- Liver biopsy grading of HCV is made by a scoring system (e.g. Knodell, Ishak or METAVIR)



114. Give the pros and cons of performing a percutaneous liver biopsy in a patient with HCV.

Issues	Argument in favor of biopsy with acceptable risk	Reasons for not performing a biopsy.
○ Prognosis	- Extent of fibrosis and inflammation are best predictors of disease progression	● Non-invasive markers may accurately stage and grade disease
○ Decision to treat	- Genotype 1: Identify those most in need of therapy (therapy longer in duration and less likely to succeed)	● Genotypes 2 and 3: Patients motivated for therapy may forgo biopsy (therapy shorter in duration and more likely to succeed)
○ Treatment-related side effects	- Severity of liver disease helps in deciding of whether to endure or stop therapy	● Commitment to therapy should be independent of disease severity
○ Previously treated	- Lower success with retreatment. Identify those most in need of therapy (advanced fibrosis)	● Motivated patients who are genotype 2 or 3, were previously treated with interferon monotherapy, are candidates for re-treatment regardless of disease severity

Printed with permission: Reddy K R. 2006 AGA Institute Postgraduate Course Syllabus: pg. 81.

SO YOU WANT TO BE A HEPATOLOGIST!

- Give the circumstances when liver biopsy needs to be considered in HCV.
 - Genotype 1, 4 – perform liver biopsy when results will change treatment of HCV
 - Genotype 2,3 – perform liver biopsy when treatment of HCV may be postponed
 - Liver biopsy not necessary if clinical, laboratory or diagnostic imaging suggests that cirrhosis is already present



Clinical Alert!

➤ HCV and autoimmune conditions

- Because autoantibodies are common in HCV, and may not be associated with disease, so be **cautious** making the diagnosis of an autoimmune condition in a person with HCV based just on seropositivity for autoantibodies.

➤ False-negative HCV serology

- Even though the EIAs (enzyme immunoassays) for HCV have excellent performance characteristics (sensitivity and specificity of ~ 99%), anti-HCV may be negative in some persons who have HCV replication in the liver.
 - This false-negative HCV serology is seen with
 - Hemodialysis
 - Immune suppression
 - If the person is not at high risk for a false negative HCV (e.g. hemodialysis, immune suppression), a negative anti-HCV on an EIA excludes HCV infection.
 - Anti-HCV positive is diagnostic of HCV infection if there is ↑ serum ALT
- Early diagnosis of HCV depends on the time after exposure when the test becomes positive:
 - HCV RNA 1 to 3 weeks
 - Anti-HCV 7 to 8 weeks

115. Give 5 reasons for biopsying the liver of persons with HCV, genotype 1, without obvious cirrhosis.

- There is no correlation between ALT or viral load, and stage of fibrosis.
- Surrogates for the presence of advanced fibrosis such as reversal of ALT/AST ratio, platelet count, pro time-INR are not sensitive.
- Markers of fibrosis such as hydroxyl proline are not sufficiently specific.
- Given the variable natural history and the complexity and cost of treatment, informed decision can only be made based on histology.



- Patients who do not respond need further advice on what is next and histology may be essential in these persons.
- Liver biopsy may be safer than treatment when you consider alternatives such as treating everyone.
- Post-liver transplantation

116. Give the **METAVIR** system for staging/grading chronic hepatitis.

	Piecemeal and lobular necrosis *(A)	Fibrosis (F)
0	None	None
1	Mild activity	Portal fibrosis without septa
2	Moderate activity	Portal fibrosis with septa
3	Severe activity	Numerous septa (bridging fibrosis), without cirrhosis
4		Cirrhosis

117. Give the basis for the simple **METAVIR** scoring system.

- Inflammation
 - None, mild, moderate, severe
- Fibrosis
 - None (0)
 - Portal (1)
 - Portal fibrosis with septa (2)
 - Bridging fibrosis (3)
 - Focal
 - Diffuse
 - Marked
 - Cirrhosis

Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier, Philadelphia, 2010, Figure 79.5, page 1323.



SO YOU WANT TO BE A HEPATOLOGIST!

Scoring systems have been used in HCV for the estimation of the extent of fibrosis and the presence of cirrhosis.

- Give reasons relating to the performance characteristics of one grading system (such as the METAVIR scoring system), which would shed light on possible limitations of liver biopsy as the test for standard of care.
 - Concordance (intra- and interobserver variation in reporting degree of fibrosis), 85% to 90%
 - Sampling error
 - False negative rate (for correct staging of cirrhosis), 15% difference in reported fibrosis
 - 1 stage, 33%
 - 2 stage, 2%

Over half of persons with acute HCV progress to chronic HCV, and about 1% of persons per year after infection will progress to do compensated cirrhosis.

118. Give 10 modifiable as well as non-modifiable factors which are associated with the **histological progression** of HCV infection.

There are numerous factors which are established or are possible contributors to the progression of hepatic fibrosis in patients with HCV infection (please see S/F, Table 79.4, page 1325 for extensive details)

- Patient
 - Age (> 40 yrs)
 - Males
 - Caucasian
- Life style
 - Obesity
 - Alcohol (> 50 g/day)
 - Smoking
 - Cannabis use (marijuana)



- Co-morbidities
 - Steatosis
 - Insulin resistance
 - Diabetes (genotypes 1 and 4)
 - Iron overload
 - Co-infection
 - HBV
 - HIV
 - Immunosuppression
 - Schistosomiasis
- Virus
 - Progression of HCV is not associated with HCV load or genotype
- Lab' / pathology
 - Elevated serum ALT levels (elevated)
 - Histology - Moderate to marked necroinflammation

Adapted from: Berenguer M, and Wright TL. *Sleisenger & Fordtran's gastrointestinal and liver disease: Pathophysiology/Diagnosis/Management* 2006: pg. 1696.; and 2010: pg. 1325.

119. Give the name of the high mortality-associated subtype variant of HCV infection ($> 3 \times 10^6$ copies/mL) seen in HCV infected persons who have immune suppression related to HIV co-infection or organ transplantation.

- Fibrosing cholestatic variant of HCV-associated hepatitis.

➤ Prognosis: natural history of HCV

○ Acute	→	chronic HCV	55% to 89%
○ Chronic HCV after infection	→	compensated cirrhosis	~1% per year
○ Compensated cirrhosis	→	HCC	~2% per year
	→	decompensation	~3% per year



➤ Treatment

Note: with the amazing success of newly introduced protease inhibitors and the possibility of interferon- and ribavirin-free treatment regimens being standard of care in the very near future, some of these terms may become used much less.

In the patient with HCV, define the terms RVR, EVR, ETR and SVR, as well as the definition and clinical implication of each of the 4 types of responses.

- RVR
 - Rapid virologic response
 - Undetectable HCV on a serum after 4 weeks of anti-HCV therapy
 - Higher chance of SVR; may respond as well with only 24 weeks of treatment
- EVR
 - Early virologic response
 - 2-log (100-fold) drop in HCV RNA load after 12 weeks of anti-HCV therapy
 - Failure to achieve EVR associated with almost no chance of SVR and treatment can usually be stopped
- pEVR
 - Partial EVR
 - > 2-log (100-fold) decrease in HBV DNA after 12 weeks of anti-HBV therapy (residual HBV RNA still present)
- cEVR
 - Complete EVR
 - No HCV RNA in serum after 12 weeks of anti-HCV therapy
 - On treatment response. Observe for SVR.
- PVR
 - Partial viral response
 - HCV RNA present in serum at 12 weeks, but not at 24 weeks
- NR
 - No response, aka will response
 - Failure to achieve EVR
- ETR
 - HCV RNA undetectable at end of treatment wk 48 – 1 genotype, wk 24 – 2,3
- SVR
 - Sustained viral response
 - Surrogate marker for eradication of SVR
 - No detectable HCV RNA in serum after 24 weeks of anti-HCV therapy

Printed with permission: Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier, Philadelphia, 2010, Figure 79.7, page 1329.



120. Give the HCV-RNA levels at week 4,12 and 24 in persons with rapid virologic response (RVR), early virologic response (EVR), slow virologic response (SVR) and no virologic response (NVR).

	HCV-RNA		
	Week 4	Week 12	Week 24
➤ Rapid virologic response (RVR)	Undetectable (<50 IU/ml) ^a	Undetectable	Undetectable
➤ Early virologic response (EVR)	>50 IU/ml	Undetectable	Undetectable
➤ Slow virologic response (SVR)	>50 IU/ml	>50 IU/ml, but >log 2 drop	Undetectable
➤ No virologic response (NVR)	>50 IU/ml	>50 IU/ml, but < log 2 drop	Detectable

^a Level of detection (LOD) changes with more sensitive test. The currently available new tests have a LOD <15 IU/ml , no prospective studies using these tests have been performed.

Abbreviations: EVR, early virologic response; NVR, no virologic response; RVR, rapid virologic response; SVR, slow virologic response

Printed with permission: Ferenci P. *Best Practise Res Clin Gastroenterol* 2008;22:1109-1122.

121. Give the management principles of persons with HCV infection.

- Prevention, screening, vaccination (none), prophylaxis on exposure
- General management strategy
- Assessment of factors predictive of viral response
- Specific treatments
- Select optimal agent
- Reassess therapy
- Screen for HCC

Adapted from: Berenguer M, and Wright TL. Hepatitis C. *Sleisenger & Fordtran's Gastrointestinal and Liver Disease: Pathophysiology/ Diagnosis/ Management* 2006. pg. 1681-1712.



- Objective of therapy
 - Eradicate HCV
 - SVR (sustained viral response)
 - Absent serum HCV RNA 6 months after
- Treatment-associated SVR depends on HCV genotype and therapy used
- I/R (interferon plus ribavirin)
 - Genotype I 40% to 50%
 - Genotype II 70% to 80%
- HCV-enters hepatocytes by attachment and transport, using proteins
 - E1 and E2 envelop proteins
 - CD81 tetraspan superfamily
 - SR-B1 scavenger receptor class B type 1
 - LDL-R LDL receptor

For details of the complex multistep life cycle of HCV, please see Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier, Philadelphia, 2010, Figure 79.1, page 1314.

122. Give 8 factors which **predict a poor treatment response** in HCV.

- Patient
 - African racial origin
 - Latino ethnicity
 - Male
 - Older (age > 40)
 - Weight: lighter patients (<75kg) more likely to respond (odds ratio 1.91) (fixed dose)
- Lifestyle
 - Poor adherence to anti-HCV treatment
 - HIV coinfection



- Co-morbidities
 - Insulin resistance
 - Diabetes
 - Obesity
 - Alcoholism
 - HBV co-infection
 - No comorbidity to prevent full drug dose (anemia, thrombocytopenia)
 - Compliant to treatment
 - Incarcerated (they get their Rx!)
 - Good social support
 - Poor immunosuppression
 - Poor renal function (ribavirin contraindicated with $\uparrow$ GFR)
 - Poor psychiatric comorbidity
 - Advanced hepatic fibrosis (high fibrosis score)
 - Steatosis
 - Decompensated cirrhosis
- Types of response to anti-HCV therapy
 - NR > pEVR > cEVR > RVR
- The virus itself
 - Genotypes 1, 4
 - High HCV load
 - No IL-28 B CT, TT genotype
 - Non-I
 - Viral genotype: Genotype 1&4 (42-46%), Genotype 2, 3 (76-82%)
 - Lower viral levels: $>2 \times 10^6$ (42-53%), $<2 \times 10^6$ (62-78%)
 - Early virologic response: negative EVR (defined as 2-log decrease in HCV RNA in first 12 weeks of treatment) is predictive negative SVR (97%)
 - Overall sustained virologic response (SVR) (undetectable HCV RNA 24 weeks after cessation of therapy) to interferon monotherapy: 5-15%, to combined interferon and ribavirin: 30-40%, to combined pegylated interferon and ribavirin: 54-56%.



- Absolute or relative contraindications
 - Pregnancy or attempting conception
 - Active autoimmune diseases
 - Significant cardiopulmonary disease
 - Uncontrolled psychiatric disease
 - Uncontrolled seizures
 - Severe cytopenias, including transfusion-dependent anemia
- Note: stop anti HVC therapy
 - pEVR in genotype 1, 4 (the use of serum HBV RNA level at week 12) to indicate an EVR, does not apply to genotype 2 or 3 infection
 - HBV RNA still present at 24 weeks for each of interferon and ribavirin, 30% of HCV patients have to stop therapy because of AEs (adverse effects)

Trick questions

- Give the management of persons with HCV.
 - When all other factors are taken into account, being in prison improves the clinical outcomes, because all treatment is given (forced high compliance rate)
- Mothers with chronic hepatitis C are allowed to breast-feed their children
 - As long as they are negative for HIV
 - Do not use intravenous drugs
 - Nipples are not cracked
- Patients with chronic hepatitis C should be vaccinated against HAV and HBV
 - Tested for HIV, and associated alcohol abuse and /or fatty liver treated appropriately

Source: EASL clinical Practice Guidelines, J Hepatol 2011; 55; 245-264.

"Simplify complex issues"
 "What part of "no" do you not understand."
 Grandad



Ribavirin (RBV)

123. Give 6 relative or absolute **contraindications** to the use of Ribavirin.

- Pregnancy
- Inadequate contraception (contraception to prevent conception for 6 mon after RBV stopped)
- End-stage renal disease
- Anemia (cannot give adequate dose, since ribavirin may cause anemia and thus require dose reduction)
- Angina pectoris (possible)
- Old age (possible)
- Known allergy to ribavirin

124. Give the common **adverse effects** (AEs) of Ribavirin (RIB) in the treatment of HCV, and give the management of these AEs.

Clinical: “flu-like symptoms”, fatigue, anorexia, nausea, nasal congestion, irritability, cognitive impairment, insomnia

○ Laboratory	Level		Other clinical considerations
○ Hemoglobin	10 gm/dL	○ Reduce ribavirin by 200 mg/day	○ Consider starting erythropoietin; if Hgb responds poorly to dose reduction, check iron studies and consider reducing peginterferon
	8.5 gm/dL	○ Stop ribavirin	○ Hold ribavirin and consider stopping; transfuse as necessary
○ White blood cells	1500/ μ L	○ Reduce peginterferon by 50%	○ Monitor more closely
	1000/ μ L	○ Stop treatment	○ Monitor more closely; consider G-CS



	Level	Other clinical considerations	
➤ Absolute neutrophils	750/ μ L	○ Reduce pegIFN by 50%	○ Monitor more closely
	500/ μ L	○ Stop pegIFN	○ Monitor more closely
➤ Platelets	50,000/ μ L	○ Reduce pIFN by 50%	○ Individualize dose adjustment
	25,000/ μ L	○ Stop IFN	○ Consider platelet transfusion or platelet stimulating factor

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- Overall dose reduction of ribavirin in 19% of Ribavirin-treated persons, with discontinuation of Ribavirin in 10%

125. Give the standard therapy for chronic HCV according to viral genotype.

Genotype	Interferon dose (per week)	Ribavirin dose (mg/day)	Duration (weeks)	SVR
1	180 μ g PEG alfa-2a or 1.5 μ g/kg PEG alfa-2b	800-1400 mg/day weight-based	48	41-42%
2	180 μ g PEG alfa-2a or 1.5 μ g/kg PEG alfa-2b	800 mg/day	24	66-75%
3	180 μ g PEG alfa-2a or 1.5 μ g/kg PEG alfa-2b	800 mg/day	24	66-75%
4	180 μ g PEG alfa-2a or 1.5 μ g/kg PEG alfa-2b	1000-1200 mg/day	48	55%
5	180 μ g PEG alfa-2a or 1.5 μ g/kg PEG alfa-2b	1000-1200 mg/day	48	64%
6	180 μ g PEG alfa-2a or 1.5 μ g/kg PEG alfa-2b	1000-1200 mg/day	48	63%

Abbreviation: SVR, sustained viral response

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126. Give the week of assessment of HCV for EVR or SVR in genotype1/4 HCV and genotype 2/3 HCV patients, and the management implications

Assessment	Week of assessment	Interpretation	Management implications
○ Genotype 1, 4	4	HCV RNA <50 IU/ml predicts 90% SVR	Duration of treatment of 24 weeks can be considered
○ RVR	12	HCV RNA <50 IU/ml predicts SVR in 70%	Duration of treatment can be 48 weeks
○ Complete EVR	12	HCV-RNA decline of >2-log but >50 IU/ml is associated with higher relapse (30%) than complete EVR (15%)	Duration of treatment should be extended to 72 weeks to reduce relapse and increase SVR
○ Partial EVR	12	HCV-RNA decline <2 log is associated with SVR in 2% with 48 weeks treatment	Treatment should be stopped
○ Non-EVR	24	HCV RNA >50 IU/ml (detectable) is associated with non-SVR	Treatment should be stopped
○ 24-week Response			
○ Genotype 2/3	4	HCV RNA <50IU/ml predicts 90% SVR	Duration of treatment of 12-16 weeks can be considered
○ RVR	4	HCV RNA >50 IU/ml predicts SVR < 50%	Consideration of treatment for duration longer than 24 weeks
○ Non-EVR			

Printed with permission: Terrault N. 2008 ACG Annual Postgraduate course book: pg. 170-171.



127. Give the clinical significance in HCV infection of CC, CT and TT **genotypes of the IL-28 gene** on chromosome 19.

➤ CC genotypes

- Codes for IFN-λ-3 (“lambda”), with ↑ production of intrinsic IFN
- ↑ efficacy of PEG-IFN + ribavirin (@x > rate of RVR, complete EVR, and SVR
- More common in European and Asian ancestry

➤ CT and TT genotypes

- No ↑ lambda IFN1, so lower rates of RVR, EVR, SVR
- More common in Latino and African ancestry
- DADs (direct acting anti-viral agents), aka STAT-C (specifically targeted anti-viral therapy) for HCV
- Telaprevir and baceprevir are linear PIs (protease inhibitors) against the NS 3/4a proteases.
- PEG-IFN-alpha + RBV (ribavirin) + PI for genotype 1 HCV

Protease Inhibitors

- In the past 35 years, three Nobel prizes have been won in the area of gastroenterology / hepatology: the H2-receptor and its antagonists (Black), the LDL receptor (Brown and Goldstein), and the rediscovery of Helicobacter pylori and the establishment of its importance in ulcer disease (Warren and Marshall).
- With the identification of the hepatitis C virus (HCV) by Heyden and the recent “game changing” development of protease inhibitors, the hope for the sustained eradication of HCV has gone from dismal to greater than 95%.
- This will have a major impact on liver transplantation rates for HCV, and more importantly to the quality of life of sufferers.
- Unfortunately, with the very high cost of these new anti-HCV medications, this revolutionary therapy may not be available to all persons with HCV infection.
- The rates of regional governmental approval will vary widely in making the drugs available even for the persons of wealth.
- Most national professional groups have not yet formulated guidelines.
- Nonetheless, the candidate coming forward for examination will be required to be aware of these existing new development.



- Therefore, included here are the summarized 2014 AASLD (American Association for Study of Liver Disease) and IDSA (Infectious Diseases Society of America) Recommendations.

These AASLD / IDSA recommendations are available online at

<http://www.aasld.org/PRACTICEGUIDELINES/Pages/default.aspx>
[http://www.idsociety.org/IDSA Practice Guidelines/](http://www.idsociety.org/IDSA_Practice_Guidelines/)

➤ Treatment

- Lifestyle recommendations
 - Persons with HCV infection should be counseled
 - to avoid sharing toothbrushes and dental or shaving equipment, and be cautioned
 - to cover any bleeding wound to prevent the possibility of others coming into contact with their blood
 - Persons should be counseled to stop using illicit drugs and enter substance abuse treatment.
 - Those who continue to inject drugs should be counseled
 - to avoid reusing or sharing syringes, needles, water, cotton, and other drug preparation equipment
 - to use new sterile syringes and filters and disinfected cookers
 - to clean the injection site with a new alcohol swab; and dispose of syringe and needles after one use in a safe, puncture-proof container
 - Persons with HCV infection should be advised
 - not to donate blood
 - to discuss HCV serostatus prior to donation of body organs, other tissue, or semen
- Pharmaceutical therapy recommendations, genotypes and interferon eligibility



Interferon (IFN) eligibility

Eligible	Not eligible
<i>Recommended regimen for treatment-naïve patients with HCV genotype 1 who are eligible to receive IFN.</i> Daily sofosbuvir (400 mg) and weight-based RBV (1000 mg [75 kg] to 1200 mg [$\geq$ 75 kg]) plus weekly PEG for 12 weeks is recommended for IFN-eligible persons with HCV genotype 1 infection, regardless of subtype. Rate: Class I, Level A	<i>Recommended regimen for treatment-naïve patients with HCV genotype 1 who are not eligible to receive IFN.</i> Daily sofosbuvir (400 mg) plus simeprevir (150 mg), with or without weight-based RBV (1000 mg [$<$ 75 kg] to 1200 mg [$\geq$ 75 kg] for 12 weeks is recommended for IFN-ineligible patients with HCV genotype 1 infection, regardless of subtype Rating: Class I, Level B
Eligible	Not eligible
<i>Alternative regimen for treatment-naïve patients with HCV genotype 1 who are eligible to receive IFN.</i> ○ Daily simeprevir (150 mg) for 12 weeks and weight-based RBV (1000 mg [$<$ 75 kg] to 1200 mg [$\geq$ 75 kg]) plus weekly PEG for 24 weeks is an acceptable regimen for IFN-eligible persons with either 1. HCV genotype 1b or 2. HCV genotype 1a infection in whom the Q80K polymorphism is not detected prior to treatment. Rating: Class IIa, Level A	<i>Alternative regimens for treatment-naïve patients with HCV genotype 1 who are eligible to receive IFN.</i> ○ Daily sofosbuvir (400 mg) and weight-based RBV (1000 mg [75 kg] to 1200 mg [$\geq$ 75 kg]) for 24 weeks is an acceptable regimen for IFN-ineligible persons with HCV genotype 1 infection, regardless of subtype; however, preliminary data suggest that this regimen may be less effective than daily sofosbuvir (400 mg) plus simeprevir (150 mg), particularly among patients with cirrhosis. Rating: Class IIb, Level B



Not recommended

The following regimens are not recommended for treatment-naïve patients with HCV genotype 1.

- PEG / RBV with or without telaprevir or boceprevir for 24 to 48 weeks

Rating: Class IIb, Level A

- Monotherapy with PEG, RBV, or a DAA

Rating: Class III, Level A

Genotype 2 – Regardless of interferon eligibility

Recommended regimen for treatment-naïve patients with HCV genotype 2, regardless of eligibility of IFN therapy:

- Daily sofosbuvir (400 mg) and weight-based RBV (1000 mg [< 75 kg] to 1200 mg [≥ 75 kg]) for 12 weeks is recommended for treatment-naïve patients with HCV genotype 2 infection.

Rating: Class I, level A

Not recommended

The following regimens are NOT recommended for treatment-naïve patients with HCV genotype 2.

- PEG / RBV for 24 weeks

Rating: Class IIb, Level A

- Monotherapy with PEG, RBV, or a DAA

Rating: Class III, Level A

- Telaprevir-, boceprevir-, or simeprevir-based regimen

Rating: Class III, Level IA



Genotype 3— Regardless of interferon eligibility

Recommended regimen for treatment-naïve patients with HCV genotype 3, regardless of eligibility for IFN therapy:

- Daily sofosbuvir (400 mg) and weight-based RBV (1000 mg [< 75 kg] to 1200 mg [≥ 75 kg]) for 24 weeks is recommended for treatment-naïve patients with HCV genotype 3 infection.

Rating: Class I, Level B

Alternative regimen for treatment-naïve patients with genotype 3 who are eligible to receive IFN.

- Daily sofosbuvir (400 mg) and weight-based RBV (1000 mg [< 75 kg] to 1200 mg [≥ 75 kg]) plus weekly PEG for 12 weeks is an acceptable regimen for IFN-eligible persons with HCV genotype 3.

Rating: Class IIa, level A

Not recommended

The following regimens are NOT recommended for treatment-naïve genotype 3.

- PEG / RBV for 24 to 48 weeks

Rating: Class IIb, Level A

- Monotherapy with PEG, RBV, or a DAA

Rating: Class III, Level A

- Telaprevir-, boceprevir-, or simeprevir-based regimen should not be used for patients with genotype 3 HCV infection.

Rating: Class III, Level A



Genotype 4– Interferon eligibility

Eligible	Not eligible
<i>Recommended regimen for treatment-naïve patients with HCV genotype 4 who are eligible to receive IFN.</i> ○ Daily sofosbuvir (400 mg) and weight-based RBV (1000 mg [< 75 kg] to 1200 mg [≥ 75 kg]) plus weekly PEG for 12 weeks is recommended for IFN-eligible persons with HCV genotype 4 infection. Rating: Class IIa, Level B Alternative regimens for treatment-naïve patients with HCV genotype 4 who are eligible to receive IFN. ○ Daily simeprevir (10 mg) for 12 weeks and weight-based RBV (1000 mg [< 75 kg] to 1200 mg [≥ 75 kg]) plus weekly PEG for 24 to 48 weeks is an alternative regimen for IFN-eligible persons with HCV genotype 4 infection. Rating: Class IIb, Level B Not recommended The following regimens are NOT recommended for treatment-naïve genotype 4. ○ PEG / RBV for 48 weeks Rating: Class IIb, Level A ○ Monotherapy with PEG, RBV, or a DAA Rating: Class III, Level A ○ Telaprevir-, boceprevir-based regimen Rating: Class III, Level A	<i>Recommended regimen for treatment-naïve patients with genotype 4 who are not eligible to receive IFN.</i> ○ Daily sofosbuvir (400 mg) weight-based RBV (1000 mg [≥ 75 kg] to 1200 mg [≥ 75 kg]) for 24 weeks is recommended for IFN-ineligible patients with HCV genotype 4 infection. Rating: Class IIb, Level B -



Genotype 5, 6– Regardless of interferon eligibility

Recommended regimen for treatment-naïve patients with HCV genotype 5 or 6.

- Daily sofosbuvir (400 mg) and weight-based RBV (1000 mg [< 75 kg] to 1200 mg [≥ 75 kg]) plus weekly PEG for 12 weeks is recommended for IFN-eligible persons with HCV genotype 5 or 6 infection.

Rating: Class IIa, Level B

Alternative regimen for treatment-naïve patients with genotype 5 or 6

- Daily weight-based RBV (1000 mg [< 75 kg] to 1200 mg [≥ 75 kg]) plus weekly PEG for 48 weeks is an acceptable regimen for persons infected with HCV genotype 5 or 6.

Rating: Class IIb, level A

Not recommended

The following regimens are NOT recommended for treatment-naïve genotype 5 or 6 HCV.

- Monotherapy with PEG, RBV, or a DAA

Rating: Class III, Level A

- Telaprevir-, boceprevir-based regimen

Rating: Class III, Level A



Initial Treatment (treatment naïve)

Genotype	Recommended	Alternative	Not recommended
1	IFN eligible: SOF + PEG / RBV x 12 weeks	IFN eligible: SMV x 12 weeks + PEG / RBV x 24 weeks*	TVR + PEG / RBV x 24 or 48 weeks (RGT) BOC + PEG / RBV x 28 or 48 weeks (RGT)
	<u>IFN ineligible:</u> SOF + SMV ± RBV x 12 weeks	<u>IFN ineligible:</u> SOF + RBV x 24 weeks	PEG / RBV x 48 weeks Monotherapy with PEG, RBV, or a DAA. Do not treat decompensated cirrhosis with PEG or SMV
2	SOF + RBV x 12 weeks	None	PEG / RBV x 24 weeks Monotherapy with PEG, RBV, or a DAA Any regimen with TVR, BOC, or SMV
3	SOF + RBV x 24 weeks	SOF + PEG / RBV x 12 weeks	PEG / x 24-48 weeks Monotherapy with PEG, RBV, or a DAA Any regimen with TVR, BOC, or SMV



<u>Genotype</u>	<u>Recommended</u>	<u>Alternative</u>	<u>Not recommended</u>
4	IFN eligible: SOF + PEG / RBV x 12 weeks <u>IFN ineligible:</u> SOF + RBV x 24 weeks	SMV x 12 weeks + PEG / RBV x 24-48 weeks	PEG / RBV x 48 weeks Monotherapy with PEG, RBV, or DAA Any regimen with TVR or BOC
5 or 6	SOF + PEG / RBV x 12 weeks	PEG / RBV x 48 weeks	Monotherapy with PEG, RBV, or a DAA Any regimen with TVR or BOC

For genotype 1a, baseline resistance testing for Q80K should be performed and alternative treatments considered if this mutation is present.

Retreatment

<u>Genotype</u>	<u>Recommended</u>	<u>Alternative</u>	<u>Not recommended</u>
Patients in whom previous PEG / RBV has failed*			
1	SOF + SMV ± RBV x 12 weeks	SOF x 12 weeks + PEG / RBV x 12 – 24 weeks SOF + RBV x 24 weeks SMV x 12 weeks + PEG / RBV x 48 weeks**	PEG / RBV ± telaprevir or boceprevir Monotherapy with PEG, RBV, or a DAA Do not treat decompensated cirrhosis with PEG or SMV
2	SOF + RBV x 12 weeks	SOF + PEG / RBV x 12 weeks	PEG / RBV ± telaprevir or boceprevir Monotherapy with PEG, or direct-acting anti-viral agent Do not treat decompensated cirrhosis with PEG



<u>Genotype</u>	<u>Recommended</u>	<u>Alternative</u>	<u>Not recommended</u>
3	SOF + RBV x 24 weeks	SOF + PEG / RBV x 12 weeks	PEG / RBV ± any current protease inhibitor Monotherapy with PEG, RBV, or a DAA Do not treat decompensated cirrhosis with PEG
4	SOF + PEG / RBV x 12 weeks	SOF + RBV x 24 weeks	PEG / RBV ± any current HCV protease inhibitor Monotherapy with PEG, RBV, or a DAA Do not treat decompensated cirrhosis with PEG
5-6	SOF x 12 weeks + PEG / RBV 12 weeks		PEG / RBV + any current HCV protease inhibitor Monotherapy with PEG, RBV, or a DAA Do not treat decompensated cirrhosis with PEG

Patients in whom previous PEG / RBV plus either telaprevir or boceprevir** has failed†† †††

1	SOF x 12 weeks + PEG / RBV x 12-24 weeks	SOF + RBV x 24 weeks‡ SOF† PEG / RBV x 24 weeks ††	PEG / RBV ± telaprevir or boceprevir or SMV Monotherapy with PEG, RBV, or a DAA Do not treat decompensated cirrhosis with PEG or SMV



*Failure (non response) is defined as partial or null response to treatment with PEG / RBV. Relapse to prior therapy should be treated the same as treatment-naïve

** For genotype 1a, baseline resistance testing for Q80K should be performed and alternative treatments considered if this mutation is present

***Failure (non-response) is defined as partial or null response to treatment with PEG / RBV plus telaprevir or boceprevir. Relapse to prior therapy should be treated the same as treatment naïve

† Consideration should be given to postponing treatment, pending release of new drugs for patients with limited (F 0-2) hepatic fibrosis

†† A recommendation for simeprevir use for patient with previous telaprevir or boceprevir exposure not provided due to potential risk of preexistent resistance to protease inhibitor treatment.

††† Given the lack of prior approval of protease inhibitor therapy for genotypes 2, 3, 4, 5, 6 and the lack of sufficient data, no recommendations are given for these genotypes at this time

‡ IFN ineligible

‡‡ IFN eligible

Genotype 1

Eligible	Not eligible
<i>Recommended regimen for HCV genotype 1 PEG / RBV (without an HCV protease inhibitor) non-responder patients:</i> ○ Daily sofosbuvir (400 mg) plus simeprevir (150 mg), with or without weight-based RBV (1000 mg [< 75 kg] to 1200 mg [≥ 75 kg]) for 12 weeks is recommended for retreatment of HCV genotype 1 infection, regardless of subtype or IFN eligibility. Rating: Class IIa, Level B	<i>Recommended regimen for HCV genotype 1 PEG / RBV (with an HCV protease inhibitor) non-responder patients:</i> ○ Daily sofosbuvir (400 mg) for 12 weeks plus weight-based RBV (1000 mg [< 75 kg] to 1200 mg [≥ 75 kg]) and weekly PEG for 12 to 24 weeks is recommended for retreatment of HCV genotype 1 infection, regardless of subtype or IFN eligibility. Rating: Class IIb, Level C



Alternative regimen for PEG / RBV (with or without an HCV protease inhibitor) non-responder patients with HCV genotype 1.

- Daily sofosbuvir (400 mg) for 12 weeks and weight-based RBV (1000 mg [75 kg] to 1200 mg [≥ 75 kg]) plus weekly PEG for 12 to 24 weeks is an alternative for retreatment of IFN-eligible persons with HCV genotype 1 infection, regardless of subtype.

Rating: Class IIb, level C

Alternative regimen for PEG / RBV (without an HCV protease inhibitor) non-responder patients with HCV genotype 1 who are eligible to receive IFN.

- Daily simeprevir (150 mg) for 12 weeks plus weight-based RBV (1000 mg [< 75 kg] to 1200 mg [≥ 75 kg]) and weekly PEG for 48 weeks is an alternative for IFN-eligible persons with HCV genotype 1 infection. (All patients with cirrhosis who are receiving simeprevir should have well compensated liver disease.)

Rating: Class IIa, Level A

Not recommended

The following regimens are NOT recommended for PEG / RBV (with or without an HCV protease inhibitor) non-responder patients with HCV genotype 1:

- PEG / RBV with or without telaprevir or boceprevir

Rating: Class IIb, Level A

- Monotherapy with PEG, RBV, or a DAA

Rating: Class III, Level A

For nonresponder patients with genotype 1 and a history of decompensated cirrhosis (moderate or severe hepatic impairment; CTP class B or C), treatment is not indicated because of the risks of PEG and boceprevir and telaprevir in this population.

Eligibility to receive IFN:

- Daily sofosbuvir (400 mg) for 24 weeks and weight-based RBV (1000 mg [< 75 kg] to 1200 mg [≥ 75 kg]) for 24 weeks is an alternative for retreatment of IFN-ineligible persons with HCV genotype 1 infection, regardless of subtype.

Rating: Class IIb, Level C



Genotype 2– Regardless of interferon eligibility

Recommended regimen for genotype 2 PEG / RBV non-responders.

- Daily sofosbuvir (400 mg) and weight-based RBV (1000 mg [< 75 kg] to 1200 mg [≥ 75 kg]) for 12 weeks is recommended for treatment of HCV genotype 2 infection. (Patient with cirrhosis may benefit by extension of treatment to 16 weeks.)

Rating: Class I, Level A

Alternative regimen for PEG / RBV non-responder patients with HCV genotype 2 infection who are eligible to receive IFN.

- Retreatment with daily sofosbuvir (400 mg) and weight-based RBV (1000 mg [< 75 kg] to 1200 mg [≥ 75 kg]) plus weekly PEG for 12 weeks is an alternative for IFN-eligible persons with HCV genotype 2 infection.

Rating: Class IIa, Level B

The following regimens are NOT recommended for non-responder patients with HCV genotype 2:

- PEG / RBV with or without telaprevir, boceprevir or simeprevir

Rating: Class IIb, Level A

- Monotherapy with PEG, RBV, or a DAA

Rating: Class III, Level A

Genotype 3

Recommended regimen for HCV genotype 3 PEG / RBV non-responders.

- Daily sofosbuvir (400 mg) and weight-based RBV (1000 mg [< 75 kg] to 1200 mg [≥ 75 kg]) for 24 weeks is recommended for retreatment of HCV genotype 3 infection.

Rating: Class IIa, Level A



Alternative regimen for HCV genotype 3 PEG / RBV non-responder patients who are eligible to receive IFN.

- Retreatment with daily sofosbuvir (400 mg) and weight-based RBV (1000 mg [< 75 kg] to 1200 mg [≥ 75 kg]) plus weekly PEG for 12 weeks is an alternative for IFN-eligible persons with HCV genotype 3 infection.

Rating: Class IIa, Level B

Not recommended

The following regimens are NOT recommended for non-responder patients with HCV genotype 3 infection:

- PEG / RBV with or without telaprevir, boceprevir or simeprevir

Rating: Class IIb, Level A

- Monotherapy with PEG, RBV, or a DAA

Rating: Class III, Level A

Genotype 4

Recommended regimen for HCV genotype 4, PEG / RBV non-responder patients.

Daily sofosbuvir (400 mg) for 12 weeks and daily weight-based RBV (1000 mg [< 75 kg] to 1200 mg [≥ 75 kg]) plus weekly PEG for 12 weeks is recommended for retreatment of IFN-eligible persons with HCV genotype 4 infection.

Rating: Class IIa, Level C

Alternative regimen for HCV genotype 4, PEG / RBV non-responder patients.

Daily sofosbuvir (400 mg) and weight-based RBV (1000 mg [< 75 kg] to 1200 mg [≥ 75 kg]) for 24 weeks is recommended for retreatment of HCV genotype 4 infection.

Rating: Class IIa, Level B



Not recommended

The following regimens are NOT recommended for non-responder patients with genotype 4 HCV infection:

- PEG / RBV with or without telaprevir or boceprevir

Rating: Class IIb, Level A

- Monotherapy with PEG, RBV, or a DAA

Rating: Class III, Level A

Genotype 5, 6

Recommended regimen for HCV genotype 5 or 6, PEG / RBV non-responder patients.

- Daily sofosbuvir (400 mg) for 12 weeks and daily weight-based RBV (1000 mg [< 75 kg] to 1200 mg [≥ 75 kg]) plus weekly PEG for 12 weeks is recommended for retreatment of IFN-eligible persons with HCV genotype 5 or 6 infection.

Rating: Class IIa, Level C

Alternate regimen for PEG / RBV non-responder patients with HCV genotype 5 or 6.

None

Not recommended

The following regimens are NOT recommended for non-responder patients with HCV genotype 5 or 6.

- PEG / RBV with or without telaprevir or boceprevir

Rating: Class IIb, Level A

- Monotherapy with PEG, RBV, or a DAA

Rating: Class III, Level A



Special considerations

Unique patient populations: Renal impairment table. Dose adjustments needed for patients with renal impairment

Renal Impairment	eGFR / CrCl level (mL/min/1.73 m ²)	Interferon	Ribavirin	Sofosbuvir	Simeprevir
○ Mild	50-80	180 µg PEG (2a) PEG (2b) 1.5 µg/kg	Standard	Standard	Standard
○ Moderate	30-50	180 µg PEG (2a) PEG alfa-2b 1 µg/kg or 25% reduction	Alternating doses 200 and 400 mg every other day	Standard	Standard
○ Severe	< 30	135 µg PEG (2a) PEG alfa-2b 1 µg/kg or 50% reduction	200 mg/d	Data not available	Standard
○ ESRD / HD		PEG (2a) 135 µg/wk or PEG (2b) 1 µg/kg/wk or standard IFN 3 mU 3x/wk	200 mg/d	Data not available	Data not available

Abbreviations: ESRD, end stage renal disease; HD, hemodialysis

➤ HIV / HCV coinfection box

Genotype	Recommended	Alternative	NOT Recommended	Allowable anti-retroviral Therapy



1	○ Treatment-naïve and prior PEG / RBV relapsers - IFN eligible: SOF + PEG / RBV x 12 weeks - IFN ineligible: SOF + RBV x 24 weeks - SOF + SMV ± RBV x 12 weeks ○ Treatment experienced (prior PEG / RBV non-responders) regardless of IFN eligibility: SOF + SMV ± RBV x 12 weeks	Treatment naïve and prior PEG / RBV relapsers IFN eligible: SMV x 12 weeks + PEG / RBV x 24 weeks* Treatment experienced (prior PEG / RBV non-responders) IFN eligibility: SOF + PEG / RBV x 12 weeks IFN ineligibility: SOF + RBV x 24 weeks	TVR + PEG / RBV x 24 or 48 weeks (RGT) BOC + PEG / RBV x 28 or 48 weeks (RGT) PEG / RBV x 48 weeks	For SOF use: ALL except didanosine, zidovudine, or tipranavir For SMV use: LIMITED to raltegravir, rilpivirine, maraviroc, enfuvirtide, tenofovir, emtricitabine, lamivudine, abacavir
2	○ SOF + RBV x 12 weeks regardless of treatment history	Treatment naïve and prior PEG / RBV relapsers: None Treatment experienced (prior PEG / RBV non-responders) IFN ineligibility: SOF + PEG / RBV x 12 weeks IFN ineligibility: Non	PEG / RBV x 24 48 weeks Any regimen with TVR, BOC, or SMV	All except didanosine, zidovudine, or tipranavir
Genotype	Recommended	Alternative	NOT Recommended	Allowable anti-retroviral Therapy

3	○ SOF + RBV x 24 weeks	- Treatment naïve and	PEG / RBV x 24-48 weeks	All except didanosine,



	regardless of treatment history	PEG / RBV relapsers: None – Treatment experienced (prior PEG RBV non-responders) – IFN eligible: SOF + PEG / RBV x 12 weeks – IFN ineligible: None	Any regimen with TVR, BOC, or SMV	zidovudine, or tipranavir
4	○ Regardless of treatment history: – IFN eligible: SOF + PEG / RBV x 12 weeks – IFN ineligible: SOF + RBV x 24 weeks	– None	PEG / RBV x 48 weeks Any regimen with TVR, BOC, or SMV	ALL except didanosine, zidovudine, or tipranavir

➤ HCV and Liver Transplantation

128. Give 4 hepatic complications following liver transplantation (LT) for HCV.

- Recurrence of HCV (~100%) post-LT
- ↑ risk of cirrhosis
 - 20% to 40% in 5 years
- Rapid progression to cirrhosis
- High risk of cirrhosis becoming decompensated
 - In 1 year, about half of decompensated HCV cirrhotics will die
- Fibrosing cholestatic hepatitis

Note: “Preemptive therapy of all HCV-infected patients within the first few weeks after [liver] transplantation is associated with substantial toxicity and a low chance of SVR; it [redemptive anti-HCV therapy] is not recommended” (Feldman M., et al. Sleisenger and Fordtran’s Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier, Philadelphia, 2010, page 1334).



129. Give a comparison of the **histologic features** of recurrent hepatitis C virus infection versus acute cellular rejection after liver transplantation.

Histological features	HCV Recurrence	Rejection
○ Portal inflammation	– Bland, uniform	▪ Activated
○ Lymphocytes, lymphoid aggregates or follicles	– Common (~50%)	▪ Uncommon
○ Eosinophils	– Uncommon	▪ Common
○ Steatosis	– Common	▪ Never
○ Acidophilic bodies	– Common	▪ Uncommon
○ Atypical features	– Cholestasis, ballooning degeneration without significant inflammation	▪ Prominent periportal and lobular necroinflammatory activity without sub-endothelial venular inflammation

Adapted from: *Sleisenger and Fordtran's Gastrointestinal and Liver Disease: Pathophysiology/ Diagnosis/ Management*. Ninth edition, 2010, Table 95.10, page 1609,

➤ HCV plus HIV co-infection

130. Give 4 effects of HIV co-infection on the clinical course of HCV.

- ↓ HCV clearance rate
- ↑ risk of chronic HCV
- ↑ risk of progression to fibrosis
- Use of interferon-based regimen is **contraindicated**, since interferon **accelerates** HIV infection
- In the setting of HIV plus HCV in the transplantation setting, there is ↑ graft rejection and loss



131. Give 4 factors which enhance the risk of **accelerated fibrosis** in the setting of HCV co-infection with HIV.

- Patient
 - Older (> 33 years)
 - Females
- HIV
 - CD4+ < 100 mm³ while on HAART
 - HIV viral load still detectable while on HAART therapy
- HCV
 - Untreated

132. Give 3 mechanisms for the **acceleration of hepatic fibrosis** in the patient with HCV and co-infection with HIV

- TGF-B1
 - HIV → ↑ TGF-B1
 - ↑ TGFB1 → ↑ HCV replication
- TJ permeability
 - HIV → ↓ CD4+
 - ↓ CD41 → ↑ TJ permeability
 - ↑ TJ permeability → ↑ bacterial translocation
- Stellate cells
 - HIV → activate hepatic stellate cells
 - ↑ activated stellate cells → ↑ production of collagen

Abbreviation: TJ, tight junctions

“There are two ways of spreading light: to be the candle or the mirror that reflects it”.

Edith Wharton



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- Give 3 scientific reasons why the development of a **vaccine** for HCV has been challenging.
 - Requires the production of both
 - Cellular immune response
 - Neutralizing antibodies
 - Anti-HCV does not lead to protective immunity (escape from antibody recognition)
 - High mutational rate of HCV
 - Heterogeneity of HCV envelop proteins

HCV and HCC

Useful background: Risk of cirrhosis, hepatocellular carcinoma (HCC) and mortality in hepatitis B and hepatitis C virus (HBV/HCV) monoinfected and coinfecting patients

Feature	Cirrhosis	HCC	Mortality (SMR)
○ HBV monoinfection	22%	OR 16-23	1.4-5.3
○ HCV monoinfection	30%	OR 8-17	2.4-3.1
○ HBV/HCV coinfection	50%	OR 36-165	5.6-49

Abbreviations: HBV, hepatitis B; HCC, hepatocellular carcinoma; HCV, hepatitis C; OR, odds ratio; SMR, standard mortality ratio

Printed with permission: Wursthorn, et al. *Best Practice Res Clin Gastroenterol* 2008;22:1063-1079. (Studies: Amin et al, 2006; Di Marco et al, 1999; Donato et al, 1998 ; Shi et al, 2005; Zarski et al, 1998)



Other Hepatotropic Viruses

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- The patient tests positive for
 - HBV DNA⁺
 - HBsAg⁺
 - IgM anti-HDV⁺
- On the basis of their IgM anti-Hbc, determine if the HDV infection represents a coinfection of HBV, or if the person previously had HBV and the HDV was acquired (superinfection) afterwards.

Type of infection	Previous HBsAg	ALT	IgM anti-HBc ⁺	Clinical course
○ Coinfection	Negative	Double peak [*]	Positive	Usually resolves as HBV improves
○ Superinfection	Positive	↑ from baseline ^{**}	Negative	Progresses to cirrhosis

^{*}first with HBV infection, then later with HDV

^{**}baseline may be increased because of initial HBV infection

➤ Hepatitis D Virus (HDV)

- Nuclear antigen in hepatocytes of persons infected with HBV.
- 3 genotypes HDV RNA encodes HDag
- HBsAg protects the complex of HDV-RNA-HDag hepatocyte injury is likely immune-mediated
- Serological markers
- HDV infection may occur
- Associated with severe HBV
 - Severe chronic HBV (decompensation)
 - Fulminant HBV
 - HBV carriers (especially IV drug users [IVDU])
 - HBV: HBV DNA, HBsAg
 - Previously HBsAg⁺, now anti-HBc⁺
 - More common in IVDUs chronic HDV in ~ 5%
 - Usually HDV resolves as HBV resolves



- After HBV (coprimary infection)
- After HBV (superimposed HDV infection)
 - Development of chronic HDV in ~70%
 - Previously HBsAg⁺, non IgM anti-HBc⁻
 - Progress to cirrhosis
- HDV replication inhibits HBV replication
- HBV DNA and HBsAg must be present for HDV replication

➤ **Hepatitis E Virus (HEV)**

- RNA virus
- More common in adults and males
- High attack and mortality rates in pregnant women (each trimester)
- Increased spontaneous abortions
 - Stillbirths
 - Neonatal deaths
- Transplacental transmission (mother-to-new-born)
- Fecal-oral transmission (water contaminated with HEV)
- Presentations
 - Acute icteric or non-icteric hepatitis
 - Fulminant hepatic failure (22%)

133. Give the PRIM countries where HEV is endemic.

- Pakistan
- Russia
- India
- Mexico

➤ **Epstein-Barr Virus (EBV)**

- Mononucleosis-like illness (IgM anti-EBV)
- Worse clinical course in persons > 30 years
- May cause
 - Chronic hepatitis
 - Granulomatous hepatitis
 - PTLT (post-transplantation lymphoproliferative disease)



➤ **Cytomegalovirus (CMV)**

134. Give 5 types of hepatobiliary disorders associated with CMV infection.

- Transminitis
- Hepatitis
 - Acute
 - Granulomatous
 - Cholestatic
- Fulminant hepatic failure
- Post liver transplantation
 - Fibrosing cholestatic hepatitis
- Graft rejection-like picture
- Typical pathological changes on liver biopsy
 - Multinucleated giant cells
 - Owl's eye nuclear inclusions
 - Mononuclear portal and parenchymal inflammatory infiltration

➤ **Herpes Simplex Virus (HSV)**

- Microcutaneous and genital HSV lesions
- Transaminitis
 - Immune suppressed persons
- Pregnant women
 - 3rd trimester
 - Fulminant hepatic failure

Acute HSV hepatitis from an infection with HSV-1 or HSV-2 may occur in immunocompetent as well as immunocompromised persons.

135. Give 4 laboratory features and which should alert the physician about the possibility of HSV hepatitis and the need to begin empiric therapy with acyclovir.

- ↑↑ ALT, AST (> 1000)
- ↓ WBC
- Fever / abdominal pain
- Associated HSV
 - Pneumonitis
 - Encephalopathy



136. Give the typical pathological changes of HSV on liver biopsy

- Focal or extensive
 - Hemorrhage
 - Necrosis
- Hepatocytes
 - Cowdry A type inclusions in hepatocytes near the necrosis
 - Hepatocytes in periportal area
 - Multinucleated
 - Ground glass

Please see: Peltekian KM, Hirsch G. Chapter 59. In: Therapeutic Choices. Grey J, Ed. 6th Edition, Canadian Pharmacists Association: Ottawa, ON, 2011, Table 7: Drug used in viral hepatitis, page 799-800.

The liver biopsy of the patient with acute viral hepatitis shows inclusions in the nuclei of the hepatocytes.

137. The histopathological features which help to differentiate between CMV- vs. HSV- associated hepatitis.

- CMV hepatitis
 - Hepatocytes contain intra-nuclear inclusion with a surrounding halo
 - This halo is aka “owl’s eye” inclusion
 - Positive CMV immunohistochemistry
- HSV hepatitis
 - Hepatocytes with “glassy” nuclear inclusions (no halo)
 - Multi-nucleated giant cells
 - Extensive necrosis

138. Give 2 infectious causes of liver disease which cause fever and **temperature-pulse dissociation.**

- Amebiasis
- Leptospirosis



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- Give the two mechanisms responsible for the common finding of cholestasis on liver biopsy from a person with **sepsis**.

Sepsis releases

- Exotoxins and endotoxins
 - Inhibits transport across hepatocyte sinusoidal and canalicular membrane
- TNF- α
 - Same effect as exo- / endotoxins
- In the context of the right upper abdominal pain and a urogenital infection, give the definition of **Fitz-Hugh-Curtis Syndrome**. Also, give its most common causes.

The Fitz-Hugh-Curtis is perihepatitis, usually caused by salpingo-oophoritis from

- Chlamydia trachomatis
- Gonococcus
- In the context of a “zoonosal infection”, give the clinical findings of **Weil syndrome**.

Weil's syndrome (leptospirosis)

- A severe infection
- Fever, jaundice, conjunctivitis, myalgias
- Bleeding
- Hepatitis

“Always do your best. What you plant now, you will harvest later.”

Og Mandino



SO YOU WANT TO BE A HEPATOLOGIST!

- Tricky terms. In the context of liver disease, give the meaning of
 - Kala- azar
 - Grey pigmentation of the skin arising from infection with visceral leishmaniasis
 - Pseudotumor of the liver
 - Plasma cell granuloma associated with ascending cholangitis, PSC, UC, and other autoimmune disorders
 - Anchoring paste
 - Red/brown “pasty” aspirate from an amebic abscess
- Give sources of bacteremia which may result in a **pyogenic liver abscess**.
 - Luminal GI tract:
perforated virus
e.g.
 - Peptic ulcer disease
 - Appendicitis
 - Diverticulitis
 - Colon cancer
 - IBD
 - Peritonitis
 - Liver
 - HCC
 - Treatment of 1^o/ 2^o hepatic neoplasm
 - Chemoembolization
 - Percutaneous ablation
 - Biliary tree
 - Cholangitis
 - Cholecystitis
 - Sphincterotomy
 - Intrahepatic stones
 - Gallbladder cancer
 - Penetrating abdominal wound
 - Heart
 - Bacterial peritonitis



➤ **Leptospirosis (aka Weil syndrome)**

Leptospira interrogans

➤ Acute plus

- General
 - Fever
 - Rigors
- Clinical
 - Eyes
 - Conjunctival suffusion
 - Heart
 - Temperature-pulse dissociation
 - Lung
 - Cough, no sputum
 - MSK
 - Myalgias
 - Kidney
 - $\downarrow\text{Na}^+$, $\downarrow\text{K}^+$
 - Renal insufficiency
 - Hematology
 - lymphadenopathy
 - Liver
 - ALF (rare)
- Laboratory
 - $\uparrow\text{AST}$, $\uparrow$ bilirubin

"There is no achievement without goals."

Robert J. McKaine



Amebic Liver Disease

- When to suspect amebic liver abscess
 - ↑ AP, leukocytes without eosinophilia
 - When to suspect poor prognosis
 - ↑ bilirubin
 - ↓ albumin
 - Diagnosis
 - Serology positive in 95% (after only 1 week of infection)
 - CT scan
 - Elevated r. hemidiaphragm (50%)
 - Solitary
 - Large, round lesion
 - Usually right lobe of liver
 - Low attenuation (dark)
 - Enhancing rim of hepatic tissue
139. Give 3 reasons why percutaneous biopsy / aspiration of a suspected amebic liver abscess is generally **contraindicated**.
- Right Lobe
 - Subcapsular peritonitis
 - Left lobe
 - Extension to
 - Peritoneum
 - Pleural space
 - Pericardium
140. Give 3 reasons why it is necessary to accept the above potential complications, and to aspirate or drain “anchovy paste” (mixture of blood and liver tissue) from a solitary hepatic amebic abscess.
- No clinical improvement after 3-5 days of metronidazole
 - Negative for amebic serology (occurs in 5% of patients)
 - Left lobe abscess
 - Rim of tissue < 1 cm large abscess

Source: Spiegel BM, Karsan AA. Acing the hepatology questions on the GI board exam. Slack Incorporated 2012, Table 38.1, page 106.

Curiosity: stool cultures are usually negative for *Entamoeba* cysts or trophozoites in persons with an amebic abscess



Echinococcal (“hydratid”) cyst of the liver

- Epidemiology
 - Sheepherder (also think of fasciolosis)
- Clinical
 - Cough
 - Hepatomegaly (especially right lobe of liver)
 - Complications of
 - enlarging cyst
 - Obstruction of biliary tree
 - Cholangitis
 - Pancreatitis
 - Compression on blood vessels
 - PV (portal hypertension)
 - HV (Budd-Chiari syndrome)
 - IVC (leg edema)
 - ↑↑ AP
- Diagnostic imaging
 - US / CT scan
 - Smooth cyst
 - Round
 - Daughter cyst
 - Internal septations
 - Calcification, especially “eggshell” calcification
 - Hydrated-sand (portions of the tapeworms)
- Treatment
 - Albendazole
 - When cysts are not active and not under pressure → aspirate (caution: may cause anaphylaxis)
 - Surgical resection for cyst ≥ 10 cm



Inherited Metabolic Disorders of Liver

Useful background: The meaning of selected genetic terms.

Terminology	Meaning
o Cosmopolitan SNPs	- Present in all ethnic groups
o Haplotype	- Group of variants or SNPs that occur together on a single chromosome
o Insertions and deletions	- One or more base pairs are inserted or deleted into the genome (rare)
o Linkage disequilibrium	- Variants that are linked to one another
o Missense mutation (non-synonymous)	- Base pair substitution that results in an amino acid change
o Polymorphism	- Variation in DNA sequence present in an allele with a frequency of 1% or greater in a population
o Population-specific SNPs	- Occur in specific ethnic groups
o Recombination	- Cross-over events that occur during meiosis that result in unlinking of genes or variants
o Sense mutation (synonymous)	- Base pair substitution that does not alter the coded amino acid
o Single nucleotide polymorphism (SNP)	- Most common form of DNA sequence variation

Printed with permission Wright TL. 2007 AGA Institute Postgraduate Course. pg. 45.

“Be aware of the big picture in the patients’ life, not just blinkers on the obvious medical problem.”

Dr. Joel Huurwitz



Hereditary Hemochromatosis (HH) and Secondary Iron Overload

➤ Pathophysiology

141. Give the role of hepcidin in iron hemostasis in iron deficiency, inflammation and hereditary hemochromatosis.
- HFE binds to TFR1 and TFR2
 - The HFE-TFR1 complex on the surface of the hepatocyte senses transferrin saturation (TS)
 - When TS↑, diferric transferrin displaces HFE from the HFE-TFR1 complex
 - HFE now binds to TFR2
 - HFE-TFR2 complex causes the hepatocytes to sense ↓ TS (and ↓ BIS), so expression of hepcidin falls, and iron absorption increases
 - As BIS increase → ↑ BMP6 binding to hepatocyte receptors → ↑ SMAD4
 - In HH, the mutation in HFE provides abnormal “sensing” of the body iron stores the intestinal crypts “sense” that the body iron stores (BIS) are low, despite these BIS actually being high in HH.
 - The sensing of ↓ BIS leads to ↓ hepcidin, ↑ active ferroportin, and ↑ iron absorption
 - The ↑ iron absorption continues, unresponsive to the ↑ BIS because of the mutation of HFE
 - Hepcidin decreases iron “release” from enterocytes (↓ transport of FE across the enterocyte BLM), and hepcidin also decreases iron release from macrophages.
 - The ↓ hepcidin in HH causes ↑ iron release from macrophages

"Goals in writing are dreams with deadlines."

Brian Tracy



SO YOU WANT TO BE A GASTROENTEROLOGIST!

- Give the mechanism of Fe overload with inflammation.
 - Iron metabolism is altered in inflammatory disorders (e.g., anemia of chronic disease)
 - In inflammatory disorders the ↑ proinflammatory IL-6 increases STAT3 signaling
 - ↑ STAT3 signaling increases hepcidin
 - This inflammation-associated ↑ hepcidin causes
 - Retention of iron in duodenocytes → ↓ iron absorption
 - Retention of iron in macrophages → loading of iron in RES (reticuloendothelial system), with less iron being available for synthesis of heme, and thus the development of anemia
- Give the mechanisms of Fe overload in ALD and HCV.
 - In ALD (alcoholic liver disease) and HCV, ↑ ROS (reactive oxygen species) are formed
 - ↑ ROS
 - Acts on a C/EBP (CCAAT / enhancer binding protein) → ↓ hepcidin expression
 - ↓ hepcidin → ↑ iron absorption and release of iron from macrophages → iron overload

➤ Genetics

142. Give the interpretation of the following genetic test results in persons suspected as having hereditary hemochromatosis (HH).

- C282Y homozygote
 - Seen in >90% of genetic Hemochromatosis (HH). Wide range of clinical iron overload from no disease to total body iron overload and organ failure. Siblings of a homozygote should be screened with genetic tests, transferrin saturation and serum ferritin, since they have a 1 in 4 chance of also being homozygous. Children of a homozygote are obligate heterozygotes but will only be homozygous if the other parent is at least a heterozygote. Testing of the second parent can identify the risk to the children with



further testing of the children only recommended if the second parent is at least heterozygous for C282Y mutation.

- False genetic results may occur but are rare.
- Approximately 50% of homozygotes do not have clinical iron overload (normal serum ferritin and transferrin saturation). Such individuals are considered to be non-expressing homozygotes and may never develop disease. They should probably be followed with repeat serum ferritin and transferrin saturation every 5 years.
- C282Y/H63D compound heterozygote
 - Patients can carry one major mutation and one minor mutation. Typically iron studies are normal, although mild to moderate iron overload may occur. Severe iron overload is typically only seen in the setting of other causes of liver disease.
- C282Y heterozygote
 - Occurs in approximately 10 per cent of the Caucasian population in which individuals carry one copy of a major mutation. Typically associated with normal iron studies. In rare circumstances that biochemical iron studies suggest significant iron overload (e.g. serum ferritin >1000µg/l) liver biopsy for hepatic iron index may be helpful in distinguishing between the genetic disorder and other causes of liver disease. It is recommended that siblings of a C282Y heterozygote be tested for this mutation.
- H63D homozygote
 - Patients carry two copies of a minor mutation. Iron studies are typically normal, although mild to moderate iron overload is occasionally seen. In patients with biochemical evidence of iron overload, liver biopsy may be helpful to quantitate hepatic iron and determine need for treatment with phlebotomy.
- H63D heterozygote
 - Occurs in approximately 20 per cent of the Caucasian population in which individuals carry one copy of a minor mutation. If biochemical iron studies are abnormal, these changes are more likely due to other non-genetic causes of iron overload.
- No HFE mutations
 - If iron overload is present without any HFE mutations, non-genetic causes of iron overload are likely. Rarely patients may have mutations of other iron-related proteins such as transferrin receptor-2, but these variants cannot be readily detected by genetic tests.

Printed with permission: Wright TL. 2007 AGA Institute Postgraduate Course. pg. 47.



The Big “WHY” – Challenges for Future Research

- 24 -58% of C284Y homozygotes have a normal serum ferritin concentration
- In a C282Y homozygote, the phenotype expression of Fe-overload is seen in < 50%.

➤ Clinical

143. Give the **physical findings** in patients with HH

- Skin
 - Increased pigmentation in sun-exposed areas
 - Porphyria cutanea tarda (PCT)
- Liver
 - Hepatomegaly
 - Cutaneous stigmata of chronic liver disease
 - Splenomegaly
 - Signs of PHT (ascites, encephalopathy, jaundice, coagulopathy)
- Joints
 - Arthritis
 - Joint swelling
 - Chondrocalcinosis
- Heart
 - Dilated cardiomyopathy
 - Congestive heart failure (CHF)
 - Arrhythmias
- Endocrine
 - Testicular atrophy
 - Hypogonadism
 - Hypothyroidism

Abbreviations: Hereditary hemochromatosis (HH); PHT, portal hypertension

Adapted from: Bacon BR, Adams PC, Kowdley KV, Powell LW, Tavill AS; American Association for the Study of Liver Diseases. Diagnosis and management of hemochromatosis: 2011 practice guideline by the American Association for the Study of Liver Diseases. *Hepatology*. 2011;54(1):328-43.



SO YOU WANT TO BE A HEPATOLOGIST!

- Give the cause of the **pigmented skin** in HH.

The pigmented skin in HH is from

- Melanocyte stimulation of ↑ melanin in skin
 - Iron in basal layers of skin
- Give the effect of phlebotomy on the following complications of HH.
 - Development of HCC
 - Regression of cirrhosis
 - Arthropathy
 - Hypogonadism
 - Little, if any.
 - Give the radiological features of the **arthropathy** of HFE-related HH.

The arthropathy of HFE-related HH has the following characteristics

- Second and third metacarpophalangeal joints, or knees
 - Joint space – narrow
 - Joint swelling
 - Chondrocalcinosis
 - Subchondral cysts
 - Osteopenia
- Give the common **causes of death** after liver transplantation (LT) for HH.

Death in HH after LT occurs from

- HCC (Hepatocellular cancer)
- Infections (↑ risk of infection in iron-loaded patients)
- Cardiac and ventricular dysrhythmias
- HF (heart failure)

144. Give the clues that the patient with HH (hereditary hemochromatosis) does not have cirrhosis.

- < 40 years
- No hepatomegaly
- Ferritin < 1000 mg/mL
- AST normal



145. Give the role of ↑ Fe in hepatocytes and development of fibrosis.

- ↑ hepatocyte Fe → lipid peroxidation of hepatocytes
- Injured hepatocytes release profibrogenic cytokines
- Profibrogenic cytokines activate stellate cells
- Activated stellate cells lead to hepatic fibrosis

➤ Laboratory tests

- Transferrin concentration (TS) > 45%
- Ferritin saturation
- ALT, AST
- Genotyping C282Y, H63D
- TS (transferrin saturation) is more sensitive and specific for HH than is serum ferritin concentration.
- Serum ferritin concentration may be normal, even when TS > 45%
- Serum iron studies but not hepatic iron levels may be abnormal in PCT (porphyria cutanea tarda), NASH, chronic HCV, and alcoholic liver disease.
- About 40% of PCT patients have a mutation in C282Y, and NASH patients have a higher prevalence of C282Y mutations.
- The prevalence of HFE mutations is not increased in chronic HCV, but
 - 22-62% of these persons have elevated serum ferritin concentrations, and
 - 18-32% have elevated transferrin saturation levels. There is no enrichment of HFE mutations in persons with alcoholic liver disease and elevated iron studies.

➤ Pathology

- Liver biopsy in the person with HH is not necessary if
 - They are young (< 40 years)
 - Liver enzymes are normal, and if serum ferritin concentration is < 1000 mg/ml.
 - Otherwise, fibrosis or cirrhosis might be suspected, and liver biopsy would be indicated
- Perl's Prussian blue stain shows excess iron in the hepatocytes in HH, with fibrosis around the portal area, especially when the hepatic iron concentration is > 16,000 µg/g liver dry weight
- Cirrhosis
- ↑ risk of HCC, even without cirrhosis



➤ Diagnostic imaging

146. Give the typical MRI findings in early HH, without cirrhosis or HCC.

- ↓ Signal intensity (darker) of liver as compared with spleen, on T-2 weighted image

A liver biopsy is performed in a C282Y / C282Y homozygote because of ↑ transaminases or serum ferritin > 1000 ng/mL:

147. Give the tests related to iron which can be performed on the liver biopsy tissue.

- Pearl's pressure blue stain
 - Location of iron
 - Hepatocytes
 - Kupffer cells
 - Semi-quantitative grading of amount of iron
- HIC (hepatic iron concentration)
 - Normal, < 1500 µg/gm liver, dry weight
 - HH with symptoms, > 10,000 µg/gm
 - HIC level when fibrosis / cirrhosis occurs, > 20,000 µg/gm
 - Note: if patient has HH and for example HCV or NASH, fibrosis / cirrhosis will develop at HIC < 20,000 µg/gm liver, dry weight
- HII (hepatic iron index) = HIC / age of patient (years)
 - > 1.9, HH
 - < 1.9, likely secondary iron overload

➤ Differential diagnosis

148. Give a **classification** of Iron Overload Syndromes.

➤ Hereditary Hemochromatosis

- *HFE*-related
 - C282Y/C282Y
 - C282Y/H63D
 - Other *HFE* mutations
- Non-*HFE*-related
 - Neonatal hemochromatosis
 - Juvenile hemochromatosis
 - Hemojuvelin (HJV)
 - Hcpidin (HAMP) Transferrin receptor-2 (TfR-2)



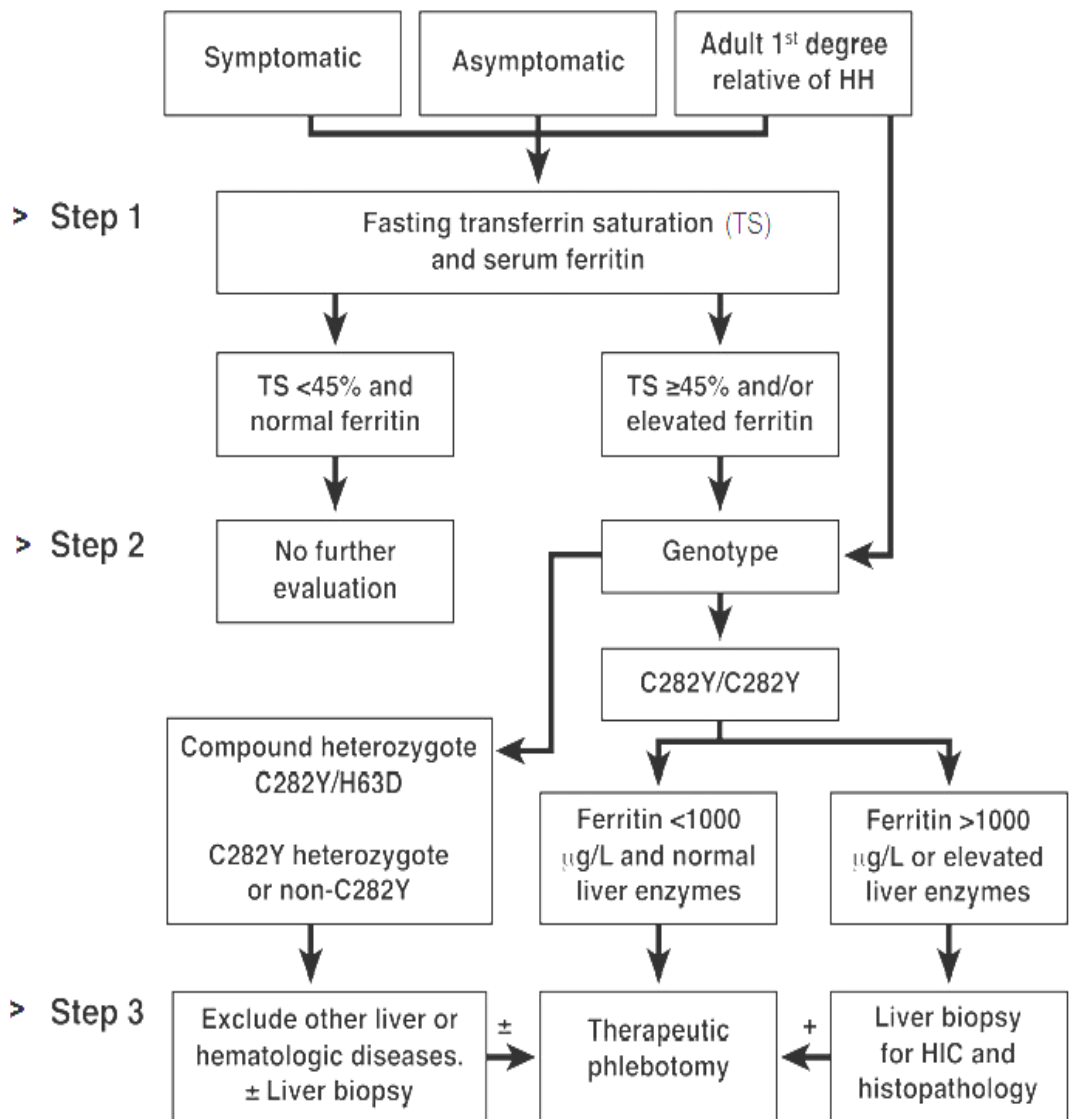
- Atransferrinemia
- Ferroportin (SLC40A1)
- Secondary Iron Overload
 - Iron-loading anemias
 - Thalassemia major
 - Sideroblastic
 - Chronic hemolytic anemia
 - Aplastic anemia
 - Ineffective erythropoiesis
 - Pyruvate kinase deficiency
 - Pyridoxine-responsive anemia
 - ↑ Fe intake
 - ↑ oral intake chronic
 - African iron overload
 - Parenteral iron overload
 - Hemojuvelin BMP (bone morphogenetic protein) binding to its receptor on the hepatocyte surface.
 - Loss-of-function mutation or gain-of-function
 - Multiple red blood cell transfusions
 - Iron–dextran injections
 - Long-term hemodialysis
 - Chronic liver disease
 - Hepatitis C
 - Hepatitis B
 - Alcoholic liver disease (ALD)
 - Nonalcoholic fatty liver disease (NAFLD / NASH)
 - Porphyria cutanea tarda (PCT)
 - Dysmetabolic iron overload syndrome
 - Miscellaneous
 - Neonatal iron overload
 - Aceruloplasminemia
 - Congenital atransferrinemia

Printed with permission: Bacon BR, Adams PC, Kowdley KV, Powell LW, Tavill AS; American Association for the Study of Liver Diseases. Diagnosis and



management of hemochromatosis: 2011 practice guideline by the American Association for the Study of Liver Diseases. Hepatology. 2011;54(1):328-43.

149. Give a suggested **algorithm** to investigate HH-based on serum transferrin saturation, serum ferritin concentration, and HFE genotype.



Algorithm for an approach to a patient with elevated transferrin saturation and/or serum ferritin.

Printed with permission: Adams PC. Evaluation of cirrhosis with an elevated ferritin. Clin Gastroenterol Hepatol. 2012;10(4):368-70.



➤ Treatment

- Phlebotomy of one unit (500 ml) of blood removes about 250 mg of iron: the serum ferritin falls by about 25 ng/mL
- Phlebotomy is performed weekly until the serum ferritin is < 50 mg/ml (removal of 1 unit of blood lowers serum ferritin concentration by about 30 mg/ml) and transferrin saturation is < 50%
- It is important to treat the patient with HH, to prevent the 20x ↑ risk of HCC. Even when the HH cirrhosis patient has a liver transplant, they remain at ↑ risk of cardiac disease.
- With phlebotomy in HH, serum ferritin falls slowly and progressively, while TS remains abnormally increased until just before body iron stores are normal, and treatment frequency for phlebotomy may be switched from a treatment to a maintenance program.
- Liver transplantation corrects the defect in HFE (in HH, but the 5 year survival rate is less than in non-HFE Fe-overload:
 - Normal iron stores (in HH), 75%
 - Non-HFE Fe overload, 63%
 - HFE, Fe overload, 34%
- Although HCC risk is increased in HH even without the presence of cirrhosis, there are no accepted guidelines for HCC screening in HH without cirrhosis.

150. Give the expected response to phlebotomy treatment in patients with HH, in addition to the fall in serum transferrin saturation and ferritin concentration.

➤ General comment

- Reduction of tissue iron stores to normal
- Improved survival if diagnosis and treatment before development of cirrhosis and diabetes

➤ Specifics

- Patient
 - ↑ sense of well-being, energy level
 - ↓ in abdominal pain



- Liver
 - No reversal of established cirrhosis
 - No (or minimal) improvement in arthropathy
 - No reversal of testicular atrophy
 - Normalization of elevated liver enzymes
 - Reversal of hepatic fibrosis (in approximately 30% of cases)
 - Decline in hepatic iron concentration (HIC) and hepatic iron index (HII)
 - Eliminate of risk of HH-related HCC if iron removal is achieved before development of cirrhosis
 - ↓ portal hypertension in patients with cirrhosis
- Extrahepatic
 - Improved cardiac function
 - Improved control of diabetes
 - Reduction in skin pigmentation

Adapted from: Bacon BR, et al. Hepatology. 2011;54(1):328-43.

151. A 30-year-old man's biological father died of cryptogenic cirrhosis, and the young man requests genetic testing for hemochromatosis. He is found to be a C282Y homozygote (C282Y +/+). What are the next steps for him and his family?*

- Normal iron studies - repeat iron studies every 5 years.
- Abnormal iron studies - liver biopsy and liver iron index, needed if >40years, ferritin >1000, ↑ AST; exclude HCV, alcohol, NAFLD/NASH
- Assess liver enzymes and function – blood, ultrasound
- Education
- Assess and treat
 - Extraintestinal manifestations (diabetes, heart, arthritis)
 - Avoid liver toxins, including alcohol
 - Screen for HCV, HCC
 - Preventative care: vaccinate against HAV, HBV
 - Phlebotomy if ↑ liver iron index
- Screen
 - Siblings – screen
 - Spouse - screen to determine if their children should be screened
 - Avoid high intake of Fe, vitamin C

*Remember, there is non-expression of the phenotypic abnormality in approximately 50% of the hereditary hemochromatosis genotype



SO YOU WANT TO BE A HEPATOLOGIST!

- Give the reason why the prevalence of HH associated with celiac disease may be underestimated.
 - Risk of CD (celiac disease) in HH (hereditary hemochromatosis), OR (odd ratio) ~ 2.2
 - The clinical expression of HH may have been reduced by CD, due to malabsorption of iron.
 - So the OR of CD + HH may be even higher

152. Give the interventions which may be used to treat 4 different liver diseases, in which the treatment may lead to the reversal of hepatic fibrosis.

Liver disease	Intervention
○ Hemochromatosis (HH)	– Phlebotomy
○ Secondary iron overload	– Desferoximine
○ Hepatitis B infection	– Antiviral therapy (entecavir)
○ Hepatitis C infection	– Antiviral therapy
○ Non-alcoholic steatohepatitis	– Weight reduction

Source: Adams P. Gastroenterology 2011; 1142-1143

“Success is not final, failure is not fatal:
It is the courage to continue that counts.”

Winston Churchill

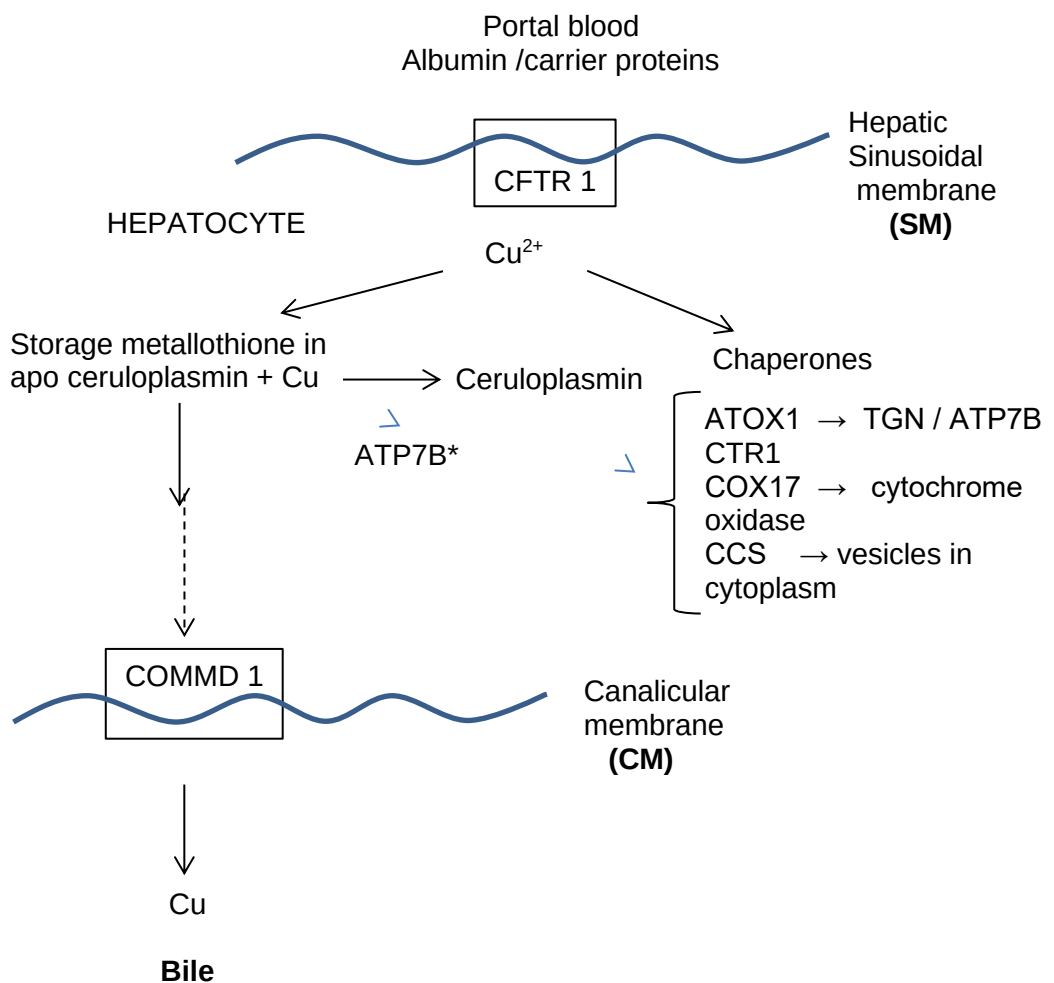


Wilson Disease

Useful background

➤ Definition

- Wilson disease (WD) is an autosomal recessive condition caused by a mutation in ATP1B WD gene on chromosome 13, resulting in reduced secretion of copper from the liver into the bile, and accumulation of excessive iron in numerous tissues such as CNS, eye, liver, red blood cells, kidney.



Exam alert

- Curiosity and Caution: WD is very rare, but is frequently tested (or over-tested) in written and clinical examinations.
- Watch out : NAFLD may occur in WD, which you should suspect from
 - Neurological symptoms / signs
 - ↓ serum alkaline phosphatase (AP), ↓ uric acid
 - Hemolytic anemia
 - Kayser-Fleisher (KF) rings
- Be sure to associate WD and liver disease plus neuropsychiatric symptoms and especially Parkinsonian symptoms, Kayser-Fleischer rings from a copper-sulfur granular complex in Descemet membrane of the cornea, and sunflower cataracts from copper deposited in the lens of the eye.
- Caution: NAFLD is common and WD is rare; fatty liver is common in W. So when you see MCQ of a person with NAFLD, always ask yourself-could this be WD?

➤ Pathophysiology

153. Give the pathophysiology of Wilson disease.

- In health
 - Copper (Cu) from albumin and other carriers in the blood is taken up into the hepatocyte by the copper transporter CTR1.
 - Copper (Cu) enters the liver and binds to Cu chaperones CTR1, COX17, and ATOX1.
 - Copper in the liver binds to apoceruloplasmin, forming ceruloplasmin (α_2 -glycoprotein).
 - Under basal conditions, the Wilson ATPase is located in the trans-Golgi network (TGN), where it receives Cu from the Cu chaperone ATOX1.
 - Cu transfer to the transmembrane domain is accompanied by ATP hydrolysis and formation of transiently phosphorylated intermediates of the Wilson ATPase ('phosphorylation').
 - The Wilson ATPase participates in the mechanism for incorporating Cu into apo-ceruloplasmin to generate holo-ceruloplasmin.



- In Wilson disease
 - Misfolding of Wilson ATPase
 - Retention of WD ATPase in the endoplasmic reticulum
 - Failure to bind to ATOX1 (not shown)
 - Abnormal trafficking of WD ATPase
 - Abnormal phosphorylation and copper transfer
 - ↓ biliary excretion of Cu
 - Copper accumulation and toxicity in hepatocytes and other tissues (e.g. eye, kidney)

Abbreviations: BC, bile canaliculus; Mt, metallothionein; RER, rough endoplasmic reticulum; SER, smooth endoplasmic reticulum; TGN, trans-Golgi network.

Printed with permission: Ferenci P, et al. Defining Wilson disease phenotypes: from the patient to the bench and back again. *Gastroenterology* 2012;142(4):692-6.

➤ Pathology

154. Give the pathological changes in the liver in WD.

- Lysosomal deposits of Cu-metallothionein (orcein stains), especially in Kupffer cells
- Inflammation, including interstitial hepatitis
- Mallory bodies
- Patchy involvement of cystic dilation of mitochondrial cristae

➤ Laboratory

155. Give 7 laboratory features that suggest the diagnosis of WD.

- Transaminases < 1500 U/L (may be normal)
- AST / ALT > 2.2
- ↓ AP (alkaline phosphatase)
- ↑↑ bilirubin (B) (from liver disease plus RBC hemolysis)
- AP/B < 4
- ↓ serum ceruloplasmin
- ↓ serum copper (ceruloplasmin-bound)
- ↑ non-ceruloplasmin-bound copper



- ↑ copper in the urine (reflects ↑ non-ceruloplasmin-bound copper)
- ↑ liver copper (> 250 µg per g dry weight of liver)

SO YOU WANT TO BE A HEPATOLOGIST!

The serum concentration of ceruloplasmin is decreased in WD, but the reduction is not diagnostic for the condition.

- Give a classification of the other causes of reduced ceruloplasmin levels.
 - Chronic liver disease
 - Malnutrition
 - Malabsorption
 - Nephrotic syndrome
 - Hereditary aceruloplasmin
- Give the reasons why measurement of liver copper may be normal or non-diagnostic in early WD.
 - In early WD the lysosomal Cu may be distributed unevenly in the liver, so there is a possible sampling error.
- Give the mechanism for the iron deficiency which may occur the WD.
 - Fe²⁺ stored in ferritin must be oxidized in order for the Fe²⁺ to become Fe³⁺ and to be then bound to transferrin and be transported to bone marrow for production of RBC.
 - Ceruloplasmin is a feroxidase (oxidase activity).
 - ↓↓ ceruloplasmin, as occurs in WD, results in less oxidation of Fe²⁺ in ferritin, so ↓ Fe³⁺ is bound to transferrin and transported to the bone marrow to produce RBC, thereby leading to anemia used for RBC.

"Life is like a bicycle.

To keep balanced, you must keep moving."

Albert Einstein



Routine tests for **diagnosis** of Wilson disease.

Test	Typical finding	False negative	False positive
Serum ceruloplasmin	Decreased by 50% of lower normal value	Normal levels in patients with marked hepatic inflammation Overestimation by immunologic assay Pregnancy, estrogen therapy	Low levels in: - Malabsorption - Aceruloplasminemia - Heterozygotes
Test	Typical finding	False negative	False positive
24-hour urinary copper	> 1.6 μmol / 24 h > 0.64 μmol / 24 h in children	Normal - Incorrect collection - Children without liver disease	Increased - Hepatocellular necrosis - Cholestasis - Contamination
Serum "free" copper	> 1.6 μmol / L	Normal if ceruloplasmin overestimated by immunologic assay	
Hepatic copper	> 4 $\mu\text{mol/g}$ dry weight	Due to regional variation - In patients with active liver disease - In patients with regenerative nodules	Cholestatic syndrome
Kayser-Fleischer rings by slit lamp examination	Present	Absent - In up to 50% of patients with hepatic Wilson - In most asymptomatic siblings	Primary biliary cirrhosis

Printed with permission: European Association for Study of Liver. EASL Clinical Practice Guidelines: Wilson disease. J Hepatol. 2012;56(3):671-85, Table 4.



➤ Clinical

156. Give 20 **clinical features** that suggest the diagnosis of WD.

- Hepatic
 - Acute liver failure
 - Acute hepatitis
 - Chronic hepatitis
 - Autoimmune-like hepatitis Asymptomatic hepatomegaly
 - Isolated splenomegaly
 - Persistently elevated serum aminotransferase activity (AST, ALT)
 - Fatty liver
 - Cirrhosis: compensated or decompensated
- Neuropsychiatric symptoms
 - Depression
 - Neurotic impulsive behavior
 - Basal ganglia involvement
 - Disorder of gait
 - Rigidity
- Neurological
 - Movement disorders (tremor, involuntary movements)
 - Drooling, dysarthria
 - Rigid dystonia
 - Pseudobulbar palsy
 - Dysautonomia
 - Migraine headaches
 - Insomnia
 - Seizures
 - Depression
 - Neurotic behaviours
 - Personality changes
 - Psychosis
- Eyes
 - Sunflower cataracts
 - Kayser-Fleisher rings
- Hemolytic anemia



- Hyperphonia (soft voice)
- Kidney
 - Aminoaciduria
 - Nephrolithiasis
 - Fanconi syndrome
 - Nephrolithiasis
- Gallbladder
 - Cholelithiasis
- Pancreas
 - Pancreatitis
- MSK
 - Arthritis of larger joints
 - Osteoporosis
 - Osteochondritis
 - Rickets
 - Rhabdomyolysis
- Heart
 - Cardiomyopathy
 - Arrhythmias
 - SCD (sudden cardiac death)
- Endocrine
 - Hypoparathyroidism
 - Amenorrhea
 - Infertility
 - Spontaneous abortion
 - Menstrual irregularities
 - Repeated miscarriages
- Skin
 - Lunulae ceruleae

Modified in part from: Roberts EA, Schilsky ML; American Association for Study of Liver Diseases (AASLD). Diagnosis and treatment of Wilson disease: an update. *Hepatology*. 2008 ;47(6):2089-111.



Clinical Gems and Pearls

- A young person with liver disease in WD who develops neurological symptoms usually has cirrhosis.
- Hemolytic anemia in WD occurs in
 - Acute hepatitis
 - ALF (acute liver failure)
- Basal ganglia symptoms / signs
 - Plus KF rings = WD
 - No KF rings ≠ WD

- The gold standard for diagnosis of WD
 - Hepatic copper > 250 µg / g dry tissue – Yes
 - ↓ serum ceruloplasmin
 - Free copper, ↑ urine copper – No (seen in heterozygotes, and other chronic cholestatic conditions)

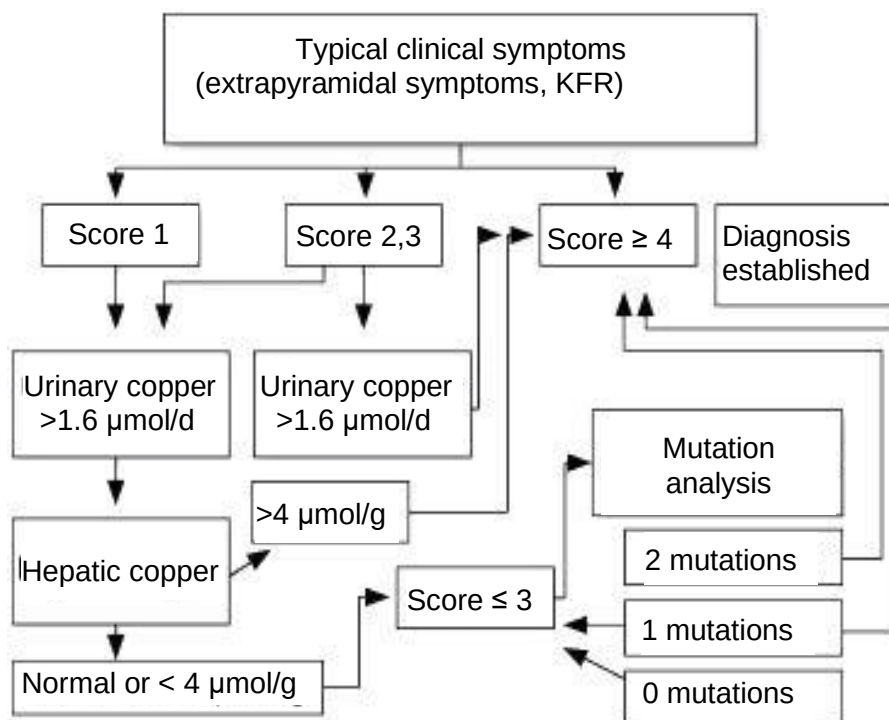
➤ Screening

- WD is caused by autosomal recessive ↓ / absent function of the gene ATP7B; who needs to be screened for WD in the patient's family.
 - First-degree relatives
- Suggested algorithm for Wilson disease, based on the Leipzig Score

"When we are no longer able to change a situation,
we are challenged to change ourselves."

Viktor Frankl





Printed with permission: European Association for Study of Liver. EASL Clinical Practice Guidelines: Wilson disease. J Hepatol. 2012;56(3):671-85, Figure 1. Approach to diagnosis of Wilson disease (WD) in a patient with unexplained liver disease.

Scoring system developed at the 8th International Meeting on Wilson disease.

Findings	Score	Findings	Score
KF rings		Liver copper	
- Present	2	- > 5x ULN (>4 μmol/g)	2
- Absent	0	- 0.8-4 μmol/kg	1
Neurologic symptoms**		- Normal (< 0.8 μmol/g)	-1
- Severe	2	- Rhodamine-positive granules	1
- Mild	1	Urinary copper (in the absence)	
- Absent	0	- Normal	0
Serum ceruloplasmin		- 1.2x ULN	1
- Normal (> 2 g/L)	0	- > 2x ULN	2
- 0.1- 0.2 g/L	1	- Normal but > 5x ULN	3
- < 0.1 g/L	2		



Findings	Score	Findings	Score
Coombs-negative hemolytic anemia		Mutation analysis	
- Present	1	- On both chromosome detected	4
- Absent	0	- On 1 chromosome detected	1
		- No mutations detected	0

TOTAL SCORE	Evaluation
≥ 4	Diagnosis of WD established
3	Diagnosis possible, more tests needed
≤ 2	Diagnosis very unlikely

Printed with permission: European Association for Study of Liver. EASL Clinical Practice Guidelines: Wilson disease. J Hepatol. 2012;56(3):671-85, Table 5.

Another MCQ Alert

You had understood that in Wilson disease (WD) the serum copper concentration was reduced, but you have seen in review self-test MCQ (multiple choice question) that gives you an option of choosing increased serum copper as a correct answer. How is this possible?

- The copper in the serum is usually all bound to ceruloplasmin
- In WD, the serum concentration of ceruloplasmin is reduced, so the serum concentration of ceruloplasmin-bound copper is reduced.
- Here is the answer – the serum “free” (non-ceruloplasmin bound) copper is increased.
- Not all labs have the expensive equipment to measure free copper in the serum.
- Take-home message: check to see if MCQ states whether the serum copper is free, or bound to ceruloplasmin



➤ Treatment

157. Give why it is important to appreciate that it takes ~ 6 months for D-penicillamine and trientine to improve neurological symptoms and liver enzymes in WD.

- So that therapy is not considered to be unsuccessful and incorrectly stopped prematurely.

158. Give the **adverse effects** of therapy of WD (Wilson disease).

➤ D-penicillamine

- CNS
 - ↑ Neurological symptoms
- Hypersensitivity reaction
 - Fever
 - Rash
 - Lymphadenopathy
 - Neutropenia
 - Thrombocytopenia
- Endocrine
 - Hypothyroid
- Skin lesions
 - Pemphigoid lesions
 - Lichen planus
- Hematology
 - ↓ RBC
 - ↓ WBC
 - ↓ platelets
 - Lymphadenopathy
- MSK
 - Lupus-like syndrome
 - Arthralgias
- Lung
 - Goodpasture syndrome
- Kidney
 - Proteinuria
- Pregnancy - toxicity
 - Iron deficiency
 - Suppression of bone marrow

➤ Trientine

- Gastritis



- Iron deficiency
- Bone marrow suppression
- Ammonium tetrathiomolybdate
 - Suppression of bone marrow
 - Hepatotoxicity

Please see: Swan MG. Chapter 58. In: Therapeutic Choices. Grey J, Ed. 6th Edition, Canadian Pharmacists Association: Ottawa, ON, 2011, Table 7: Wilson disease, page 780.

- Clinical Alert in Treatment of WD: Stopping Rules
 - **Do not** suddenly stop chelating treatment in WD
 - Suddenly stopping chelating therapy may
 - ↑ neurological defects
 - ↑ risk of fulminant hepatic failure
 - ↑ risk of being refractory to treatment when Cu-chelating therapy is introduced

α1- Trypsin (α 1-AT) Deficiency

- Genetics
 - Autosomal recessive disorder associated autosomal co-dominant mutation in A1AT (serine protease inhibitors) on chromosome 14
 - Leading to chronic disease of lungs (emphysema) and liver (cirrhosis)
- Pathophysiology

159. Give the pathogenesis of α1-AT deficiency.

- Replacement of glutamine with lysine from a mutation at position 342 of the α1-AT (SERPINA 1) gene leads to degradation of the serine proteases in the serum and tissues
- Loss of serum α1-AT activity results in
 - Loss of normal inhibition of the activity of the elastase protease
 - ↑ neutrophil elastase activity
 - ↑ proinflammatory effect of ATZ polymers on neutrophils
- The AT protein is misfiled and polymerized and malprocessed.
- This abnormal structure of the AT2 protein lead to its retention in the ER, and ↓ intracellular degeneration (abnormal “quality control” of the protein)
- Loss of normal inhibition of the activity of the elastase protease



- The gain-in-function alter intracellular signaling pathways, with the changes in processes include
 - ↑ autophagy
 - Mitochondrial injury
 - ↑ apoptosis

➤ Pathology

160. Give the histopathology of α 1-AT deficiency.

- ↓ bile ducts
- Intracellular cholestasis
- Inflammation
- Steatosis
- PAS (periodic acid-Schiff) – positive, diastase-resistant globular inclusions of polymers of α 1-ATZ protein in periportal hepatocytes and Kupffer cells
- IHC (immunohistochemistry)
 - Staining with monoclonal antibody to α 1-ATZ confirms α 1-ATZ proteins in the globular inclusions.

➤ Clinical

- Pulmonary emphysema
- Hepatic cirrhosis
- Panniculitis, ulcerative, neutrophilic
- Aneurysm of aorta, cervical artery

Note; recombinant plasma A1AT replacement therapy useful for lung but not liver A1AT changes

➤ Treatment

- Liver transplantation corrects the metabolic disorder
- 5-year survival rate for α 1-AT
 - Children, 83%
 - Adults, 90%

Curiosity!

- “Liver transplantation with grafts from donors with unrecognized α 1-AT deficiency appear to have a comparable outcome to transplants using grafts without unrecognized liver disease” (Feldman M., et al. *Sleisenger and Fordtran’s Gastrointestinal and Liver Disease*. 9th Edition. Saunders/Elsevier, Philadelphia, 2010, page 1216).



Autosomal Dominant Polycystic Kidney Disease (ADPKD)

The patient with ADPKD (autosomal dominant polycystic kidney disease) develops esophageal varice but no ascites. There are no signs of portal hypertension /cirrhosis.

161. Give explanation for the non-cirrhotic portal hypertension, and the lack of ascites.

- In the high liver (massive hepatomegaly), the cysts may compress veins and lead to non-cirrhotic portal hypertension.
- Depending upon which vein(s) is obstructed determines that hepatic complications:

Compression	Sign
- PV (portal vein)	▪ EV (esophageal varices)
- HV (hepatic vein) / IVC (inferior vena cava)	▪ Ascites
○ Peal and Gem: remember that portal hypertension can occur in ADPKA the absence of obstruction of PV, HV or IVC, due to the association of ADPKD with CHF (congenital hepatic fibrosis)	
- The large hepatic cysts may also cause gastric outlet obstruction	

162. Give a cause of the disease in which there is no cirrhosis, almost no hepatic synthetic dysfunction, a low MELD score, and yet liver transplantation is still performed.

- The patient with massive hepatic cysts from APPKD may have no cirrhosis, normal hepatic function, and a low MELD score, but liver transplantation is justified for their non-cirrhotic portal hypertension, esophageal varices and ascites.
- A MELD exception may be requested to make the ADPKD patient with massive hepatic cysts and non-cirrhotic PHT eligible for liver transportation.

163. Give the most common causes of abdominal pain in the patient with ADPKD.

- Renal
 - Cyst
 - Hemorrhage
 - Infection
 - Perforation
- Abdominal wall
 - Hernia
- Colon
 - Diffuse diverticulitis



Cystic Fibrosis (CF)

164. Give the hepatic lesions which are specific to CF itself, and those secondary to extrahepatic disease.

- Specific
 - FBC (focal biliary cirrhosis)
 - Obstruction of small bile ducts
 - Inflammatory
 - Steatosis
 - Proliferation of bile ducts
 - Portal fibrosis
 - Multilobular biliary cirrhosis (MBC)
 - 10% of FBC progress to MBC and portal hypertension
- Secondary
 - Cardiopulmonary disease
 - Centrilobular necrosis
 - Drug hepatotoxicity
 - Cirrhosis
- Specific and / or secondary
 - Muscococele
 - Mucous hyperplasia
 - Microgallbladder
 - Biliary sludge
 - Cholelithiasis
 - Cholangiocarcinoma
 - Bile duct compression / stricture from pancreatic fibrosis

➤ Suspecting and Diagnosing Liver Disease in CF

- “Liver biochemical test levels may remain relatively normal despite histological evidence of cirrhosis” (Feldman M., et al. Sleisenger and Fordtran’s Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier, Philadelphia, 2010, page 1277).
- Hepatic lesions may be focal (FBC), so there is considerable sampling error, and liver biopsy may underestimate the severity of the associated liver disease.
- A normal abdominal ultrasound does not exclude clinically important hepatic fibrosis.



165. Give 6 hepatobiliary complications of **sickle cell disease**.

- Liver diseases
 - Acute sickle hepatic crisis
 - Hepatic sequestration
 - Sickle cell intra-hepatic cholestasis
 - Hepatic infarction
 - Hepatic iron overload
 - Viral hepatitis
- Biliary system
 - Cholelithiasis and choledocholithiasis
 - Acute cholecystitis and cholangitis
 - Ischemic cholangiopathy

Printed with permission: Ahmed S, et al. *Best Practice & Research Clinical Gastroenterology* 2005;19(2): 299.

166. Give the causes and features of **mitochondrial cytopathies**.

- Causes
 - Acute fatty liver of pregnancy
 - Reye syndrome
 - Genetic defects in mitochondrial function
 - Drug-related liver injury (DILI)
- Features
 - Vomiting and apathy
 - Lactic acidosis
 - Hypoglycemia
 - Hyperammonemia
 - Microvesicular fat in organs

Adapted from: Leonis, Mike A and Balisteri, William F. *Sleisenger & Fordtran's gastrointestinal and liver disease: Pathophysiology/Diagnosis/Management* 2006: 1621-1622.



167. Give 6 other **inherited disorders** that involve the liver.

- Alagille syndrome
- Benign intrahepatic cholestasis
- Cholesterol ester storage disease
- Dubin-Johnson syndrome
- Gilbert syndrome
- Progressive familial intrahepatic cholestasis
- Wolman disease
- Zellweger syndrome

Printed with permission: Wright TL. 2007 AGA Institute Postgraduate Course. pg. 44.

“What is not started today is never finished
tomorrow.”

Johann Wolfgang von Goethe



168. Give the dietary therapy of 5 **hereditary liver diseases** (in addition to always avoiding alcohol).

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)
○ Wilson disease	– Low-copper diet, zinc supplementation (together with chelating agent); green tea
○ Cystic fibrosis	– High-fat diet, pancreatic enzyme supplements, fat-soluble vitamin supplements, medium chain triglycerides (MCT)
○ Hereditary fructose intolerance	– Low fructose, low sucrose diet
○ Galactosemia	– Galactose-free diet
○ Tyrosinemia	– Low phenylalanine and tyrosine diet
○ Glycogen storage disease	– Continuous glucose feeding
○ Cerebrotendinous xanthomatosis	– Deoxycholic acid supplementation

Adapted from: Thapa BR. *Indian J Pediatr.* 1999; 66(1 Suppl): S110-9.



Drug- Induced Liver Injury (DILI)

SO YOU WANT TO BE A HEPATOLOGIST!

- Give the meaning of Phase I, II and III reactions involved in hepatic drug metabolism.
 - Phase I reactions
 - Microsomal drug oxidases and the CYP gene superfamily
 - Involves the hemoprotein of the CYP gene
 - Drugs are converted to a toxic metabolite (e.g. acetaminophen → NAPQI)
 - Phase II
 - Conjugation
 - Through glucuronic acid or inorganic sulfate by formation of ester links with the drug
 - Phase III
 - Secretion of drugs or their metabolites by transporters
 - ATP-binding cassette (ABC) protein
 - MDR1 (multidrug resistance protein C1)
 - MRP1 (multidrug resistance-associated proteins)
 - MRP-3 sinusoidal membrane of hepatocytes
 - MRP2 canalicular membrane (CM) of hepatocytes
- Give the reason why DILI resulting from drugs metabolized by phase I reactions (e.g. acetaminophen) is localized in zone 3 (around the terminal hepatic venules [THV]).
 - Phase I reactions are catalyzed by microsomal drug oxidase, the key component of which is a hemoprotein of the CYP gene superfamily.
 - CYP2E1 is located in hepatocytes which form a 1 to 2 hepatocyte thick rim around the THV.



169. Give 5 drugs that have been reported to have an increased risk of hepatotoxicity in patients with chronic liver disease.

Drug	Underlying liver disease as a risk factor
○ Methotrexate	– Alcoholic liver disease, NAFLD
○ Vitamin A (high doses)	– Alcoholic liver disease
○ Rifampin	– Primary biliary cirrhosis
○ Methimazole	– Chronic hepatitis B
○ Ibuprofen (NSAIDs)	– Hepatitis C
○ Antiretrovirals (e.g. zalcitabine, saquinavir)	– Hepatitis B, C
○ Antiandrogens	– Chronic viral hepatitis B, C
○ Oral contraceptives	– Women with liver tumours, or history of jaundice of pregnancy

Adapted from: Gupta NK, and Lewis JH. *Aliment Pharmacol Ther* 2008; 28(9): 1021-41.

170. Give 5 major **mechanisms** of drug-induced liver injury, leading to hepatocyte apoptosis and necrosis.

- Direct hepatotoxicity
 - Injury to
 - Mitochondria
 - Plasma membrane
- ROS (reactive oxygen species)
 - “the liver is exposed to oxidative stress by the propensity of hepatocytes to reduce oxygen....”
 - Some drugs (e.g. acetaminophen) may be converted by CYP into pre-oxidant reactive metabolites
 - CYP-mediated metabolism → formation of reactive metabolites → ↓ glutathione → injury to mitochondria → 1) release of cytochrome C and 2) operation of MPT (mitochondrial permeability transition) → activation of caspase → apoptosis
 - Formed from injured hepatocytes and kupffer cells
 - Reactive metabolites undergo covalent binding to proteins
 - Protein-drug adducts
 - Inactive important enzymes
 - May be acted upon by immunodestructive processes



- Glutathione system
 - Pro-oxidants signal Nrf (the redox-sensitive transcription factor)
 - Nrf → ↑ CYP 2E1 expression → ↑ hepatic glutathione synthesis (from cysteine) → ↑ antioxidant effects
 - Cystolic glutathione
 - In the reduced state, resulting from the effect of NADPH and glutathione reductase
 - Glutathione deficiency injures mitochondria, releases cytochrome C and MPT (mitochondrial membrane permeability transition), leading to activation of caspases and apoptosis
- Biochemical pathways of cellular damage
 - Covalent binding of drug to cellular proteins
 - Oxidation of proteins
 - Post-translational modification of proteins
 - Lipid peroxidation
 - Cleavage of DNA
 - ↑ Ca^{2+} (intracellular concentration of Ca^{2+})
- Hepatic non-hepatocyte cells
 - Kupffer cells
 - Act as macrophages and antigen-presenting cells
 - Activated Kupffer cell may release TNF, ROS and as-L, which may lead to hepatocyte apoptosis / necrosis
 - Endothelial cells
 - Their low glutathione context make them susceptible to vascular injury
 - Stellate cells
 - When activated, will deposit matrix and lead to fibrosis
- Immunologic mechanisms
 - Formation of ligands with death receptors
 - Porin-mediated introduction of granzyme
 - “altered antigen” drug metabolite interacts with cellular proteins to form drug-protein adducts (haptens)
 - Drug-induced autoimmunity



171. In the context of DILI, give the meaning of Hy's law

- In DILI, the finding of clinical jaundice plus increased ALT or AST has a mortality rate of ~ 10%.

Please see Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier, Philadelphia, 2010, Table 86.3, page 1427 for "Risk Factors for Acetaminophen Induced Hepatotoxicity".

Clinical Tip

- ".....the presence of underlying liver disease does not predispose to acetaminophen hepatotoxicity" (Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier, Philadelphia, 2010, page 1427).

➤ For further details please see

- Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier, Philadelphia, 2010, Table 86.4, page 1431, "Type of Drug-Induced acute Hepatitis: Immunoallergic Reaction Versus Metabolic Idiosyncrasy".
- Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier, Philadelphia, 2010, Table 86.7, page 1443, "Risk Factors for Methotrexate-Induced Hepatic Fibrosis".
- Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier, Philadelphia, 2010, Table 86.8, page 1445, "Types of Drug-Induced Hepatic Vascular Disorders: Clinical Pathologic Features, Outcome, and Implicated Etiologic Agents".
- Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier, Philadelphia, 2010, Table 87.1, page 1448, "Clinical Pathological Features of Halothane Hepatitis".

172. Give 7 types of **histopathological changes** in the liver seen in DILI

- Acute hepatitis
- Fulminant hepatic failure
- Chronic granulomatous hepatitis
- Chronic hepatitis
- Autoimmune hepatitis
- Cholestasis with/without hepatitis



- Steatohepatitis with / without fibrosis
- Vascular toxicity
 - SOS (sinusoidal obstruction syndrome; aka veno-occlusive disease)
 - Sinusoidal dilation
 - Cavernous hemangioma
 - NRH (nodular regenerative hypertension)
 - Peliosis hepatitis
- Tumor
 - FNH
 - Hepatic adenoma
 - HCC
 - Cavernous hemangioma

173. Give 15 **risk factors** of the development of DILI (drug-induced liver injury).

- Older age
- Female gender
- Polypharmacy
- Past history of adverse drug reaction
- Alcohol
 - ↓ dose threshold and ↑ severity of hepatotoxicity of some drugs, e.g. acetaminophen, isoniazid, niacin, methotrexate
- Nutritional status
 - Obesity
 - Halothane
 - Malnutrition
 - Methotrexate
 - Tamoxifen
- Pre-existing liver disease
 - Methotrexate
 - HBV, HCV, HIV / AIDs
 - Anti-TB drugs
 - HAART therapy
 - Anti-cancer drugs
 - Ibuprofen
 - Myeloablation
 - Anti-androgens
 - Sulfonamides
 - HCV sinusoidal obstruction syndrome



174. Give 6 risk factors for **methotrexate induced hepatic fibrosis**, their clinical importance, and their implications for prevention.

Risk factors	Importance	Implications for Prevention
○ Age	– Increased risk >60 yr, possibly related to renal clearance and/or biological effect on fibrogenesis	● Care in use of methotrexate in older persons
○ Dose	– Incremental dose – Dose frequency – Duration of therapy – Cumulative (total) dose	● 5-15 mg/wk is safe Weekly bolus (pulse) safer than daily schedules Consider liver biopsy every 2 years Consider liver biopsy after each 2 g methotrexate
○ Alcohol consumption	– Increased risk with daily levels > 15 g (1-2 drinks)	● Avoid methotrexate use if alcohol intake not curbed. Consider pre-treatment liver biopsy with relevant history of alcohol use.
○ Obesity	– Increased risk	● Consider pre-treatment and interval liver biopsies
○ Diabetes mellitus	– Increased risk in obese persons (type 2 diabetes mellitus)	● Consider pre-treatment and interval liver biopsies
○ Pre-existing liver disease	– Greatly increased risk, particularly related to alcohol, obesity, and diabetes (NASH)	● Pretreatment liver biopsy mandatory Avoid methotrexate, or used scheduled interval biopsies according to severity of hepatic fibrosis, total dose, and duration of methotrexate therapy



Risk factors	Importance	Implications for Prevention
○ Systemic disease	– Possibly risk greater with psoriasis than rheumatoid arthritis (may depend on preexisting liver disease, alcohol intake)	● None
○ Impaired renal function	– Increased risk because of reduced clearance of methotrexate	● Reduced dose, greater caution with use
○ Other drugs	– NSAIDS, vitamin A and arsenic may increase risk	● Greater caution with use ● Monitor liver biochemical tests

Abbreviations: Nash, non-alcoholic steatohepatitis; NSAIDS, nonsteroidal anti-inflammatory drugs

Printed with permission: *Sleisenger and Fordtran's Gastrointestinal and Liver Disease: Pathophysiology/ Diagnosis/ Management*. Ninth edition, 2010, Table 86.7, pg 1443.

- Other diseases
 - Rheumatoid arthritis
 - Salicylates
 - Sulfasalazine
 - Diabetes, obesity
 - Methotrexate
 - Chronic renal disease
 - Methotrexate → fibrosis
 - Renal transplantation → azathioprine-associated hepatic vascular damage

CLINICAL CHALLENGE

Jaw clenching and teeth grinding (**bruxism**) are uncommon extrahepatic manifestations of liver disease. In the patient with these signs plus tender hepatomegaly, sweating, fever and transaminases > 1000, give the likely diagnosis.

- Acute hepatitis with sweating, fever, jaw clenching and teeth grinding would be suggestive of drug induced liver injury, for example from “ecstasy”.
- For an extra mark, give the chemical name for ecstasy (clue: MDMA).
- Ecstasy is **methylenedioxy**methamphetamine.



175. List 10 drugs which are **relatively contraindicated** and must be used cautiously in persons with liver disease.

- Clonazepam
- Conjugated estrogen/medroxyprogesterone
- Dantrolene
- Felbarnate
- Gemfibrozil
- Lovastatin and other HMG-CoA reductase inhibitors (statins)
- Metformin
- Methotrexate
- Naltrexone
- Niacin
- Pemoline
- Phenelzine
- Tacrine (in persons with prior jaundice)
- Ticlopidine
- Tolcapone
- Valproic acid
- Zalcitabine

Suggestion from the author: you have better things to do than to memorize this list. In the patient with liver disease, look up this list, or look up the drugs to be used

Adapted from: Gupta NK, and Lewis JH. *Aliment Pharmacol Ther* 2008; 28(9): 1021-41.

176. Give 10 drugs for which lower doses are recommended in patients with cirrhosis ("**hepatic dosing**").

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

Adapted from: Gupta NK, and Lewis JH. *Aliment Pharmacol Ther* 2008; 28(9): 1021-41.



177. Give 7 hepatobiliary complications of the **use of oral contraceptive agents** (OCAs).

- Gallstones
- Cholestasis
- Unmasking PBC, and other cholestatic diseases
- Unmasking porphyria
- Tumours
 - Adenomas
 - ↑ size of FNH (focal nodular hyperplasia)
 - Hepatocellular carcinoma (rare)
- Increased risk of NASH
- Vascular
 - Budd-Chiari syndrome
 - Peliosis hepatic (sinusoidal dilation)

178. Give the pharmacological treatment of mushroom poisoning and DILI (drug-induced liver injury)..

- Mushroom poisoning (*Amanita phalloides*)
 - NAC, in IV or po doses as per acetaminophen toxicity, plus
 - Penicillin G IV 1 million units / kg BW / day, plus
 - Silibinin (silymarin, milk thistle) IV / po 30-40 mg / kg BW / day for 3-4 days.
- Drug-induced liver injury (DILI)
 - Glucocorticosteroids, only for DRESS syndrome:
 - Drug rash
 - Eosinophilia
 - Systemic symptoms
 - NAC, at doses suggested for acetaminophen

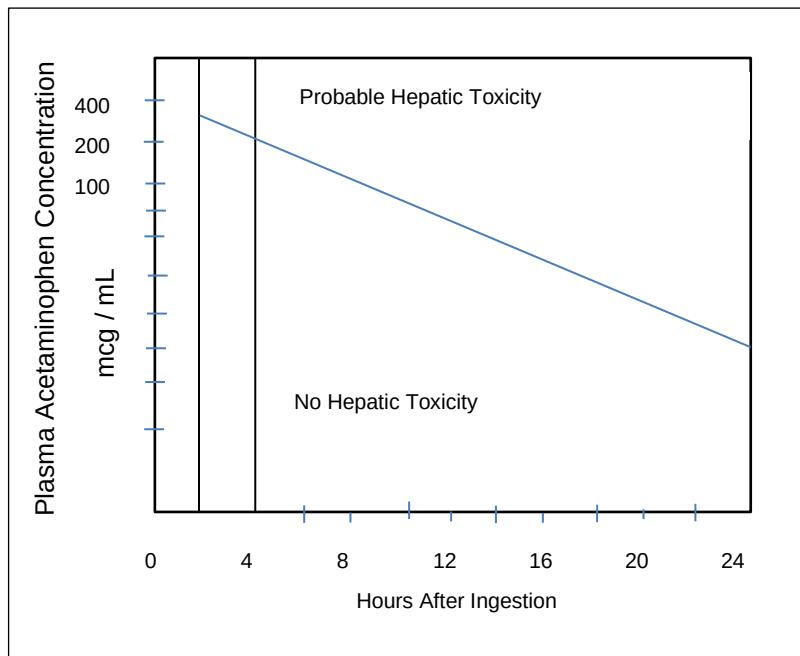


Acetaminophen Overdose

179. Outline the management of the patient with acetaminophen (ACM) overdose.

- Initial measures
 - Suspect acetaminophen overdose if the transaminases are > 1000 IU/mL, and if the serum bilirubin concentrations are normal (in the absence of possible ischemic hepatitis, i.e. hypotension or CV collapse).
 - ABC's
 - Determine likelihood of hepatotoxicity from nomogram (except in non-intentional cases)
 - Immediately give activated charcoal (1gm/kg body weight [BW] po in a slurry (does not reduce the effect of NAC [N-acetylcysteine]) if presenting within 12 hours
 - Rule out other co-ingestions
 - Serum acetaminophen (ACM) level, urine toxicology screen, LFT's, LEs, INR, arterial lactate
 - Stratify risk for possible need for liver transplantation
 - Contact liver transplantation centre

Acetaminophen toxicity **nomogram**



Printed with permission: Spiegel BM, Karsan AA. Acing the hepatology questions on the GI board exam. Slack Incorporated 2012, Figure 27-1, page 83.

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CLINICAL PEARL: DILI

The dose of acetaminophen which places the ordinary patient at risk for acute liver failure (ALF) is 8 gm, but the dose level may be lower, especially for the smaller person. It is better to remember the threshold as < 150 mg/kg, rather than 6-8 gm.

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- Give the reason why drinking alcohol and fasting lower the threshold of acetaminophen hepatotoxicity.

Alcohol and fasting → ↑ CYP2E1 expression → ↑ NAPQI (the toxic metabolite) ↓ glutathione stores below a critical level, thereby allowing NAPQI to cause hepatic damage

- Give the reason why NAC has to be given PO or IV within 12 to 16 hours of an acetaminophen overdose.
 - NAC provides the cysteine to stimulate the hepatocytes to synthesize glutathione and to protect against NAPQI
 - After 12 to 16 hours, the NAPQI-associated hepatocyte damage and the cell death pathways cannot be reversed.
 - Further, as the hepatocytes are destroyed, there are not enough metabolically healthy cells to convert the cysteine from NAC to glutathione.
- If this is true, give the reason why is NAC given for acetaminophen toxicity even 36 hours after poisoning.
 - NAC will stabilize vascular reactivity in persons with liver failure, so it may have some benefit beyond the mechanisms of glutathione and NADPQI.



SO YOU WANT TO BE A HEPATOLOGIST!

A toxic nomogram is available to predict how long after ingestion NAC remains effective. Because of the relative safety of the use of NAC, and that it may be efficacious even 48 hours after overdose, or in persons with non-acetaminophen ALF, the nomogram is **not always strictly followed**. In addition, the nomogram may have limitations.

- Give 3 examples of when the standard acetaminophen toxicity nomogram may not correctly reflect possible severe liver disease.
 - Multiple doses of acetaminophen taken, rather than > 4 g taken at once
 - Unknown time of overdose ingestion
 - Alcoholic patient

Fasting patient

○ N-acetylcysteine (NAC), and other measures

- Oral N-Acetylcysteine (NAC)
 - Loading dose: 140 mg/kg po/NG x 1
 - 70 mg/kg q 4 hours x 17 doses
 - Stopping rules after 72 hours, or when liver chemistry improves
 - 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 hour
 - 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 hours.
 - Dose 4. 150 mg/kg NAC in 1000 ml D5W over 24 hours.
 - Dose 5. 150 mg/kg NAC in 1000 ml D5W over 24 hours.
- Caution regarding use of NAC
 - NAC should be given within 4 hours of overdose, but may still be of value 48 or more hours after ingestion.
 - 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 anaphylactoid/hypersensitivity reactions in 3 to 5% most commonly during loading dose.



- Hold and reduce infusion rate by 50% if rash/nausea occurs. Administer fluids, IV benadryl, IV steroids as needed.
- For causes of ALF other than acetaminophen, and in patients with stages I or II encephalopathy, NAC may improve outcomes.

180. Give the use of NAC (N-acetylcysteine) in non-acetaminophen ALF.

End point	NAC	No-NAC
➤ Adults		
○ Liver transplantation-free survival		
- All patients	40%	27%
- Stages ½ at entry	52%	31%
○ MOFS		
- ↑ tissue oxygenation		
➤ Children		
○ ↓ LOS (length of hospital stay)		
○ ↑ rate of spontaneous recovery		
○ Manage coma (stages III-IV in ALF)		
- Intubation		
- Epidural monitoring of intracerebral pressure (ICP) of < 25 mmHg, and cerebral perfusion pressure of 50-80 mmHg		
- 30° elevation of the head of the bed		
- Factor VII or FFP to get INR < 1.8		
- Mannitol infusion		
- Hypothermia, or indomethacin		
- Cultures		
- Antifungal coverage		
- Vasopressors (norepinephrin)		
- To maintain cerebral perfusion pressure > 50 mmHg, enteral nutrition		
○ Psychological assessment of overdose		
○ Treat complications if ALF present		

Abbreviations: ALF, acute liver failure; ICP, intracerebral pressure; MOFS, multiple organ failure syndrome

Adapted from: Chun LJ, et al. *J Clin Gastroenterol* 2009;43(4):342-9.



Amanita Phalloides Poisoning

XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX
SO YOU WANT TO BE A HEPATOLOGIST!

- Give the mechanism of hepatotoxicity caused by Amanita phalloides.
 - Alpha-amatoxin
 - ↓ mRNA
 - ↓ protein synthesis
 - Phalloidin
 - Interferes with polymerization of actin
 - Disrupts cell membranes

Vascular Diseases

181. Classify, and give 6 examples of the vascular diseases of the liver.

- Disorders of portal venous inflow
 - Acute mesenteric/portal venous thrombosis (PVT)
 - Chronic mesenteric/PVT
- Disorders of hepatic arterial (HA) inflow
 - HA thrombosis
 - Hepatic arteriovenous fistula
 - Ischemic hepatitis
- Disorders of hepatic venous outflow
 - Veno-occlusive disease (VOD)
 - Budd-Chiari syndrome (BCS)

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➤ **Portal colopathy**

182. Define “portal colopathy” and give 3 causes.

- Portal colopathy is the “...vascular manifestations of portal hypertension in the colon” (Feldman M., et al. Sleisenger and Fordtran’s Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier, Philadelphia, 2010, page 602).

➤ **Causes**

- Varices
- Hemorrhoids
- Telangiectasias (spider—nevi-like lesions)
- Patchy diffuse redness, colitis-like

SO YOU WANT TO BE A GASTROENTEROLOGIST!

- What is the postulated pathogenesis of the hemangioblastomas seen in persons with von Hippel-Lindau disease (vHLD).
 - In vHLD, the vHL protein is lost, there is increased hypoxia-inducible factor, and increased production of VEGF (vascular endothelial growth factor).

Note: Inhibitors of VEGF receptor 2 (eg semaxanib) reduce the elevated VEGF in vHLD, and have been found to be useful to treat the hemangiomas.

- **Budd-Chiari Syndrome (BCS)**

- Definition: obstruction of the hepatic venous outflow from the right atrium to the small hepatic venules.



➤ Etiology

183. Give 10 causes of the Budd-Chiari Syndrome (BCS).

- Hypercoagulable states
 - Inherited
 - Factor V Leiden mutation
 - Prothrombin mutation
 - Antithrombin deficiency
 - Protein C deficiency
 - Protein S deficiency
 - Antiphospholipid syndrome
 - Acquired
 - Myeloproliferative disorders
 - Cancer
 - Pregnancy
 - Oral contraceptive use
 - Paroxysmal nocturnal hemoglobinuria (PNH)
 - Polycythemia rubra vera (PRV)
- Tumour invasion
 - Hepatocellular carcinoma
 - Renal cell carcinoma
 - Adrenal carcinoma
- Miscellaneous
 - Aspergillosis
 - Behçet's syndrome
 - Inferior vena cava webs
 - Trauma
 - Inflammatory bowel disease
 - Dacarbazine therapy
- Idiopathic
- Commonest causes
 - Africa, Asia
 - MOVOC (membranous obstruction of the inferior vena cava)
 - NA/Europe



- Thrombosis of hepatic veins, from thrombogenic states, e.g. myeloproliferative disorders (JAK₂ mutations of the gene coding for tyrosine kinase Janus kinase 2)

➤ Clinical

- Abdominal pain
- Hepatomegaly
- Ascites
- Hepatic failure (if acute)
- Note: Presentation: BCS “....should be considered in patients presenting with decompensated cirrhosis or refractory ascites out of proportion to the magnitude of liver biochemical test abnormalities (Feldman M., et al. Sleisenger and Fordtran’s Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier, Philadelphia, 2010, page 1373).

➤ Diagnostic imaging/histology

- Doppler ultrasound
- MRI (contrast enhanced); multiphasic CT
- Liver biopsy (zone 3 congestion)

CLINICAL CHALLENGE

A young woman presents with a rapid onset of abdominal pain, hepatomegaly and ascites. MRI demonstrates an enlarged caudate lobe.

- Give clinical diagnosis, and explain the changes on diagnostic imaging.
 - Budd-Chiari syndrome (BCS) is caused by obstruction of blood flow in the hepatic vein, with flow away from the liver.
 - The damage occurs mostly in zones 3 and 2; because of the ↓ total in the HV, and because the caudate lobe has additional blood flow through the accessory hepatic veins, the caudate lobe may hypertrophy.
 - If a venogram were performed, it might show a “spider web” appearance suggestive of BCS (BCS → ↓ HV flow → ↑ accessory HV flow → spider appearance on venography).
 - Curiosity: a very large caudate lobe may compress the IVC (inferior vena cava) and further ↓ HV outflow.



➤ Pathology

184. Give the acute and chronic **pathological changes** of Budd-Chiari Syndrome.

- Acute centrilobular
 - Congestion
 - Sinusoidal distention
 - Hemorrhage
 - Necrosis
 - Little inflammation
- Chronic
 - Patchy, asymmetrical involvement
 - Perivenular sclerosis
 - Hepatocellular necrosis
 - Regenerative nodules
 - Cirrhosis
- Management
 - Cause
 - Treat any esophageal varices
 - Anticoagulants, thrombolysis, venesection
 - Cytotoxic drugs
 - Surgical
 - Porta-caval shunt
 - TIPS (if incomplete obstruction)
 - Embolectomy (selected cases)
 - Liver transplantation
- Histopathology
 - Central venules
 - Wide subendothelium
 - Portal sinusoids
 - Congestion
 - Portal sinusoids

Abbreviations: HV, hepatic vein; IVC, inferior vena cava; PV, portal vein

Adapted from: Stevens WE. *Sleisenger & Fordtran's gastrointestinal and liver disease: Pathophysiology/Diagnosis/Management* 2006: pg. 1756.; and Printed with permission: Kamath PS. *Clinic Gastroenterology and Hepatology Board Review* 2008: pg. 343; and 2010, pg. 1372.



- Note: the “uncorrected” MELD score does not take into account the refractory ascites which is common in BCS

➤ Treatment

- Acute
 - Supportive care, including
 - Large volume paracentesis of ascites
 - Treating underlying condition
 - Anticoagulation
 - Thrombolysis
 - Angioplasty (obstruction of IVC plus HV → form portocaval shunt)
 - Stent placement
 - TIPS (“bridge” to liver transplantation)
- Fulminant
 - Hepatic failure (↑ MELD score)
 - Liver transplantation (LT)
- Chronic
 - If acute care as per above fails and there is decompensated cirrhosis, then
 - TIPS
 - Liver transplant
 - Portosystemic shunt surgery (PSS)
 - PV becomes the hepatic outflow tract
 - No IVC stenosis
 - IVC pressure < 20 mm Hg

"The real voyage of discovery consists not in seeking new lands but seeing with new eyes."

Marcel Proust



185. Give the **treatment** options and indications for the use of 4 different modalities in the patient with Budd-Chiari Syndrome (BCS), and give their advantages and disadvantages

Treatment	Indication	Advantages	Disadvantages
○ Thrombolytic therapy	Acute thrombosis	Reverses hepatic necrosis	Risk of bleeding Limited success
○ Angioplasty with and without stenting	IVC webs IVC stenosis Focal hepatic vein stenosis	No long-term sequelae Averts need for surgery	High rate of restenosis or shunt occlusion
○ TIPS	Possible bridge to transplantation in fulminant BCS Acute BCS (HE)	Low mortality Useful even with compression of IVC by caudate lobe	High rate of shunt stenosis Extended stents may interfere with liver transplantation
○ Surgical shunt	Subacute BCS if portacaval pressure gradient <10 mm Hg or occluded IVC	Definitive procedure for many patients Low rate of shunt dysfunction with portacaval shunt	Risk of procedure-related death Limited applicability
○ Liver transplantation	Subacute BCS Portacaval pressure gradient >10 mm Hg Fulminant BCS Presence of cirrhosis Failure of portosystemic shunt	Reverses liver disease May reverse underlying thrombophilia	Risk of procedure-related death Need for long-term immunosuppression

Abbreviations: HE, hepatic encephalopathy; IVC, inferior vena cava; TIPS, transjugular intrahepatic portosystemic shunt

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186. What must be excluded in the patient with Budd-Chiari Syndrome before considering LT?

- Associated malignancy

- **Sinusoidal Obstruction Syndrome (SOS, aka Veno-occlusive disease)**

- Definition
 - Obstruction of the terminal hepatic venules and hepatic sinusoids, resembling BCS clinically
- Causes
 - Common associations
 - Bone marrow transplantation (BMT) occurs
 - Within 2 weeks after BMT
 - In 50% of BMT
 - 70% mortality rate
 - Chemotherapy
 - Azathioprine
 - Hepatic irradiation
 - Older age
 - HCV
 - C282Y (HH, hereditary hemochromatosis)
 - Other pre-existing chronic liver diseases
 - Recent bacterial / viral infections
- Lab' abnormalities
 - Conjugated hyperbilirubinemia
 - Thrombocytopenia
- Differential
 - SOS develops after BMT on days 10 to 20
 - Distinguish from GVHD (graft-versus-host disease) which develops after day 15
 - Sepsis and drug toxicity do not usually cause painful hepatomegaly or ascites, as does SOS
- Predictors of severity
 - Jaundice
 - Ascites
 - HVPg (hepatic venous pressure gradient) > 20 mm Hg
 - Multiorgan failure
 - Mortality rate ~25% from multiorgan failure, and not liver failure



Note: be prepared for questions such as: without performing a liver biopsy, distinguish between SOS and GVHD of the liver (easy – see above)

187. Give the clinical and laboratory features which suggest the diagnosis of SOS (sinusoidal obstruction syndrome), aka VOD (veno-occlusive disease).

- Definition: SOS is diffuse, idiopathic endothelial injury causing non-thrombotic obstruction of central hepatic venules, leading to dilation of sinusoids and hepatic congestion.
 - Clinical associations
 - BMT (bone marrow transplantation)
 - Chemotherapy
 - Jamaican herbal teas
 - Azathioprine use
 - Symptoms / signs
 - Painful hepatomegaly
 - Rapid weight gain
 - Ascites
 - Laboratory
 - Conjugated hyperbilirubinemia > 2 mg/dL
 - Thrombocytopenia

188. Give the non-specific changes seen on diagnostic imaging (abdominal ultrasound, CT or MRI) which suggest the diagnosis of SOS (Sinusoidal Obstruction Syndrome).

- Liver, spleen
 - Hepatosplenomegaly
- Portal vein (PV)
 - Dilated
 - Flow in PV slow or reversed
- Umbilical vein
 - Recanalization
- Gallbladder thick wall



189. Give the timing and method of diagnosis of 5 liver and biliary diseases following **stem cell transplantation**.

Disease	Timing	Diagnosis
○ Sinusoidal obstruction syndrome	Onset before day 20	- Typical clinical features plus exclusion of other causes of jaundice and weight gain - Imaging (Doppler ultrasound or CT) - Transvenous measurement of wedged hepatic venous pressure gradient and liver biopsy - Note atypical presentations (acute hepatitis, anasarca)
○ Cholestasis of infection (cholangitis lenta)	Following sepsis or neutropenic fever (usually before day 30)	- Exclude other causes of cholestasis - Inferential diagnosis in a patient with cholestatic jaundice
○ Acute GVHD	Day 15-50	- Confirm GVHD in skin, gut - Exclude other causes of cholestasis - Liver biopsy
○ Acute viral hepatitis	HSV, day 20-50 Adenovirus, day 30-80 VZV, day 80-250 HBV and HCV, during immune reconstitution	- Pre-transplant blood test (antigen, antibodies, PCR results) - Isolation of virus from other sites (stool and urine for adenovirus) - PCR of serum for specific viruses
○ Fungal abscess	Day 10-60	- Liver biopsy histology/PCR/immunostains - Hepatic pain, fever
○ Bacterial infection	Day 10-80	- Liver imaging (MRI>CT) - Serum fungal antigen(s) - Hepatic pain, fever - Liver imaging - Liver biopsy, culture



Disease	Timing	Diagnosis
○ Drug-liver injury	Day 0-100	- Clinical evidence linking elevations of serum ALT or alkaline phosphatase to drugs known to cause liver injury
○ Ischemic liver disease	Day 0-30 Day 15-60	- Clinical evidence linking shock to subsequent rises in serum ALT
○ Biliary obstruction	Day 10-50	- History, examination - Biliary ultrasound
○ Idiopathic hyperammonemia	After day 80	- ERCP>magnetic resonance cholangiography - Unexplained confusion, coma - Blood ammonia
○ Chronic hepatitis C	Pre-transplant Long-term follow-up after transplant	- HCV RNA in serum - Elevation of serum ALT after immune reconstitution
○ Iron overload	After day 80	- Transferrin saturation - Marrow iron qualification - Liver iron quantification (Ferriscan MRI, liver biopsy quantification)
○ Chronic GVHD	Years after transplant	- Prior acute GVHD history - Chronic GVHD in other organs - Consistent elevations of serum ALT, alkaline phosphatase - Note hepatitis presentation
○ Nodular regenerative hyperplasia (NRH)		- Liver biopsy (reticulin stain) - Signs of portal hypertension but preserved liver function - Laparoscopic appearance of the liver

Printed with permission: McDonald, G.B., and Frieze, D. *Gut* 2008; 57:987-1003, Table 3 pg. 995.



- **Portal Vein Thrombosis (PVT)**

190. Classify and give 10 causes of portal vein thrombosis (PVT).

- Hypercoagulable states
 - Antiphospholipid syndrome
 - Antithrombin deficiency
 - Factor V Leiden mutation
 - Methylenetetrahydrofolate reductase mutation TT677
 - Myeloproliferative disorders
 - Nephrotic syndrome
 - Oral contraceptives
 - Paroxysmal nocturnal hemoglobinuria
 - Polycythemia rubra vera
 - Pregnancy
 - Prothrombin mutation G20210A
 - Protein C deficiency
 - Protein S deficiency
 - Sickle cell disease
- Impaired portal vein flow
 - Budd-Chiari syndrome
 - Cirrhosis
 - Nodular regenerative hyperplasia
 - Sinusoidal obstruction syndrome
- Inflammatory diseases
 - Umbilical vein (infants)
 - Behçet syndrome
 - Inflammatory bowel disease
 - Pancreatitis
- Infections
 - Appendicitis
 - Cholangitis



- Cholecystitis
- Diverticulitis
- Liver abscess
- Intraabdominal cancer
 - Pancreas
 - Cholangiocarcinoma
 - HCC
 - Bladder cancer
- Intra-abdominal procedures
 - Alcohol injection
 - Abdominal surgery
 - Colectomy
 - Fundoplication
 - Gastric banding
 - Hepatic chemoembolization
 - Hepatobiliary surgery
 - Islet cell injection
 - Liver transplantation
 - Peritoneal dialysis
 - Radiofrequency ablation of hepatic tumour (s)
 - Sclerotherapy of esophageal varices
 - Splenectomy
 - TIPS procedure
 - Umbilical vein catheterization

Adapted from: Stevens WE. *Sleisenger & Fordtran's gastrointestinal and liver disease: Pathophysiology/Diagnosis/Management* 2006: pg. 1762; and 2010, 1378.

For more details, please see Feldman M., et al. *Sleisenger and Fordtran's Gastrointestinal and Liver Disease*. 9th Edition. Saunders/Elsevier, Philadelphia, 2010, Table 83.2, page 1378, for "Causes of Portal Vein Thrombosis".



Clinical Alert!

“...long-term anti-coagulation does not increase the risk or severity of variceal bleeding and prevents further portal and mesenteric venous thrombotic complications” (Feldman M., et al. Sleisenger and Fordtran’s Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier, Philadelphia, 2010, page 1379).

➤ Clinical

191. Give the **clinical features and treatment** of hepatic artery stenosis and thrombosis, as well as portal vein stenosis or thrombosis.

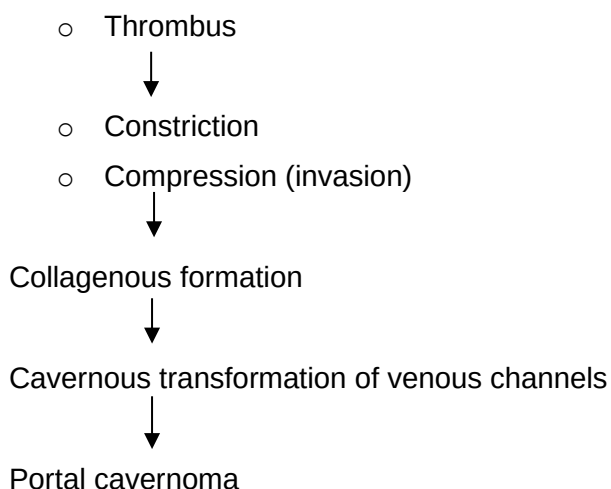
Time of occurrence	Leading symptoms	Treatment
➤ Hepatic artery thrombosis		
○ Early	– Fulminant increase in LFTs – Acute liver failure – Hemodynamic instability	▪ Urgent acute thrombectomy or ▪ Urgent retransplantation
○ Late	– Biliary complications – Strictures – Intrahepatic abscesses – Cholangitis and sepsis	▪ Management of biliary complications using ERC, PTC Rt-PA lysis therapy ▪ Elective retransplantation
➤ Hepatic artery stenosis	– Slight increase in LFTs – Mild or late biliary complications	▪ Reoperation, with resection of the anastomosis and end-to-end reconstruction
○ Early	– Acute liver failure – Fulminant increase in LFTs – Hemodynamic instability – Ascites – Variceal bleeding	▪ Urgent thrombectomy ▪ Urgent retransplantation



Time of occurrence	Leading symptoms	Treatment
○ Late	– Slight increase in LFTs – Portal hypertension – Ascites – Variceal bleeding	▪ Endoscopic treatment Rt-PA lysis therapy ▪ Elective retransplantation
➤ Portal vein stenosis	– Slight increase in LFTs, Portal hypertension, Ascites	▪ Resection and end-to-end reconstruction

Printed with permission: Mueller AR, Platz KP, and Kremer B. *Best Practice & Research Clinical Gastroenterology* 2004;18(5): pg. 884.

➤ Progression over time of obstruction of PV



➤ **Obstruction in hepatic artery or vein, and portal vein**

192. Give the anatomical reasons why thrombosis of the splenic vein (SV) may cause gastric fundal varices, but not esophageal varices.

- Thrombosis of SV (SVT) causes ↑ pressure in short gastric veins.
- Obstruction of SV is distant to the joining of the SV to the SMV (superior mesenteric vein), which form the portal vein and from there the esophageal veins.
- Thus, EV do not form with SVT (but do form with PVT)



A Trick Question

The usual surgical treatment for isolated gastric fundal varices due to splenic vein thrombosis (SVT) is splenectomy.

- Give the circumstance where splenectomy would not be curative for SVT.
 - A SVT combined with a portal vein thrombosis (PVT) would not be cured by splenectomy.

• Ischemic Hepatitis

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- Give reasons why “Ischemic” or “Hypoxic” hepatitis may not be a satisfactory term.
 - Reduced hepatic blood flow from any cause, such as congestive heart failure, respiratory failure, systemic hypotension, cause the following pathological changes:
 - Very little inflammatory infiltrate (i.e. no “hepatitis”)
 - Centrilobular necrosis
 - Loss of hepatocytes
 - RBC in sinusoids
 - May progress to centrilobular fibrosis
- Give 4 laboratory measurements which suggest ischemic hepatitis.
 - ↑ AST
 - ↑↑ LDH
 - ALT-to-LDH ratio of < 1.5
 - Rapid fall of LDH and AST, usually within 4 days
 - In congestive hepatopathy
 - ↑ SAAG
 - ↑ protein in ascites
- In the context of chronic centrilobular vascular congestion, give the meaning of “reverse lobulation”.
 - Reverse lobulation is the formation of bridging necrosis between central veins, (the reverse of bridging necrosis between portal tracts), which is characteristic of cardiac cirrhosis.

Note: Same answer for different question: Give the pathological feature distinguishing portal cirrhosis from cardiac cirrhosis.



Hepatic Artery Aneurysm (HAA)

- Causes
 - Atherosclerosis (may also cause hepatic infarction)
 - Mycotic infection
 - Vasculitis
 - Pseudoaneurysms
 - Liver biopsy
 - Percutaneous transhepatic cholangiogram
 - Liver transplantation

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Atherosclerosis may involve the hepatic artery, and cause a hepatic artery aneurysm (HAA), which may rupture, and is associated with a 30% mortality rate.

- Give another but chronic hepatobiliary complication of atherosclerosis of the hepatic artery.
 - Slow obstruction of the hepatic artery may reduce the blood supply to the bile duct (aka [common bile duct]), leading to
 - Ischemic cholangiopathy
 - CBD strictures
 - Obstruction

➤ Clinical

193. Give the physical finding on the abdominal wall of the person the person with cirrhosis which suggests that the hepatic bruit is from recanalization of the umbilical vein.

- The presence of a caput medusae suggests ↑ blood flow in the abdominal wall veins, arising from recanalization of the umbilical vein, producing the C-B (Cruveilhier – Baumgarten) murmur.

Specific patient with ascites despite salt restriction plus complaint in taking of appropriate diuretics loses the ascites when a hepatic bruit develops.



194. Give the name of the bruit, and the mechanism of the spontaneous clearance of ascites.

- C-B (Cruveilhier – Baumgarten) murmur.
- The development of spontaneous portosystemic shunt as a result of portal hypertension helps to partially bypass the liver blood flow blocked by the cirrhotic nodules; the result is ↓ PHT and ↓ ascites.

➤ Treatment

Abdominal ultrasound demonstrates a cystic mass, and CT which confirms a HAA (hepatic artery aneurysm).

195. Give the surgical management of HAA.

- Extrahepatic
 - Proximal to gastroduodenal artery
 - Proximal and distal ligation of HA (collateral blood supply still occurs in gastroduodenal artery)
 - Distal to gastroduodenal resection artery
- Intrahepatic
 - partial hepatic resection

- Mortality rate of ruptured HAA ○ ~ 30%

Acute Liver Failure (ALF)

➤ Definitions

- A sudden (usually < 24 weeks length of illness) loss of hepatic function in a patient without preexisting liver disease, with the development of coagulopathy (INR > 1.5) and hepatic encephalopathy (Ritt DJ, et al. *Medicine (Baltimore)* 1969:151-72.)
- ALT is defined as “...the rapid development of hepatocellular dysfunction, specifically coagulopathy and mental status changes (encephalopathy) [and often jaundice] in a patient without prior liver disease”.
- Coagulopathy (INR ≥ 1.5) and encephalopathy in patient without previous cirrhosis and with an illness of < 26 weeks duration



- ALF is “....a clinical syndrome that represents the final common pathway of severe liver injury resulting from numerous infections, immunologic, metabolic, vascular and infiltrative disorders”, leading to severe cellular or mitochondrial dysfunction and hepatocellular necrosis”.
- “Hepatic encephalopathy is a defining criteria” for ALF. (Feldman M., et al. Sleisenger and Fordtran’s Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier 2010, page 1557).
- The time interval between the onset of illness and the development of ALF is < 8 weeks, although some authors suggest a range of different time intervals:

– Hyperacute	≤ 1 week
– Acute	1 to 4 weeks
– Subacute	4 to 24 weeks

Note: since these subgroups have no prognostic significance, the use of these terms is no longer wide-spread

➤ Demography

- < 1 / 10⁵ per year
- 1-year survival ~ 2/3

➤ Types

- ALF (acute liver failure) syndrome
 - HE (hepatic encephalopathy)
 - Coagulation abnormalities
 - Jaundice
 - No prior liver disease
 - ↑ inflammatory cytokines
 - ↓ immunity
 - ↓ metabolism of albumin-bound toxins
- Acute on chronic liver failure (AoCLF)
 - ↑ NO (nitric oxide)
 - ↑ vasodilation
 - ↓ cardiac output

➤ Causes

- The causes of ALF in America are as follows:
 - Acetaminophen overdose, 46%
 - Indeterminate, 14%



- Drug-related (other than acetaminophen), 11%
- HBV, 7%
- Other causes, 7%
- Autoimmune, 5%
- Ischemic, 4%
- HDV, 3%
- Wilson disease, 2%

Useful background

- Worldwide the commonest known causes of ALF are
 - Acetaminophen overdose
 - HBV
 - HAV
 - DILI (drug-induced liver injury) from drugs other than acetaminophen.
- Other less common drugs and toxins causing ALF are isoniazid, propylthiouracil, phenytoin, valproic acid
- Don't forget the mushroom! – Amanita phalloides poisoning

196. Give the factors which increase the clinician's suspicion that the patient's ALF is due to malignant infiltration of the liver.

- Massive hepatomegaly
- History of cancer
 - Breast
 - Lung (small cell)
 - Lymphoma
 - Melanoma
 - Myeloma
- The spontaneous recovery rate is 58-64% for acetaminophen, ischemia and HDV, and 20-25% for all other causes of ALF (Lee WM, et al. *Hepatology* 2008;47:1401-15.)

“Motivation is what gets you started,
Habit is what keeps you going.”

Jim Rohn



197. Give a **classification** of the causes of acute hepatic failure (ALF), and give 15 examples.

- Viral infections
 - Hepatitis A-E
 - With the extent of international travel, it remains mindful for us to recall the countries where HEV is endemic, and therefore should be suspected as cause of ALF, especially in a pregnant woman.
 - Cytomegalovirus (CMV)
 - Epstein-Barr virus (EBV)
 - Herpes simplex (HSV)
 - Parvovirus B19
 - Adenovirus
 - Viral hemorrhagic fever
 - Rarely Herpes zoster, Human herpes virus-6, West Nile virus, coxsackie B virus
- Drugs (Iatrogenic)
 - Acetaminophen, isoniazid, NSAIDs, sulfonamides
 - Tetracycline, rifampin, valproic acid, phenytoin, halothane
 - Telithromycin, orlistat, amiodarone
- Immune reconstitution
 - In HBV use and then withdrawal of steroids, chemotherapy or anti-TNF drugs (immune suppression, followed by immune reconstitution with withdrawal of these drugs).
- Inherited
 - Wilson disease
 - Alpha-1 antitrypsin deficiency
 - Galactosemia
 - Tyrosinemia, Reye's syndrome, hereditary fructose intolerance
 - Neonatal iron storage disease
 - Lecithin-cholesterol acyltransferase deficiency
- Ischemic
 - Left heart failure
 - Shock (cardiogenic / non-cardiogenic)
 - Venocclusive disease (SOS, sinusoidal obstruction syndrome)
 - Budd-Chiari syndrome (BCS)
 - Heat stroke (Inadvertent occlusion of portal vein at surgery)



- Infiltration
- Leukemia, lymphoma, metastatic carcinoma
- Pregnancy
 - Eclampsia
 - Preeclampsia
 - HELLP
 - AFLP (acute fatty liver of pregnancy)
 - HEV
- Syncytial giant cell hepatitis
- Primary graft non-function post-liver transplantation
- Post-liver transplantation
 - Primary graft non-function
- The cause of ALF is not always identified

Adapted from: Khashab M, et al. *Curr Gastroenterol Rep* 2007;9(1):66-73.

➤ Laboratory

Trivia

- Give the standard laboratory changes in ALF from acetaminophen which helps to distinguish it from the other common causes.
 - ALF from acetaminophen has ALT > 2000 (often higher), ↑ INR but normal or non-normal serum bilirubin concentration.
- Give the cause of ALT in which there are the following changes:
 - Typical liver enzymes ↑ ALT, ↑↑ LDH, ALT / LDH < 4
 - EHS (exertional heat stroke)



SO YOU WANT TO BE A HEPATOLOGIST!

Major complications of ALF include HE, coagulopathy, jaundice, GI bleeding, and hypoglycemia.

- Give 4 other major complications of ALF.
 - Bacterial and fungal infections
 - Bacterial infections in 80% of ALF patients (Staphylococcus and gram-negative aerobes)
 - Bacteremia in 25%
 - Fungal infections (Candida albicans, Aspergillus) in ~30%
 - MOFS (multiple Organ Failure Syndrome)
 - Hypotension (↓ MAP [mean arterial pressure] from peripheral vasodilation)
 - Pulmonary edema
 - Renal failure
 - DIC
 - Acute pancreatitis
 - Seen in 44% of patients dying from ALF, especially from acetaminophen overdose
 - Acute respiratory failure
 - Pulmonary edema
 - ARDS (acute respiratory distress syndrome); DAD, diffuse alveolar damage)
 - Acute renal failure
 - Acute renal failure in 50% of ALF, from HRS (hepatorenal syndrome) and ATN (acute tubular necrosis)
 - Intermittent hemodialysis, continuous hemofiltration, hemoadsorption, MARS (albumin dialysis using the molecular adsorbent recirculating system)



198. Give the pathogenesis of 6 major **complications** of acute liver failure

Complication	Pathogenesis
○ Hypoglycemia	– ↓ hepatic glucose synthesis
○ Encephalopathy	– Cerebral edema
○ Infections	– Reduced immune function – Invasive procedures
○ Gastrointestinal hemorrhage	– Stress ulceration – Esophageal varices (PHT)
○ Coagulopathy	– ↓ clotting factor synthesis – Thrombocytopenia – Fibrinolysis
○ Hypotension	– Hypovolemia – Decreased vascular resistance
○ Respiratory failure	– ARDS (DAD)
○ Pancreatitis	– Unknown
○ Renal failure	– Hypovolemia – Hepatorenal syndrome – Acute tubular necrosis – NSAID damage

Abbreviations: ARDS, Acute respiratory distress syndrome; CT, computed tomography; DAD, diffuse alveolar damage; ICP, intracranial pressure; NSAIDs, nonsteroidal anti-inflammatory drugs; PHT, portal hypertension.

Adapted from: *Sleisenger and Fordtran's Gastrointestinal and Liver Disease: Pathophysiology/ Diagnosis/ Management*. Ninth edition, 2010, Table 93-4: pg. 1561.

➤ Differential

- The diagnosis of ALF is based on clinical findings, and must be differentiated from conditions with similar clinical findings:



199. Give the 7 important hepatic and non-hepatic conditions which may **mimic** the clinical presentation of ALF.

- Acute decompensation of chronic liver disease
- Acute HBV
- Acute flares of chronic HCV
- Alcoholic hepatitis
- Sepsis (low factor VIII in sepsis; normal factor VIII in ALF)
- SLE (systemic lupus erythematosus)
- TTP (thrombotic thrombocytopenic purpura)

SO YOU WANT TO BE A HEPATOLOGIST!

The AASLD Position Paper on ALF defines ALF as coagulopathy and encephalopathy

“..... In a patient without pre-existing cirrhosis and with an illness of < 26 weeks duration”.

- Give the 3 hepatic conditions in which often unrecognized pre-existing cirrhosis may be present.
 - HBV, vertically-acquired
 - WD (Wilson disease)
 - AIH (autoimmune hepatitis)

- Risk stratification

200. Give the **King's College Criteria** (KCC) risk stratification criteria for liver transplantation in ALF.

- Acetaminophen
 - INR > 6.5 (PT > 100 sec), serum creatinine > 3.4 mg/dl, stage 3 or 4 encephalopathy
 - Arterial lactate > 3.5 at 4 hours after resuscitation
 - pH < 7.30 or arterial lactate > 3.0 at 12 hours after resuscitation
- 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
- Etiology: drug reaction

Printed with permission: Fontana RJ, and Chung RT. *AGA Institute 2007 Spring Postgraduate Course Syllabus*: 636.

201. Give the **performance characteristics** of 4 scoring systems for ALF.

System	Sensitivity	Specificity	PPV	NPV
KCC ≥ 1	26 – 47%	83 – 92%	0.63 – 0.70	0.65 – 0.69
Apache II				
≥ 12	67%	76%	0.69	0.75
≥ 20	68%	87%	0.77	0.81
MELD ≥ 35	61%	71%	0.54	0.76
SOFA ≥ 12	67%	80%	0.74	0.74

Abbreviations: APACHE, acute physiology and chronic health evaluation; KCC, Kings College Criteria; MELD, Model for End-Stage Liver Disease; NPV, negative predictive value; PPV, positive predictive value; SOFA, sequential organ failure assessment

Adapted from: Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. *Saunders/Elsevier* 2010, Table 93.6, page 1564.

➤ Laboratory

- Blood work
 - AFP
 - ALT, AST, AP, GGT
 - Albumin, INR, bilirubin
 - 1° /2° electrolytes
 - Type and screen
 - Factor V, lactate
 - Serum copper, ceruloplasmin, 24 hour urine copper
 - Ferritin, iron, % saturation
 - Alcohol, drug screen
 - Autoimmune markers



- Serologies
 - HIV
 - HAV – IgM
 - HBV - sAg, sAb, IgM anticore
 - HDV (if HBV positive), HEV (if pregnant)
 - HCV
 - CMV/HSV/EBV/Toxo' titers
 - Cultures/Microbiology
 - Blood, urine, and peritoneal fluid
 - PPD and Candida
202. Give 3 laboratory measures which suggest a poor prognosis in ALF (acute liver failure), including ALF from EHS (exertional heat stroke).
- AFP < 3.9 ng/mL on the day after the value of ALT reaches a peak.
 - Normal phosphate (yes, a normal phosphate is a sign of poor prognosis in ALF, since the liver is not taking up $\uparrow \text{PO}_4^-$ to help the liver regenerate).
 - $\downarrow$ factor V
203. Give the cause of ALF in which there is a marked increase in both ALT and LDH.
- Acute ischemic injury of the liver
204. Give specific treatments for the causes of ALF
- Acetaminophen-n-acetylcysteine (NAC)
 - AFLP (acute fatty liver of pregnancy), pre-eclampsia
 - Delivery of fetus
 - Amanita phalloides poisoning
 - NAC IV / po
 - Penicillin G IV
 - Silibinin IV
 - Herpes
 - Acyclovir
 - Autoimmune hepatitis
 - Steroids



- HBV
 - Nucleoside or nucleotide analogues
- Amanita phalloides poisoning
 - NAC, penicillin G, silibinin
- DILI plus DRESS syndrome
 - Glucocorticosteroids, NAC
- Diagnostic Imaging
 - Liver US with Doppler
 - Chest x-ray
 - CT head
 - CT of the head in ALF is neither sensitive nor specific to detect early intracerebral hypertension, but can identify the advanced stages of intracerebral hypertension and brainstem herniation (Larsen FS, Wendon J. *Liver Transpl* 2008;14:S90-6.)
 - Cardiopulmonary evaluation
 - ECG
 - 2-D surface echo with Doppler
 - Pulmonary function tests
 - Cancer Surveillance
 - Pelvic, prostate, breast, colon and HCC, as indicated

Adapted from: Gill RQ, and Sterling RK. *J Clin Gastroenterol* 2001;33:191-8.

- Assess for possible adrenal insufficiency (present in ~ 2/3 of ALF patients) with a cosyntropic stimulation test, or empirically treat with IV steroids
- Assess for possible liver transplantation (LT), using MELD or modified MELD scores.
- List for LT if no contraindications
 - Medical/Surgical Candidacy
 - Transplant hepatology evaluation
 - Transplant surgery evaluation
 - Transplant social work/psychosocial/nutritional evaluation
 - Dental examination
 - Risk stratification (MELD or modified MELD)



Portal Hypertension (PHT) and Cirrhosis

Portal Hypertension (PHT)

➤ Definition of PHT

- Hepatic sinusoidal pressure ≥ 6 mm Hg

➤ Physiology

- After a meal, portal blood flow increases, with no $\uparrow$ portal pressure, because the hepatic sinusoids have
 - High
 - Compliance
 - Accommodation
 - Low
 - Resistance
- Blood supply to the liver is
 - 70% portal vein (PV, blood from mesenteric circulation)
 - 30% hepatic artery (HA, from celiac artery)
- With the dual blood supply (portal venous inflow) to the liver, when blood flow increases in the PV, it decreases in the AA, and vice versa, through an autoregulatory mechanism
 - Recall that we are dealing with three distinct vascular beds
 - Intrahepatic
 - Splanchnic
 - Systemic

205. Give 6 components of each of the vasodilating and vasoconstricting systems involved in the **disturbed hemodynamics** in cirrhosis.

➤ Vasodilator systems

○ Adenosine	○ Glucagon
○ Adrenomedullin	○ Histamine
○ Arterial natriuretic peptide (ANP)	○ Hydrogen sulphide
○ Bradykinin	○ Interleukins
○ Brain natriuretic peptide (BNP)	○ Natriuretic peptide of type C (CNP)
○ Calcitonin gene-related peptide (CGRP)	○ Nitric oxide (NO)
○ Carbon monoxide (CO)	○ Prostacyclin (PGI ₂)
○ Endocannabinoids	○ Substance P
○ Endothelin-3 (ET-3)	○ Tumour necrosis factor- α (TNF- α)
○ Endotoxin	○ Vasoactive intestinal polypeptide (VIP)
○ Enkephalins	



- Vasoconstrictor systems
 - Adrenaline and noradrenaline
 - Angiotensin II
 - Endothelin-1 (ET-1)
 - Neuropeptide Y
 - Renin-angiotensin-aldosterone system (RAAS)/
 - Sympathetic nervous system (SNS)
 - Vasopressin (ADH)

Printed with permission: Møller S, and Henriksen JH. *GUT* 2008; 58: pg. 271.

206. Give the **pathophysiological components** producing the hyperdynamic circulation and cardiovascular dysfunction in persons with cirrhosis.

- The overall effect is
 - ↓ intrahepatic NO and ↓ intrahepatic vasodilation (effect on endothelial cells as well as possibly on HSCs) → ↑ intrahepatic vasoconstriction → ↑↑ intrahepatic resistance (law of Poiseuille)
- ↑ Portal flow and resistance
 - ↑ portal flow
 - ↑ resistance
 - Mechanical factors
 - Regenerative nodules
 - Fibrotic bands
 - Defenestration and capillarization of sinusoids
 - Swelling of hepatocytes and Kupffer cells
 - Vascular factors
 - ↑ collaterals (↑ angiogenesis)
 - ↓ fenestration
 - Ohm's law

$$\Delta P = F \times R$$

F, flow

ΔP , change in pressure

R, resistance



- Hepatic vasoconstriction and ↑↑ increased intrahepatic resistance
 - ↑ shear stress on sinusoids
 - ↑ eNOS → NO (nitric oxide) → intrahepatic vasodilation
 - ↑ ET-1 (endothelin-1) → binds to
 - ET-A receptors on HSC → ↑ HSC contraction → intrahepatic vasoconstriction
 - Also binds to ET-B receptors on endothelial cells → activates eNOS → vasodilation
 - In cirrhosis, there may be ↑ NO production
 - In splanchnic endothelial cells from ↑ shear stress → ↑ cytokines, and ↑ phosphorylation of eNOS → vasodilation in splanchnic and systemic vascular beds (note below that in cirrhosis there is ↓ intrahepatic NO, ↓ intrahepatic vasodilation, ↑ intrahepatic vasoconstriction)
 - In cirrhosis
 - ↓ activation of eNOS protein in endothelial cells → ↓ production of NO
 - ↑ caveolin-1 (an eNOS inhibiting protein)
 - ↓ AKT (protein kinase B)
 - Phosphorylation of eNOS
 - ↑ GRK (G protein-coupled receptor kinase, which inhibits eNOS)
 - ↑ VEGF (vascular endothelial growth factor) from shear stress may ↑ eNOS (VEGF is a NO stimulatory growth factor)
 - ↑ intestinal endotoxin (LPS) → ↑ TGF-β, ↑ ET-1, with binding to ET-A receptors on HSC → intrahepatic vasoconstriction
 - Law of poiseuille $R = 8 \eta L / \pi r^4$
 - Resistance (R) is affected by the length and radius (r) of the vessel, and by the viscosity of the blood; in cirrhosis, the radius becomes less as a result of the vasoconstriction; because the effect of radius (r) on resistance (R) is to the fourth power (r^4), a small fall in r causes a large ↑ R.
 - Give NO in cirrhosis will restore the intrahepatic vasodilation arising from the endothelial cells, but the HSC in cirrhosis contribute to the vasoconstriction and are less responsive to NO. Replacement in cirrhosis, so benefit of restoring ↓ NO levels does not fully restore the vessel diameter to normal
- Peripheral and splanchnic arterial vasodilatation
 - Baroreceptor-induced increase in heart rate



- The vasodilation in splanchnic and systemic (peripheral) vascular beds leads to
 - ↑ cardiac output (hyperdynamic circulation)
 - ↓ mean arterial pressure
 - ↑ systemic blood flowing into splanchnic circulation
- Autonomic dysfunction
 - ↑ sympathetic nervous system (SNS) activity → ↑ intrahepatic vasoconstriction from
 - Norepinephrine
 - Angiotension
 - Leukotrienes
 - Thromboxane
 - Vagal impairment
- Alterations in cardiac preload
 - ↑ portosystemic shunting
 - ↑ blood volume
 - Effects of posture
 - ↓ blood viscosity
- Alterations in oxygen exchange
 - Anemia
 - Hypoxemia
 - Hepatopulmonary syndrome
 - Portopulmonary hypertension
- Collateral Circulation
 - As the portal pressure increases
 - There is ↑ flow of blood into the portal vein-systemic collateral circulation
 - The direction of blood flow reverses, and blood flows abnormally from the portal circulation into the venous component of the systemic system.

Abbreviations: HSC, hepatic stellate cell; LPS, lipopolysaccharide; eNOS, endothelial NO synthase



207. In the setting of the portal hypertension (PHT) and hepatic cirrhosis, give the meaning of “**hepatofugal**” **blood flow**.

- In PHT, when the HVPG (hepatic venous portal gradient) > 12 mm Hg, blood flows backwards up into the esophageal vein, and from there into portal vein.

208. Give 4 sites of communication of the portal to the systemic circulation which develop in portal hypertension, and name the involved / connected blood vessels in this abnormal flow.

Site	Vessel(s)
○ Rectum	Inferior mesenteric vein → pudendal vein
○ Umbilicus	Umbilical vein → left portal vein
○ Retroperitoneum (in women)	Ovarian vessels → iliac veins
○ Gastroesophageal area	Hepatic venous pressure gradient - > 10 mm Hg for collaterals to develop - > 12 mm Hg for esophageal varices to bleed - > 16 mm Hg for gastric varices to bleed Most common site of bleeding, palisade zone, do not drain to periesophageal veins, and from there to the azygous system

Printed with permission: Møller S, and Henriksen JH. *Gut* 2008; 58:271.

209. Give the **classification** of the causes of portal hypertension based on the site of increased resistance.

- Prehepatic
- Intrahepatic
 - Presinusoidal
 - Sinusoidal
 - Post-sinusoidal
- Posthepatic

210. Give the anatomical site of increased resistance when liver disease is associated with ↑ portal pressure (PP) and HVPG is normal.

- There will be ↑ PP but normal HVG when the site of increased resistance is presinusoidal.



211. Give 5 causes of liver disease in which there may be **portal hypertension without cirrhosis**, due to a presinusoidal component of the intrahepatic disease.

- ALD (alcoholic liver disease) presinusoidal perivenular lesions
- AIH (autoimmune hepatitis)
- PBC (primary biliary cirrhosis)
- HH (hereditary hemochromatosis)
- Schistosomiasis (*S. mansoni*, *S. japonicum*)
 - Presinusoidal granulomas
 - Inflammation
 - Periportal fibrosis
- Sarcoidosis (early disease; later the site of ↑ intrahepatic resistance is postsinusoidal)
- 1^o or 2^o liver malignancy

The Stomach in Portal Hypertension

➤ Hypertensive gastropathy, Gastric antral vascular ectasia, Gastric varices

212. Give the mucosal changes in the stomach associated with portal hypertensive gastropathy*.

- Mosaic- like mucosal pattern
 - Small, polygonal areas surrounded by a whitish- yellow depressed border (snake skin appearance) can be categorized as mild (pink mucosa), and moderate (diffuse red mucosa)
- Red point lesions
 - Small (<1 mm), red, flat, point like marks
- Cherry red spots
 - Large (>2 mm), round, red coloured, protruding lesions
- Black-brown spots
- Irregularly shaped black and brown flat spots that do not fade upon washing (these changes might represent intramucosal hemorrhage)

* These changes are characterized endoscopically by the presence of four main findings, as described by the New Italian Endoscopic Club (NIEC).

Printed with permission: Macmillan Publishers Ltd: Perini et al. *Nature Clinical Practice Gastroenterology and Hepatology* 2009; 6(3):150-8.



213. Compare and contrast portal hypertensive gastropathy (PHG) and gastric antral vascular ectasia (GAVE).

	PHG	GAVE
➤ Distribution	Proximal stomach	Distal stomach
➤ Mosaic pattern	Present	Absent
➤ Red signs	Present	Present
➤ Biopsy		
○ Thrombi	-	+++
○ Spindle cell proliferation	+	++
○ Fibrohyalinosis	+	+++
➤ Treatment	Beta-blockers TIPS	Argon laser Banding Cryotherapy Antrectomy

Printed with permission: Garcia-Tsao G., and Kamath PS. 2007 AGA Institute Postgraduate Course: pg. 619.

TIPS – Tranjugular Intrahepatic Portosystemic Shunt

- In about 10% of TIPS, thrombosis occurs within 24 hrs, and the prophylactic use of anticoagulation is not established.
- Over the longterm, dysfunction of the shunt will occur in ~ half because of pseudointimal hyperplasia in the parenchymal tract or outflow hepatic vein, associated with development of a coating of collagenous matrix covered by endothelial cells.
- Doppler ultrasound may be used to establish the patency of the TIPS.
- There are numerous signs reported on Doppler ultrasound which have been used to predict the presence of dysfunction of the shunt, but these signs have a low sensitivity rate (10% - 26%) and an acceptable specificity (88% - 100%).
- Patency of TIPS is best demonstrated with re-catheterization of the TIPS.
- Overall, TIPS causes
 - ↓ rebleeding from
 - Esophageal varices (EV)
 - A gastric varices (GV)



- ECTV (ectopic varices)
- ↑ HE (hepatic encephalopathy)
- No change in overall survival
- Proven benefit of TIPS
 - Primary prophylaxis of bleeding from EV or GV - No
 - Prevent rebleeding from
 - EV, GV, ECTV - Yes
 - PHG failing BB - Yes
 - GAVE - No
 - Refractory cirrhotic ascites, intolerant to LVP - Yes
 - Hepatic hydrothorax, resistant to ↓ Na⁺ & diuretics - Yes
 - Budd-Chiari syndrome, moderate disease, failed anti-coagulation
 - Yes (controversial)
 - HRS

Abbreviations: BB, beta blocker; ECTV, ectopic varices; EV, esophageal varices; GAVE, gastric antral vascular hyperplasia; GV, gastric varices; HRS, hepatorenal syndrome; LVP, large volume paracentesis; PHG, portal hypertensive gastropathy

214. Give 5 **relative contraindications** to TIPS

- Liver failure
 - Hepatic encephalopathy
 - Jaundice (serum bilirubin > 5 mg / dL)
 - Coagulopathy (INR > 2)
- Progressive renal failure
- Associated acute infection
- Severe cardiopulmonary disease
- MELD > 18
- R-HF

Abbreviations: HE, hepatic encephalopathy; R-HF, right heart failure; TIPS, transjugular intrahepatic portosystemic shunts

215. Give 8 **complications** of the TIPS (transjugular intrahepatic portosystemic shunt) procedure.

- Technical complications
 - Neck puncture
 - Inadequate access to hepatic vein



- Creation of parenchymal tract to portal vein
- May make later liver transplantation technically more difficult
- Vessels
 - Puncture of pulmonary artery (PA), pulmonary vein (PV), liver capsule
 - Ischemia (hepatic artery thrombosis)
- Stent
 - Inadequate deployment of stent across parenchymal tract
 - Stent-related complications – thrombosis, stenosis
 - Stent migration into portal vein or inferior vena cava (IVC)
- Liver
 - Hepatic encephalopathy (HE) (new, or worse, or chronic)
 - Intraperitoneal bleeding
 - Hepatic infarction
 - Hepatic rupture
 - Fulminant hepatic failure (acute liver failure [ALF])
- CPS
 - Pulmonary hypertension and right heart failure
- Unique
 - Unique complications of TIPS – hemolytic anemia, infectious endotipsitis
- Systemic
 - Sepsis
 - Multiple organ failure syndrome
 - Long-term presence of foreign body

Abbreviation: CPS: cardiopulmonary systems

Adapted from: Sanyal AJ. 2006 AGA Institute Postgraduate Course: pg. 195.



Practical Tips for Liver Biopsy (LBx)

Peri-LBx management	Days to stop before LBx	Days to restart after LBx
○ Drugs		
– Antiplatelet drugs	10	2-3
– Anti-coagulants	5	1
– Heparin	1	
○ Restrictions		
– Food	No	
– Exercise	No	
– Sedation	No	
– Heavy lifting	Probably a good idea	
○ Post-biopsy		
– Monitoring of vital signs	Yes	
– Observation time	4 hr	
○ Hemostasis		
– “the time to spontaneous cessation of surface bleeding (from the liver after biopsy with a 1.8 mm diameter Menghini needle) did not correlate with abnormalities in the PT, platelet count, or whole-blood clot time”.		
– In patients with hemophilia, correct bleeding diathesis before LBx		
– Inpatients on hemodialysis or with chronic renal failure		
▪ DDAVP (desmopressin) 0.3 mg/kg BW may be given pre-LBx		
▪ Patients on chronic hemodialysis should be dialyzed before LBx.		

Cirrhosis

➤ Pathophysiology

216. Give 7 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 (HGF)



- 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(3):223-9.

➤ Causes

217. Classify and give 8 **causes of cirrhosis**.

- Viral hepatitis
 - HBV, HCV, HDV
- Metabolic
 - NASH
 - Hemochromatosis
 - Wilson disease
 - α -1-antitrypsin deficiency
 - Galactosemia
 - Tyrosinemia
 - Autoimmune
 - Sclerosing cholangitis
 - Primary biliary cirrhosis
 - Autoimmune Hepatitis
- Drugs/toxins
 - Alcohol
- Congestive
 - Cardiac failure
 - Budd-Chiari Syndrome
- Cystic fibrosis



➤ Clinical

218. Give 6 hepatic/extrahepatic signs of **cirrhosis** on hepatic DI (diagnostic imaging), CT and/or 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.

"The only thing that stands between you and your dream is the will to try and the belief that it is actually possible."

Joel Brown Denis Waitley



219. Give 5 examples of **endocrine complications** affecting patients with PBC-, alcohol -, or hemochromatosis – associated cirrhotic disease.

- Alcoholic cirrhosis
 - Gonadal insufficiency
 - Hypothalamic dysfunction
 - Gynecomastia
- Hemochromatosis
 - Gonadal insufficiency
 - Hypothalamic dysfunction
 - Diabetes mellitus
- Primary biliary cirrhosis
 - Autoimmune thyroid disease
 - Metabolic bone disease

Adapted from: Fitz JG. *Sleisenger & Fordtran's Gastrointestinal and Liver Disease: Pathophysiology/Diagnosis/Management* 2006: pg. 1982.

220. Give 2 examples of the effect of cirrhosis on the assessment of endocrine function.

- Hypothyroidism
 - ↓ T3
 - N/↑ thyroxine binding globulin (TGB) level
 - ↑ ALT/AST (also seen with hyperthyroidism)
- Diabetes mellitus (or insulin resistance)
 - Elevated fasting blood glucose level
- Feminization and hypogonadism
 - ↑ estrogen level
 - ↑ sex hormone-binding globulin level
 - ↓ total and free testosterone levels



- Loss of diurnal variation
- Hypothalamic dysfunction
- Testicular atrophy

Adapted from: Fitz JG. *Sleisenger & Fordtran's Gastrointestinal and Liver Disease: Pathophysiology/Diagnosis/Management* 2006; pg. 1982.

➤ Preventive care

221. Give 10 factors to consider in 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)
- Beta-blockers
- Prevention of bacterial infections after GI bleeding (antibiotic prophylaxis)
- Prevention of SBP (antibiotics for previous SBP)
- 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; usual screening for breast, prostate, cervix, colon
- Medialert bracelet
- Ongoing evaluation for possible liver transplantation



➤ Treatment

222. Give the mechanism(s) of action of **5 drugs** used to treat portal hypertension (PHT).

Drugs used for treatment of PHT generally are selected to act to

- ↓ portal blood flow, or
- ↓ intrahepatic resistance
- ↓ Portal Blood Flow → ↓ PP (Portal Pressure)
 - Octreotide
 - ↓ glucagon
 - ↑ splanchnic vasoconstriction
 - ↓ portal and azygous blood flow
 - ↓ postprandial splanchnic blood flow
 - ↓ GT-1-dependent contraction of HSC (hepatic stellate cells)
 - β-adrenergic blocking agents (non-selective)
 - ↓ cardiac output (CO)
 - Vasodilation of mesenteric circulation
 - ↑ “unopposed action of α1-adrenergic receptors →
 - ↓ portal flow
 - ↓ intrahepatic resistance
 - Vasopressin
 - Splanchnic vasoconstriction
 - ↓ PV (portal vein) inflow
 - ↓ CO (inotropic)
 - ↓ HR (chronotropic)
- ↓ Intrahepatic Resistance
 - Under study
 - A1-adrenergic antagonists
 - ARBs (angiotensin II receptor type I blockers)
 - Nitrates



➤ Nitrates

- Venodilation from ↓ Ca_i^{2+} in smooth muscle in venous wall

Coagulopathy

223. Give 10 factors which contribute to the **coagulation disorders** in cirrhosis

- Mechanism of ↓ synthesis of procoagulant factors
 - Vitamin K-dependent factors II, VII, IX, X
 - Factor V
 - Factor XI
- Mechanism of thrombocytopenia in cirrhosis
 - Hypersplenism
 - ↓ hepatic synthesis of thrombopoietin
 - Bone marrow toxicity
 - HCV
 - Alcohol
 - ↓ thrombin produced by platelets
- Mechanisms of dysfibrinogenemia
 - Altered production of activators / inhibitors of fibrolysis
 - Endotoxemia-associated activation of coagulation cascade
 - ↓ clearance of fibrinolytic proteins
 - ↑ D-dimer
 - ↑ fibrinogen degradation products
 - ↑ clot lysis time

"A pessimist sees the difficulty in every opportunity;
An optimist sees the opportunity in every difficulty."

Sir Winston Churchill



A Practice Curiosity

In cirrhosis, the increase in INR predicts a bad prognosis, but the risk of spontaneous bleeding is not increased by $\uparrow$ INR (of course $\uparrow$ INR is associated with serious bleeding, if and when bleeding occurs from a pathological cause, such as bleeding esophageal varices).

So what is the curiosity? The evidence is not strong that the severity of bleeding esophageal varices is reduced by giving

- Vitamin K
- FFP (fresh frozen plasma)
- rVIIa (recombinant factor VIIa)
- Platelets
- Desmopressin

So, why do we sometimes do this in common everyday practice?

- Well, because it “makes sense”, or “it’s the local standard of care”, or “if I don’t, the lawyers will eat we alive”!

Idiopathic Portal Hypertension (IPH) and Hepatoportal Sclerosis (HPS)

- IPH and HPS are associated with $\uparrow$ PP (portal pressure) and no obstruction of the extrahepatic portion of the PV (portal vein).

224. Give the distinctive hepatic histopathological feature of IPH versus HPS seen on liver biopsy.

- IPH
 - Normal
- HPS
 - Intrahepatic portal veins show
 - Subendothelial thickening
 - Thrombosis
 - Recanalization

Hereditary Hemorrhagic Telangiectasia (HHT) / Osler-Weber-Rendu Disease (OWRD)

- HHT / OWRD may be associated with portal hypertension and bleeding esophageal varices.



225. Give the diagnostic criteria for HHT / OWRD.

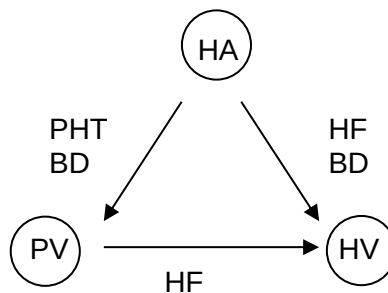
The diagnostic criteria for HHT / OWRD include

- Positive family history
- Epistaxis
- Telangiectasias
- AV fistulas (lung, liver)

Intrahepatic Shunts

In hereditary hemorrhagic telangiectasic (HHT) liver disease, clinical manifestations are the result of the development of shunts between the hepatic artery (HA), hepatic vein (HV), or portal vein (PV).

226. Give the different clinical presentations arising from shunting between HA (hepatic artery), HV (hepatic vein) and PV (portal vein) in HHT (hereditary hemorrhagic telangiectasia)



Abbreviations: BD, biliary disease; HF, heart failure; PHT, portal hypertension

- High-output heart failure (HF) (hepatic artery [HA] and/or portal vein[PV] to hepatic vein [HV] shunt)
 - Shortness of breath on exertion
 - Orthopnea
 - Ascites
 - Edema
- Portal hypertension (PHT) (hepatic artery [HA] to portal vein [PV] shunt)
 - Esophageal varices
 - Nodular regenerative hyperplasia



- Biliary disease [BD] (hepatic artery [HA] to hepatic vein [HV] and/or portal vein [PV] shunt)
 - Severe cholestasis
 - Recurrent cholangitis
- Hepatic disintegration

Abbreviation: BD, biliary disease; HA, hepatic artery; HV, hepatic vein; PHT, portal hypertension ; PV, portal vein.

Adapted from: Sabbà C, Pompili M. Review article: The hepatic manifestations of hereditary hemorrhagic telangiectasia. *Aliment Pharmacol Ther* 2008;28(5):523-33.

Ascites

➤ Clinical

Clinical Examination

- Give the volume of ascites fluid which must be present to detect flank dullness on percussion.
 - 1500 mL

If there is no flank dullness, there is a 90% likelihood that there is no ascites.

- Give the options to increase the diagnostic yield.
 - Test for shifting dullness, or perform an abdominal ultrasound.

➤ Physiology

- The peritoneal surface absorbs up to 500 mL/day of ascitic fluid.
- Excessive use of diuretics above this physiological level of mobilization of ascitic fluid of 500 mL/day causes depletion of fluid from intravascular spaces.
- Contraction alkalosis develops, together with prerenal azotemia.
- Prerenal azotemia is diagnosed from
 - $\text{Na}^+ < 10 \text{ mmol/L}$



➤ Pathogenesis

227. Give the current theory of the **pathogenesis** of ascites.

- PHT → ↑ NO → vasodilation → ↓ effective arterial BP
 - ↑ vasoconstrictors
 - ↑ vasopressin
 - ↑ renin-aldosterone
 - ↑ sympathetic nervous system (SNS) activity
 - ↑ Na⁺ -retaining hormones
- ↑ renal vasoconstriction → ↓ renal function → ↑ retention of Na⁺ / H₂O → Ascites

➤ Laboratory

SAAG

- In NA (North America, Canada and USA), the usual cause of ascites is cirrhosis, but don't forget that "...approximately 5% of patients have two causes of ascites...." (Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier, Philadelphia, 2010, page 1527).

228. Give the use of the serum ascites albumin gradient (SAAG) and ascites protein to determine the cause of ascites

SAAG	Ascites Protein <2.5 g/dL	Ascites Protein >2.5 g/dL
>1.1	Portal hypertension due to cirrhosis	Portal hypertension due to hepatic venous outflow obstruction (including right heart failure)
<1.1	Nephrotic syndrome	Malignancy, tuberculosis

Abbreviation: SAAG, serum ascites albumin gradient



➤ “When the SAAG sags”

- The SAAG (serum-ascites albumin gradient” is an index of portal pressure: if the SAAG is ≥ 1.1 g/dL, there is a 97% accuracy of the test for the patient having portal hypertension ($\uparrow$ hydrostatic pressure gradient between portal blood and ascitic fluid).
- A “falsely low” SAAG may be caused by
 - Hyperglobulinemia (> 5 g/dL)
 - During diuretics for cardiac cirrhosis
- The commonest cause of a $\downarrow$ SAAG is peritoneal carcinomatosis, but the low SAAG is not diagnostic for this condition.

Please see Feldman M., et al. Sleisenger and Fordtran’s Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier, Philadelphia, 2010, Table 91.3, page 1523, for a “Classification of Ascites by Serum-Ascites Albumin Gradient”.

In both cirrhotic and cardiac ascites, SAAG > 1.1

229. Give an approach to distinguish between hepatic and cardiac causes of ascites:

Sample	Cirrhotic	Cardiac
➤ Ascitic fluid		
○ Protein	$\downarrow$	$\uparrow$
➤ Blood		
○ Hematocrit < 32	Yes (in 32%)	No
○ PbnP median concentration (pg/mL)	166	6100

Abbreviation: pbnP, pro-brain-type natriuretic peptide

➤ Pointers on ascites

- $\uparrow$ ascitic fluid amylase (> 2000 U/L, or 5x serum amylase) suggests
 - Acute pancreatitis
 - Intestinal perforation



- If ascitic fluid contains ↑ lymphocytes (not PMNs), suspect
 - Tuberculous peritonitis
 - HCC / hepatic metastases
 - Pancreatitis
 - Chylous ascites
 - Ascitic fluid becomes creamy coloured (chylous) when the concentration of triglyceride in ascites > 200 mg/dL.
 - Chylous ascites occurs with cirrhosis, rupture of the intra-abdominal lymphatics (e.g. malignancy surgery – retroperitoneal, radical pelvic)
 - Dark brown ascites
 - Dark brown (not pink or red) ascitic fluid (bilirubin concentration in ascitic fluid > 6 mg/dL) suggests perforation of
 - Biliary tree
 - Duodenum / jejunum
- What makes ascites fluid cloudy?
- Increased neutrophils, or fat (chylous ascites) makes ascetic fluid cloudy
 - In a patient with chronic renal failure on hemodialysis, look hard for causes of ascites before diagnosing idiopathic (nephrogenous) ascites.

Staff Stumpers !!!!!

- In the context of the patient with ascites, give the meaning of “ovarian hyperstimulation syndrome” (OHS), “Poems syndrome”, and “hemophagocytic syndrome”.
 - OHS
 - Excess stimulation of the ovaries with sex hormones may lead to ascites
 - Poems syndrome
 - Polyneuropathy, organomegaly, endocrinopathy, M component, skin changes → may be associated with ascites
 - Hemophagocytic syndrome
 - Leukemia or lymphoma, associated with ascites



➤ Treatment

- Salt restriction, 2 g/ day
- Diuretics
 - Furosimide blocks active Cl^- reabsorption from the loop of Henle, aldactone blocks active Na^+ reabsorption in the distal renal tubule
 - Too aggressive diuretic therapy may be complicated by renal failure, hepatic encephalopathy, and electrolyte disturbances ($\uparrow\text{Na}^+$, $\uparrow$ or $\downarrow\text{K}^+$)
- LVP (large volume paracentesis)
 - Large volume paracentesis (> 5 L) is safe as long as 6-8 g albumin are given per liter fluid removed
- TIPS
 - Transjugular intrahepatic portosystemic shunt (TIPS) decreases sinusoidal portal pressure, and decreases Na^+ reabsorption in the proximal renal tubules, producing a diuresis
 - TIPS will mobilize ascites in 70% of persons with diuretic-resistant ascites, but there is a 50% risk of the TIPS precipitating hepatic encephalopathy, and the shunt may become stenotic, requiring angiography and dilation of the shunt
 - TIPS should not be performed for ascites mobilization in the patient who already has hepatic encephalopathy, whose MELD score is greater than 20 points

230. Which laboratory value predicts an ascitic patient's likely response to diuretics?

- When a patient has ascites and the SAAG is > 1.1 g/dL, there is likely to be a response to diuretics.

Clinical Pearls

- The cirrhotic patient often will have a systolic blood pressure (SBP) of ~ 70 mm Hg, and as long as there has been
 - No recent further drop in SBP
 - No Azotemia
 - No confusion
- There is no need to stop the once daily dosage of furosemide and aldactone.
- Remember, “....complete remission of ascites should not be a prerequisite for discharge from the hospital” (Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier, Philadelphia, 2010, page 1538).



231. Give 8 examples of **non-diuretic treatments** for ascites.

- Peritoneal carcinomatous from ovarian cancer
 - Surgical debulking
- Tuberculous ascites
 - Appropriate antituberculous therapy
- Chlamydia ascites
 - Tetracycline
- Lupus
 - Glucocorticosteroids
- Nephrogenous ascites
 - Hemodialysis
- Alcoholic cirrhosis
 - Stop drinking alcohol
- NASH
 - Weight loss
 - Treatment of metabolic syndrome
 - Vitamin E (possibly)
- AIH
 - Corticosteroids / immune suppression
- Portal hypertension
 - Low salt / fluid restriction
- HBV
 - Interferon, or oral nucleoside
- HCV
 - Interferon plus ribavirin plus third agent
- Preoperative
 - Change IV from normal saline
- Paracentesis
 - Continue regular paracentesis, including LVP
- TIPS
 - Doppler ultrasound to exclude possible vascular obstruction (eg. Budd-Chiari syndrome)
 - Consider inserting new stent

Abbreviation: LVP, large volume paracentesis

Refractory Ascites

- Definition and diagnostic criteria for refractory ascites in cirrhosis
 - Diuretic-resistant ascites
 - Ascites that is difficult to mobilize, as defined by a failure to lose at least 1.5 kg/week of fluid weight, despite maximal diuretic therapy with spironolactone (400 mg/day) and furosemide (160 mg/day) or an equivalent dose of a distal-acting and loop-acting diuretic respectively.



- Diuretic-intractable ascites
 - Ascites that is difficult to mobilize, as defined above, due to the inability to effectively dose diuretics because of diuretic-induced adverse effects e.g. azotemia, hyponatremia, etc.
- Prerequisites
 - Treatment duration
 - Patients must be on intensive diuretic therapy (spironolactone 400 mg/day and furosemide 160 mg/day) for at least 1 week and on a salt-restricted diet of less than 90 mmol/day
 - Lack of response
 - Mean weight loss of <0.8 kg over 4 days and urinary sodium output less than the sodium intake
 - Early ascites recurrence
 - Reappearance of grade 2 or 3 ascites within 4 weeks of initial mobilization
 - Diuretic-induced complications
 - Diuretic-induced hepatic encephalopathy is the development of encephalopathy in the absence of any other precipitating factor
 - Diuretic-induced renal impairment is an increase of serum creatinine by >100% to a value >2 mg/dl (177 mol/L) in patients with ascites responding to treatment
 - Diuretic-induced hyponatremia is defined as a decrease of serum sodium by >10 mmol/L to a serum sodium of <125 mmol/L
 - Diuretic-induced hypo- or hyperkalemia is defined as a change in serum potassium to <3 mmol/L or >6 mmol/L despite appropriate measures

Printed with permission: European Association for the Study of the Liver. EASL clinical practice guidelines on the management of ascites, spontaneous bacterial peritonitis, and hepatorenal syndrome in cirrhosis. J Hepatol. 2010;53(3):397-417, Table 3.

➤ Definitions

- “.....ascites unresponsive to a sodium-restricted diet [2 gm per day, 88 mEq per day] and high-dose diuretic treatment [e.g. furosemide 160 mg/day and aldosterone 400 mg/day]) (Feldman M., et al. Sleisenger and Fordtran’s Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier, Philadelphia, 2010, page 1538).
- Ascites that is not eliminated even with maximum and optimal diuretic therapy, or



- Ascites that is not eliminated because maximum dosages of diuretics cannot be attained, given the development of diuretic induced complications (renal failure)
- 1 year mortality rate for ascites refractory to medical care ~ 68%

➤ Treatment

232. Give a management strategy for refractory ascites.

- Recommended therapy
- Total paracentesis plus IV albumin (6-8 g of albumin per liter of ascites removed)
 - Note recent recommendation:
 - “Consider albumin infusion [10 g albumin per L ascitic fluid drained] optional after taps of a larger volume [> 5 L] in patients with diuretics-resistant ascites” (Feldman M., et al. Sleisenger and Fordtran’s Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier, Philadelphia, 2010, page 1540)
 - If <5 L of ascites is removed, a synthetic plasma volume expander may be used instead of albumin
 - Continue with salt restriction and diuretic therapy, as tolerated

233. Give the pros and cons of **albumin infusion** being given in conjunction with a therapeutic paracentesis.

- Pros
 - Prevents post-paracentesis $\uparrow$ renin concentration and development of paracentesis-induced circulation dysfunction
 - Con
 - No benefit on survival
 - $\downarrow$ opsonin in ascitic fluid
 - Considerable cost
 - Increasing serum albumin concentration leads to
 - $\uparrow$ breakdown of albumin
 - $\downarrow$ synthesis of albumin
- Alternative therapy
- TIPS for patients who require frequent paracentesis (every 1-2 weeks) and whose CHLD score is <11
 - Peritoneovenous shunt for patients who are not suitable for TIPS or liver transplantation



- When using a coated stent for the treatment of refractory ascites (in patients with low or high MELD, there is
 - No survival advantage
 - ↑ HE (hepatic encephalopathy)
 - Consistent superiority over TIPS

Abbreviations: TIPS, transjugular intrahepatic portosystemic shunt

Printed with permission: Garcia Tsao, et al. *The American Journal of Gastroenterology* 2009; 104:1816.

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- In the context of refractory ascites, give the meaning of “paracentesis-induced circulation dysfunction (PICD).
 - Paracentesis-induced circulatory dysfunction is an ↑ renin concentration in the blood after a paracentesis.
 - Associated with ↓ life expectancy

Malignancy-Associated Ascites

234. Give 4 causes of malignancy-associated ascites.

- Peritoneal carcinoma (1°, 2°)
- Massive liver metastases
- Peritoneal carcinomatosis with massive liver metastases
- Hepatocellular carcinoma (HCC)
- Malignant lymph node obstruction
- Malignant Budd-Chiari syndrome (BCS, from tumour emboli in hepatic veins)

Source: Runyon, Bruce A. *Sleisenger & Fordtran's gastrointestinal and liver disease: Pathophysiology/Diagnosis/Management* 2006: pg. 1946.

235. Give 4 types of tumors which commonly metastasize to the peritoneum.

➤ Adenocarcinoma	○ GI	- Stomach
		- Colon
		- Pancreas
➤ Lymphoma	○ Non-GI	- Ovary
		- Lung
➤ Sarcoma		



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Tumors which commonly metastasize to the peritoneum include adenocarcinomas (stomach, colon, pancreas; ovary, lung) , lymphoma and sarcomas.

- In this context, what is “**pseudomyxoma peritonei**”?
 - Pseudomyxoma peritonei is a metastatic mucinous cyst adenocarcinoma of the appendix or ovary which results in a jelly-like tumor implant on the peritoneum, and may cause malignant ascites.
- Give the features which help to distinguish between peritoneal carcinomatosis (CA) versus tuberculous peritonitis (TB) as causes of high-lymphocyte-count ascites.

	CA	TB
○ Prevalence	+++	+
○ Fever	+	-
○ Ca125 (ovary)	+	+
○ AD	-	+

Abbreviation: AD, adenosine deaminase

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- Give 4 mechanisms by which tumors may cause ascites.
 - Peritoneal carcinomatosis
 - Extraperitoneal carcinomatosis
 - Hepatic 2^o
 - Hepatic 1^o (HCC), 2^o (metastases)
 - Lymph node obstruction
 - Budd-Chiari syndrome ± IVC obstruction

Abbreviation: HCC, hepatocellular cancer; IVC, inferior vena cava

➤ Diagnostic tip

- Cytology of ascitic fluid is ~ 100% sensitive to detect peritoneal carcinomatosis, but the sensitivity to detect 1^o/2^o liver tumor is low.



Spontaneous Bacterial Peritonitis (SBP)

➤ Demography

- In the cirrhotic with ascites admitted to hospital
 - About 1/3 have bacterial peritonitis
 - 2/3 SBP, 1/3 MNB
 - Commonest monomicrobial organisms: E. Coli, Streptococci (pneumococci), Klebsiella
- In the cirrhotic patient who is hospitalized for GI bleeding, 40% develop SBP (that's why treatment of all cirrhotics with GI bleeding and ascites are given prophylactic antibiotics).
- SBP is present in at least 20% of cirrhotics at the time they are admitted to the hospital
- SBP worsens vasodilation, and thereby contributes to early variceal rebleeding and to the development of renal failure (HRS, hepatorenal syndrome)
- Persons at risk of developing SBP include those with a previous episode of SBP, SBP occurring with variceal hemorrhage, or low protein ascites
- Once SBP has occurred, the one year mortality rate is 50-70%
- Early treatment of SBP is associated with a mortality rate (MR) of (only) 5%, with higher MR with creatinine > 350 µmol/L, or if shock has developed.
- Initiation of the beta-blocker nadolol in cirrhotic patients with high risk esophageal varices delays or prevents the first occurrence of ascites seen in patients who had an improvement by 10% or more from baseline HVPG pressure.
- Consider SBP and perform diagnostic paracentesis if:
 - Symptoms/signs (abdominal pain, fever, chills)
 - Patient is in emergency room or admitted
 - Worsening renal function or development of hepatic encephalopathy

➤ Laboratory

- The median colony count of bacteria in the ascitic fluid in SBP is only 1 organism per mL
- When ascitic fluid contains 10⁴ organisms per mL, the gram stain becomes positive.
- Ascitic fluid gram stain may be useful in 2^o BP (bacterial peritonitis [2^o] to intestinal perforation), but not in SBP.



- In neutrocytic ascites, bed-side inoculation of ascitic fluid placed in blood culture bottles demonstrates bacterial growth in ~ 80%
- Ascitic fluid concentration < 2.5 g/dL protein reflects a low opsonin concentration, and a low opsonin concentration increases the risk of SBP (the concentration of opsonin in ascitic fluid is directly related to its total protein concentration).

236. Give the 4 types of spontaneous bacterial peritonitis (SBP).

	>250 neutrophils	Ascitic culture
○ Classical SBP (culture-positive neutrocytic ascites)	+	+
○ Culture-negative neutrocytic ascites (CNNA)	+	-
○ Monomicrobial nonneutrocytic bacterial ascites (MNB; aka bacterascites)	-	+
○ Polymicrobial non-neutrocytic* ascites (aka secondary bacterial peritonitis [2 ^o BP])	-	+

*Usually from needle perforation of the gut, is associated with

- Severe symptoms and signs
- ↓ ascitic fluid glucose (< 50 mg/dl)
- ↑ ascitic fluid LDH
- Polymicrobial anaerobic infection
- Strictly speaking, this is not included in the term “spontaneous” BP

Abbreviations: SBP, spontaneous bacterial peritonitis; TIPS, transjugular intrahepatic portosystemic shunt

➤ False-positive neutrocytes in ascitic fluid

- An ascitic fluid neutrocyte count > 250 mm³ is diagnostic of neutrocytic ascites. Give the condition under which this count may be falsely elevated.
- “during diuretics in patients with cirrhotic ascites, the WBC count can concentrate to more than 1000 cells / mm³ (Feldman M., et al. Sleisenger and Fordtran’s Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier, Philadelphia, 2010, page 1523).



- How to diagnose neutrocytic ascitic fluid in the presence of blood.
 - If there are RBC in the tap (pink colour, RBC > 10,000 / mm³; red, RBC > 20,000 mm³), for each 250 RBCs, subtract 1 PMN in order to achieve a corrected count to diagnosis neutrocytic ascites.
 - Caution: if a blood contaminated tap has sat for some time, or if the leakage of blood into the ascitic fluid occurred at a time in the distance, the PMNs will have disappeared (lysis), and when the correction formula is used, the count may be low or even negative.
- Diagnosing secondary bacterial peritonitis (2° BP)
 - Secondary bacterial peritonitis from bowel perforation is polymicrobial, but unless gene probes are used for rapid diagnosis, a serious time delay will ensure.
 - Measure the ascitic fluid total protein, glucose and LDH; if 2 or 3 of these are abnormal, the patient likely has secondary rather than spontaneous BP excluded perforation rather than diagnosing neutrocytic spontaneous bacterial peritonitis (SBP).
 - Total protein > 1 g/dL
 - Glucose < 50 mg/dL
 - LDH > ULN for serum
 - PMNs contain LDH, so when PMNs increase in SBP, there is ↑ LDH; in secondary BP, there is ↑↑↑ PMNs, so ↑↑↑ LDH (LDH in ascites > serum LDH)

Clinical Pearls

- If you think the patient might have ascites from secondary peritonitis, don't play around with measuring ascitic fluid concentrations of glucose or LDH (lactate dehydrogenase): do diagnostic imaging (such as CT scan) to find the source of the suspected perforation, or laparoscopy to find and biopsy metastatic deposits.

A perforated viscus usually leads to **polymicrobial bacterial infection**.

237. Give the circumstance when a perforated intestinal viscus leads to monomicrobial bacterial peritonitis, rather than expected polymicrobial infection.
- Perforation of the gallbladder is suspected when the ascitic fluid is brownish and its bilirubin concentration is > 6 mg/dL. This secondary bacterial peritonitis may be monomicrobial.



With a perforated viscus bacterial peritonitis and ascites there is usually a high ascitic fluid amylase concentration,

238. Give the exception.

- With ascites associated with rupture of the gallbladder, the ascitic fluid amylase concentration will be normal.

➤ Clinical

- In the cirrhotic patient with ascites, suspect SBP when there is
 - Abdominal pain
 - Abdominal tenderness
 - Rebound tenderness
 - Unexplained fever
 - Change in mental status
 - Clinical deterioration
 - On hospitalization (all ascitic admitted to hospital should have a peritoneal tap to exclude SBP)

➤ Treatment

• **SBP and CNNA (Culture-negative neutrocytic ascites)**

239. Give the indications for treatment of spontaneous bacterial peritonitis(SBP), including recurrent SBP.

- Indications
 - Prior history of SBP
 - GI bleeding without ascites
 - GI bleeding, with ascites (even without SBP [PMN > 250; WBC > 500]), acute treatment)
 - Low ascitic fluid protein concentration
- Culture negative neutrocytic ascites (CNNA) Rx = spontaneous bacterial peritonitis

Please see: Swan MG. Chapter 58. In: Therapeutic Choices. Grey J, Ed. 6th Edition, Canadian Pharmacists Association: Ottawa, ON, 2011, Table 2: Spontaneous Bacterial Peritonitis, page 774.



- General management
 - Avoid therapeutic paracentesis during active infection
 - Intravenous albumin (1.5 g/kg of body weight for 3 days, then 1 g/kg) if BUN >30mg/dl, creatinine >1mg/dl, bilirubin >4 mg/dl, and repeat at day 3 if renal dysfunction persists
 - Avoid aminoglycosides
- Specific management
 - Cefotaxime (2 g IV q 6-12 h) (98% of organisms are susceptible), or
 - Ceftriaxone (2g IV q 24 h) or
 - Ampicillin/clavulanate (2g/1g i.v q 6 h)
 - Continue therapy for 7 days
 - Repeat diagnostic paracentesis at day 2
 - If ascites PMN count decreases by at least 25% at day 2, intravenous therapy can be switched to oral therapy (quinolone such as ciprofloxacin or levofloxacin 250 mg po bid) to complete 7 days of therapy
 - Oral norfloxacin 400 mg p.o q.d (preferred) or
 - Oral ciprofloxacin 250-500 mg q.d* or
 - Oral levofloxacin 250 mg q.d*
- Alternative therapy
 - TMP-SMX 1 double strength tablet p.o q.d
 - (Patients who develop quinolone resistant organisms may also have resistance to TMP-SMX)
- Duration
 - Prophylaxis should be continued until the disappearance of ascites or until liver transplantation
- IV albumin

* Empirical doses

Abbreviations: BUN, blood urea nitrogen; PMN, Polymorphonuclear (neutrophil) cell count; PO, orally; QD, once daily; RBC, Red blood cell count; SBP, spontaneous bacterial peritonitis; TMP-SMX, trimethoprim sulfamethoxazole

Printed with permission: Garcia-Tsao G, et al. Management and treatment of patients with cirrhosis and portal hypertension. *The American Journal of Gastroenterology*: page 1811.; and adapted from: Rimola A, et al. *J Hepatol* 2000;32(1):142-53.



240. Give the rational for using IV albumin (1.5 g / kg BW at diagnosis, then 1 g / kg on day 3) together with an empirical antibiotic when treating SBP)

- SBP is associated with type I HRS in about 1/3 of patients, and this is associated with an ↑ risk of mortality

	Cefotaxime alone	Cefotaxime plus albumin
HRS type 1	30%	10%
Mortality	29%	10%

- This positive outcome was obtained in patients with jaundice (serum bilirubin $\geq 68 \mu\text{mol / L}$) and renal failure (serum creatinine $\geq 88 \mu\text{mol / L}$).
- Until more information is available, we recommend who develop SBP should be treated with broad spectrum antibiotics and intravenous albumin” (EASL Clinical Practice Guidelines, J. Hepatol 2010; 53: 399-417).

- **MNB (monomicrobial non-neutrocytic bacterial ascites)**

- Repeat DP, and if
 - Neutrophils $> 250 / \text{mm}^3$, treat as for classical SB or CNNA
 - Neutrophils $< 250 / \text{mm}^3$, follow patient
- “Paracentesis should be repeated after 48 hours of treatment if the [clinical] course is atypical” (Feldman M., et al. Sleisenger and Fordtran’s Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier, Philadelphia, 2010, page 1534).
- “....spontaneous ascitic fluid infection is a good marker of end-stage liver disease” [ESLD] and has been proposed as an indication for liver transplantation in a patient who is otherwise a candidate” (Feldman M., et al. Sleisenger and Fordtran’s Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier, Philadelphia, 2010, page 1534).

- **Secondary polymicrobial bacterascites**

- Cefotaxime plus metronidazole
- In 80% of patients treated with cefotaxime have ↓ PMN in ascitic fluid within 48 hours



SO YOU WANT TO BE A GASTROENTEROLOGIST!

The most common causative organisms of SBP are gram-negative aerobes such as E.Coli, and these should be sensitive to first line use of quinolones such as ciprofloxacin.

- Give circumstances when you would **avoid quinolones** for an empiric diagnosis of SBP, and instead start with
 - Cephataxime, 4 g / day IV for 5 days, or
 - Amoxicillin / clavulanic acid IV, then po
 - Previously taking quinolones for prophylaxis of SBP
 - High prevalence of quinolone-resistant bacterial in practice area
 - SBP developing in hospital (nosocomial SBP)

➤ Prophylaxis

- Indications
 - Primary prevention of SBP with norfloxacin or ciprofloxacin has survival advantage and is recommended for
 - Previous SBP
 - Variceal bleeding
 - Ascitic fluid protein < 1g/dL
- First line
 - Oral ciprofloxacin 250-500 mg qd* or
 - Oral levofloxacin 250 mg q.d*
- Alternative therapy
 - TMP-SMX 1 double strength tablet po qd
 - Patients who develop quinolone resistant organisms may also have resistance to TMP-SMX
- Duration
 - Prophylaxis should be continued until the disappearance of ascites or until liver transplantation

Abbreviations: po: Orally; SBP: Spontaneous bacterial peritonitis; TMP-SMX: Trimethoprim sulfamethoxazole, q.d: Once daily

*Empirical doses

Source: Garcia Tsao et al. *The American Journal of Gastroenterology* 2009; 104:1806-1829.



SO YOU WANT TO BE A GASTROENTEROLOGIST!

The most common causative organisms of SBP are gram-negative aerobes (GNA) such as E.Coli, and these should be sensitive to first line use of quinolones such as ciprofloxacin.

- Give the reason why selective intestinal decontamination with norfloxacin (400 mg / 12 h po for 7 days) is no longer recommended for the prophylaxis of SBP in patients with cirrhosis who develop bleeding from the GI tract.
 - This is a kind of a trick question
 - Prophylaxis is needed of course, but there is
 - ↑ incidence of quinolone resistant GNA
 - ↑ incidence of quinolone resistant gram-negative bacterial (GNB)
 - ↑ incidence of gram-positive bacteria in SBP (likely related to endoscopic procedures)
 - Ceftriaxone is more effective than norfloxacin in prevention of SBP in the cirrhotic with GI bleeding, especially if they have 2 or more of the following
 - Ascites
 - Severe malnutrition
 - Hepatic encephalopathy
 - Bilirubin > 3 mg / dL

Clinical Alert

- Once SBP has developed, the patient's prognosis is poor, and they should be referred for consideration of liver transplantation
 - While awaiting LT, give prophylactic antibiotics to prevent recurrent SBP:
 - Cotrimazole (800 mg sulfamethoxazole and 160 mg trimethoprim po od.
 - If the total protein concentration of the ascitic fluid is < 15 g/L in the patient with severe liver disease, norfloxacin 400 mg/day po ↓ risk of SBP and death.



Spontaneous Bacterial Hydrothorax (SBH)

- SBH may develop in cirrhotic pleural effusion (hydrothorax) with / without ascites.
- Perform DP (diagnostic paracentesis) of hydrothorax
- If hydrothorax fluid
 - $> 250 / \text{mm}^3$ neutrophils, plus positive culture → treat $> 500 / \text{mm}^3$ but negative culture (in the absence of pneumonia) →
- Why ascites matters
 - Once ascites develops in the patient with cirrhosis, the 2 year mortality rate is 50%
 - Ascites may become complicated by SBP (spontaneous bacterial peritonitis), which may cause or worsen decompensation.

Clinical tips

- Cirrhotic ascites plus pleural infusion(s)
 - L. – side
 - Suspect TB
 - R. – side
 - Likely “sympathetic” to ascites
- Cirrhotic ascites plus hernia of abdominal wall
 - Elective surgical repair after drainage of ascites to ↓ complications of strangulation, or perforation.
- Recurrence of abdominal hernia when preoperative drainage of ascites is
 - Performed, 14%
 - Not performed, 73%

Hepatorenal Syndrome (HRS)

➤ Definition

- A functional and potentially reversible form of prerenal azotemia with a cascade of events associated with intense dilation of the splanchnic arterial vasodilation in the setting of cirrhosis or acute liver injury and resulting in profound renal arterial vasoconstriction and progressive renal failure” (Feldman M., et al. Sleisenger and Fordtran’s Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier 2010, page 1546).
- Functional renal failure in the person with cirrhosis and ascites



➤ Other important definitions

- Most cirrhotics with renal dysfunction do not have HRS (only 15-20% have HRS)
- Hyponatremia may precede the development of HRS
- Type I HRS is associated with intense vasoconstriction, which may cause the HRS to progress to ATN
- Parenchymal renal disease as defined by
 - Proteinuria <0.5 g/day
 - No microhematuria (<50 red cells/high powered field), and
 - Normal renal ultrasonography
- Absence of hypovolemia as defined by no sustained improvement of renal function (creatinine decreasing to <133 mol/L) following at least 2 days of diuretic withdrawal (if on diuretics), and
- If renal dysfunction persists despite stopping diuretics and correction of hypovolemia, diagnose HRS
- No or insufficient improvement in serum creatinine level (remains > 1.5 mg/dL) 48 hr after diuretic withdrawal and adequate volume expansion with intravenous albumin
- Consider the possibility of HRS in any patient with cirrhosis and ascites, as well as a serum creatinine level of >1.5 mg/dl (133 mmol/L)

➤ Demography

- HRS occurs in cirrhotics with ascites, ~8% per year
 - Admitted for SBP or other infections, 30%
 - Needing large volume paracentesis, 10%
- Severe alcoholic hepatitis, HRS develops in ~25%
- Reduces 3 year survival from liver transplant to 60% versus ~75% when there is no HRS

Printed with permission: EASL clinical practice guidelines on the management of ascites, spontaneous bacterial peritonitis, and hepatorenal syndrome in cirrhosis. *J Hepatol.* 2010;53(3):397-417, Table 8.



➤ Types

241. Give 5 features to distinguish between Type 1 and Type 2 HRS.

Characteristics	Type 1	Type 2
○ Progression	Fast (< 2 wks)	Slow
○ Serum creatinine	> 2.5 mg/dL	< 2.5 mg/dL
○ Triggers	Bacterial infection (SBP) GI bleeding Surgery	Diuretic resistant ascites
○ ↓ Sys BP	↓↓↓ ALF	↓
○ Adrenal insufficiency with sepsis	Common (80%)	Uncommon
○ Cross-over	No, but may progress to ATN	Yes (HRS 2 → HRS 1)

Abbreviations: ALF, acute liver failure; ATN, acute tubular necrosis; MAP, mean arterial pressure; SBP, spontaneous bacterial peritonitis; SBP, systolic blood pressure

Please see: Swan MG. Chapter 58. In: Therapeutic Choices. Grey J, Ed. 6th Edition, Canadian Pharmacists Association: Ottawa, ON, 2011, Table 1: Ascites, pg 773.

“Being happy doesn’t mean that everything is perfect. It means that you’ve decided to look beyond the imperfections.”

Unknown

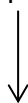


➤ Pathophysiology

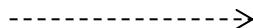
242. Give the pathophysiology of renal arterial vasoconstriction.

➤ When there is no cirrhosis

- Fluid loss
 - Diarrhea
 - GI bleeding
 - Diuresis
 - Serial large volume paracentesis
 - SBP
 - Sepsis



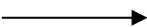
○ CBV



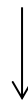
- Renal
 - ↑ RAAS
 - ↑ plasma ADH
 - ↑ Na⁺ / H₂O retention

○ Drugs

- NSAIDs
- ARBs
- ACEIs
- Diuretics
- Lactulose
- Nephrotoxic antibiotics
- Cyclosporine
- Tacrolimus



Splanchnic and peripheral vasodilation



EBCV

↑ plasma ADH

- ↓ clearance
- ↑ activity
- ↑ ADH regulated water channel

↑ production / action

- Endothelins
- Kalikreins
- F2-isoprostanes

- Lower setpoint for renal response to ↓ SBP and cardiac output
- ↑ blood norepinephrine and ↑ plasma renin activity



○ CVS

- ↓ systemic BP
- ↑ HR / ↑ cardiac output
- ↑ SNS activity
- Hyperdynamic circulation



○ Renal arterial vasoconstriction



- ↓ GFR
- ↓ renal perfusion
- ↓ HRS (inappropriate and intense vasoconstriction)

➤ When there is cirrhosis

Infection
Inflammation
Vasoactive mediators



- Vasodilates

- NO
- CO
- Glucagon
- Prostacyclin
- Adenomedullin
- Endogenous opiates



Ascites

SBP

↓ Na⁺



Renal



- Cirrhotic cardiomyopathy
- Hyperdynamic circulation → LV hypertrophy → diastolic dysfunction → ↓ B-adrenergic signaling
- ↓ cardio-myocyte function
 - ↑ QTC



Abbreviations: ACEIs, angiotensin-converting enzyme inhibitors; ADH, antidiuretic hormone; ARBs, angiotensin receptor blockers; BP, blood pressure; CBV, circulating blood volume; CC, cirrhotic cardiomyopathy; CO, carbon monoxide; ECBV, effective circulating blood volume; GFR, glomerular filtration rate; NO, nitric oxide; RAAS, renin-angiotensin-aldosterone system; SBP, systemic blood pressure

➤ Diagnosis

243. Give the major and minor criteria for the diagnosis of the hepatorenal syndrome, and distinguish this from acute tubular necrosis (ATN).

- Major criteria

- Presence of cirrhosis
 - Renal failure (creatinine >1.5mg/dl); if no previous renal impairment, or a serum a ↑ by 50% over baseline
- Lack of improvement in serum creatinine after ≥48 hrs of diuretic withdrawal and volume expansion with 1.5 L of normal saline
 - Sepsis
 - Volume depletion
 - Use of vasodilators
- Absence of:
 - Shock
 - Use of nephrotoxic drugs (eg: aminoglycosides)
 - Parenchymal renal disease (urine protein > 500 mg/day, granular or red cell casts, hematuria, urinary obstruction by sonography)

“Rewarding anticipation activates a reward network: that is the success of the not-so-common random acts of kindness.”

Grandad



- Minor criteria (suggests HRS, or prerenal failure)

Parameter	Osmolarity mOsm/Kg	Urine (Na) mmol/l	Sediment	Protein mg/day
Prerenal				
○ Hypovolemia	>500	<20	Normal	<500
○ Hepatorenal	>500	<10	Normal	<500
• Renal				
○ Acute tubular	<350	>40	Granular casts	500-1500
○ Interstitial	<350	>40	WBC eosinophils	500-1500

Adapted from: Fitz GJ. *Sleisenger & Fordtran's Gastrointestinal and Liver Disease: Pathophysiology/Diagnosis/Management* 2006: pg. 1979.

244. Give the laboratory variables used differentiate between prerenal azotemia (PRA), hepatorenal syndrome (HRS) and acute renal failure (ARF) diagnosis for HRS.

Variable	PRA	HRS	ARF
○ Urinary sodium concentration, mEq/L	<10	<10	>30
○ Urine to plasma creatinine ratio	>30:1	>30:1	<20:1
○ Urine osmolality	At least 100m Osm >plasma osmolality	At least 100m Osm > plasma osmolality	Equal to plasma osmolality
○ Urine sediment	Normal	Normal	Casts, debris

Abbreviation: Osm_p, osmolality of plasma; Osm_u, osmolality of urine

➤ Treatment

- Consider HRS in a patient with cirrhosis and ascites and
- Creatinine level of >1.5 mg/dl
 - NSAIDs, diuretics, other nephrotoxic drugs



- Diuretics should be discontinued, and intravascular volume expanded with IV albumin, 1 g/kg per day, up to a maximum of 100 gm albumin per day
- SBP may precipitate type I HRS, and this risk can be reduced by using albumin with the initial antibiotic therapy for SBP
- Vasopressin vasoconstrictor therapy
 - Terlipressin 1 mg / 4-6 h intravenous bolus, plus IV albumin, to ↓ serum creatinine
 - < 133 $\mu\text{mol} / \text{L}$ (1.5 mg /dL)
 - > 25% over 3 days (partial response)
 - Increase terlipressin to 2 mg / 4 hr if there is not a partial or complete response over 3 days treatment.
 - If serum creatinine does not fall or normalize within 14 days of terlipressin, stop therapy.
 - If HRS recurs after terlipressin is stopped, repeat course of Rx.
 - There is less data for the efficacy of norepinephrine or midodrine, plus octreotide plus albumin.
- Alternative (bridging therapy)

Vasoconstrictors plus albumin for ≥ 7 days	Octreotide	100-200 mcg SC t.i.d	Goal : $\uparrow$ MAP by 15 mmHg
	PLUS		
	Midodrine, or	5-15 mg p.o t.i.d	
	Terlipressin ^a	0.5 – 2.0 mg IV every 4-6 h 50-100 g IV q.d	

- 35-50% of type I HRS responds to vasoconstrictors (midodrine, terlipressin, norepinephrine)
- Renal dialysis (“support”) for type I HRS may be a necessary bridge to liver transplantation
- Liver transplant (priority dependent on MELD score)
 - Liver transplantation is the definitive treatment for type I HRS
 - If patient is not on transplant list, packet should be prepared urgently
 - If patient is on transplant list, MELD score should be updated daily and communicated to transplant center

➤ Prevention of HRS



- Severe alcoholic hepatitis – pentoxifylline
- Severe cirrhosis – Norfloxacin ↓ risk of HRS
- SBP
 - Antibiotics + albumin
- Drugs avoid
 - NSAIDs
 - ACEI
 - Antibiotics
- Combined kidney-liver transplantation
 - HRS, non-response to vasopressors, prolonged renal support > 12 weeks

Abbreviations: I.V., intravenous; HRS, hepatorenal syndrome; MAP, mean arterial pressure; MELD, model for end stage liver disease; t.i.d thrice a day; s.c subcutaneously

Adapted from: Garcia Tsao et al. *The American Journal of Gastroenterology* 2009; 104:1802-1829.

- TIPS
 - Role unproven: “TIPS may be considered in appropriately selected patients who meet criteria similar to those of published randomized trials” (Runyon BA. *Hepatology* 2009; 49: 2087-2107, Table 4).

Abbreviations: HRS, Hepatorenal syndrome; PO, Orally; QD, once daily; SC, subcutaneously; TID, thrice a day.

Printed with permission: Garcia-Tsao, et al. *The American Journal of Gastroenterology* 2009;104: 818.

“Success is liking yourself, liking what you do, and liking how you do it.”

Maya Angelou

Hepatic Encephalopathy (HE; aka PSE, portosystemic encephalopathy)



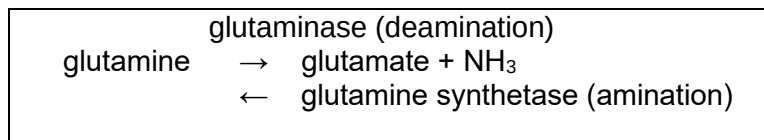
➤ Demography

- HE occurs in $\frac{1}{2}$ to $\frac{3}{4}$ of cirrhotics
- Effects of HE non-transplanted mortality rate > 50% in 3 year

➤ Pathophysiology

245. Outline the contribution of the small and large intestine, liver, skeletal muscle, kidney and brain in patients with liver failure and HE.

- Small bowel and large intestine
 - Dietary amino acids and urease-positive bacteria → glutamine



- Activity of gut glutaminase increased in liver disease
- Uptake of glutamine
- Liver
 - Portosystemic shunting, by-passing portovenous system with less hepatic detoxification of ammonia via the urea cycle
 - $\text{NH}_3 \rightarrow$ urea, periportal hepatocytes → glutamine, perivenous hepatocytes
 - In presence of hyponatremia, myoinositol falls, with less compensation for $\uparrow$ intracellular glutamine
- Skeletal muscle
 - Normally responsible for uptake of 50% of NH_3
 - In cirrhosis, atrophy of skeletal muscles → $\downarrow$ muscle synthesis of glutamine
- Kidney
 - $\uparrow$ NH_3 production in presence of hypokalemia
- Brain



- NH_3 and glutamate are normally converted and detoxified to glutamine by glutamine synthetase in astrocytes
- In cirrhosis
 - $\uparrow$ brain blood flow
 - $\uparrow$ blood brain barrier permeability $\rightarrow \uparrow$ brain NH_3 and glutamate $\rightarrow$ astrocyte swelling
- In presence of hypokalemia and metabolic alkalosis, $\text{NH}_4 \rightarrow \text{NH}_3$, which crosses BBB
- Plasma $\text{NH}_3 > 150 \mu\text{mol}$ is associated with brain herniation
- Abnormal form and function of astrocytes, with reduced glutamine synthetase and peripheral type benzodiazepine receptors (PTBR)
 - $\uparrow$ mitochondrial permeability $\rightarrow \uparrow$ astrocyte swelling $\rightarrow \uparrow$ brain edema
- $\uparrow \text{NH}_3$ activates N-methyl-D-aspartate-nitric oxide-C-guanylate cyclase (NMDA-NO-C6MP) signal transduction pathway $\rightarrow$ impairment of
 - Memory
 - Learning
 - Sleep

Neurotransmitter system	Findings in HE
○ $\uparrow$ GABA, $\uparrow$ serotonin	-
○ $\downarrow$ glutamine receptors	-
○ $\downarrow$ dopamine / noradrenaline	
○ Glutamate (neuro-excitation)	- $\downarrow$ receptors $\rightarrow \downarrow$ uptake of glutamate
	- $\downarrow$ glutamatergic neurotransmitter function
○ GABA/BZ (neuro-inhibition)	- $\uparrow$ endogenous BZs
○ Dopamine/Noradrenaline (motor/cognitive)	- $\downarrow$ false neurotransmitters
○ Serotonin (arousal)	- $\uparrow$ serotonin turnover, synaptic defect

Abbreviations: BZ, benzodiazepine; GABA- γ -aminobutyric acid



- Brain
 - ↑ BB permeability → ↑ NH₃ uptake
 - ↑ NH₃ taken uptake into
 - Cerebellum
 - Basal ganglia
 - ↑ brain edema
 - ↑ swelling of astrocytes - ↑ neurosteroids → ↑ activity of GABA-benzodiazepine system
 - ↑ benzodiazepine system
 - ↑ production of glutamine by astrocytes

➤ Pathology

SO YOU WANT TO BE A HEPATOLOGIST!

- Give the pathological changes in the brain of persons dying from hepatic encephalopathy (HE).
 - Capillaries
 - Vacuolization of basement membranes (↑ permeability of blood-brain barrier)
 - Edema
 - Brain
 - Endothelial cells
 - Astroglial cell
 - Herniation
 - Brainstem

➤ Clinical

246. Give a grading of the mental state of persons with HE.

Stage 0	- No clinical findings, but abnormal psychometric tests may progress to higher stages of HE
Stage 1	- Minor changes in ▪ Affect ▪ Sleep ▪ Concentration - Trivial lack of awareness - Euphoria or anxiety - Shortened attention span - Impaired performance of addition; sleep-wake disorder; tremor



Stage 2	- Dowiness - Disorientation - Confusion - Lethargy or apathy - Minimal disorientation of time or place - Subtle personality changes - Inappropriate behavior - Impaired performance of subtraction
Stage 3	- Somnolence - Incoherence - Somnolence to semi-stupor, but responsive to verbal stimuli - Confusion - Gross disorientation
Stage 4	- Coma (unresponsiveness to verbal or noxious stimuli), with ▪ Minimal response (4a) ▪ No response (4b)

Adapted from: Fitz GJ. *Sleisenger & Fordtran's Gastrointestinal and Liver Disease: Pathophysiology/Diagnosis/Management* 2006: pg. 1966.; and 2010, pg. 1545.

Patients with stage 0 to 2 HE and who can co-operate with the physical examination will have tremor and asterixis. Patients with stage 3 or 4 may not be able to cooperate for the clinical testing for these signs.

247. Give the 3 upper motor neuron signs in stage 3 or 4 HE which can be demonstrated without the patient's co-operation.
- Hyperreflexia
 - Clonus
 - Hyperrigidity
 - Positive Babinski sign



Clinical Tips when Assessing Risk of HE

“The absence of papilledema on fundoscopy and of typical features of cerebral edema on computer tomography (CT) of the head do not preclude the presence of cerebral edema complicating worsening encephalopathy” (Feldman M., et al. Sleisenger and Fordtran’s Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier 2010, page 1601).

➤ Laboratory

248. The finding of an elevated serum ammonia concentration is not specific for the diagnosis of hepatic encephalopathy. Give 15 causes of hyperammonemia

- Liver/GI tract
 - Acute liver failure
 - Cirrhosis
 - Gastrointestinal bleeding
- Renal
 - Chronic kidney disease
- Inborn errors of metabolism
 - Proline metabolism disorders
 - Urea cycle disorders (e.g carbamyl phosphate synthetase I deficiency, ornithine transcarbamylase deficiency, argininosuccinate lyase deficiency, *N*-acetyl glutamate synthetase deficiency)
- Medications
 - Alcohol
 - Diuretics (e.g. acetazolamide)
 - Narcotics
 - Valproic acid
- Muscle exertion and ischemia



- Blood sampling
 - Tourniquet use
 - High body temperature
 - High protein diet
- Diet
- Cigarette smoking

Adapted from: *Sleisenger and Fordtran's Gastrointestinal and Liver Disease: Pathophysiology/ Diagnosis/ Management*. Ninth edition, 2010, Table 92-1

➤ Diagnosis

- Exclude other causes of metabolic encephalopathy
- Exclude possible precipitating factors of HE
- Clinical examination
- Altered neuropsychiatric testing
 - Number connection tests (Trail making)
 - Visuomotor skills
 - Mental tracking and concentration
 - Digit symbol test
 - Block design test
 - Standardized test battery, the psychometric HE score (PHES)
 - Digit span test (Weschler adult intelligence scale – passive auditory, working attention)
 - Critical flicker frequency (correlates with PHES [Psychometric hepatic encephalopathy score])
 - Quality of life measures: SE-36, chronic liver disease questionnaire (CLDQ)
- Scoring systems
 - PSET (portosystemic encephalopathy syndrome test)
 - Psychometric tests



- Blood concentrations of NH_3
 - Arterial or venous NH_3 concentrations are neither sensitive nor specific
 - please see Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier, Philadelphia, 2010, Table 92.1, for the Differential Diagnosis of Hyperammonemia.
 - Arterial hyperammonemia in 90% of HE
 - Arterial $\text{NH}_3 \geq 200$ mg/L predict brain edema and herniation of the brain stem
 - MRI based techniques
- EEG abnormalities
 - Bilateral slow wave activity
 - Neither sensitive nor specific

Clinical caution:

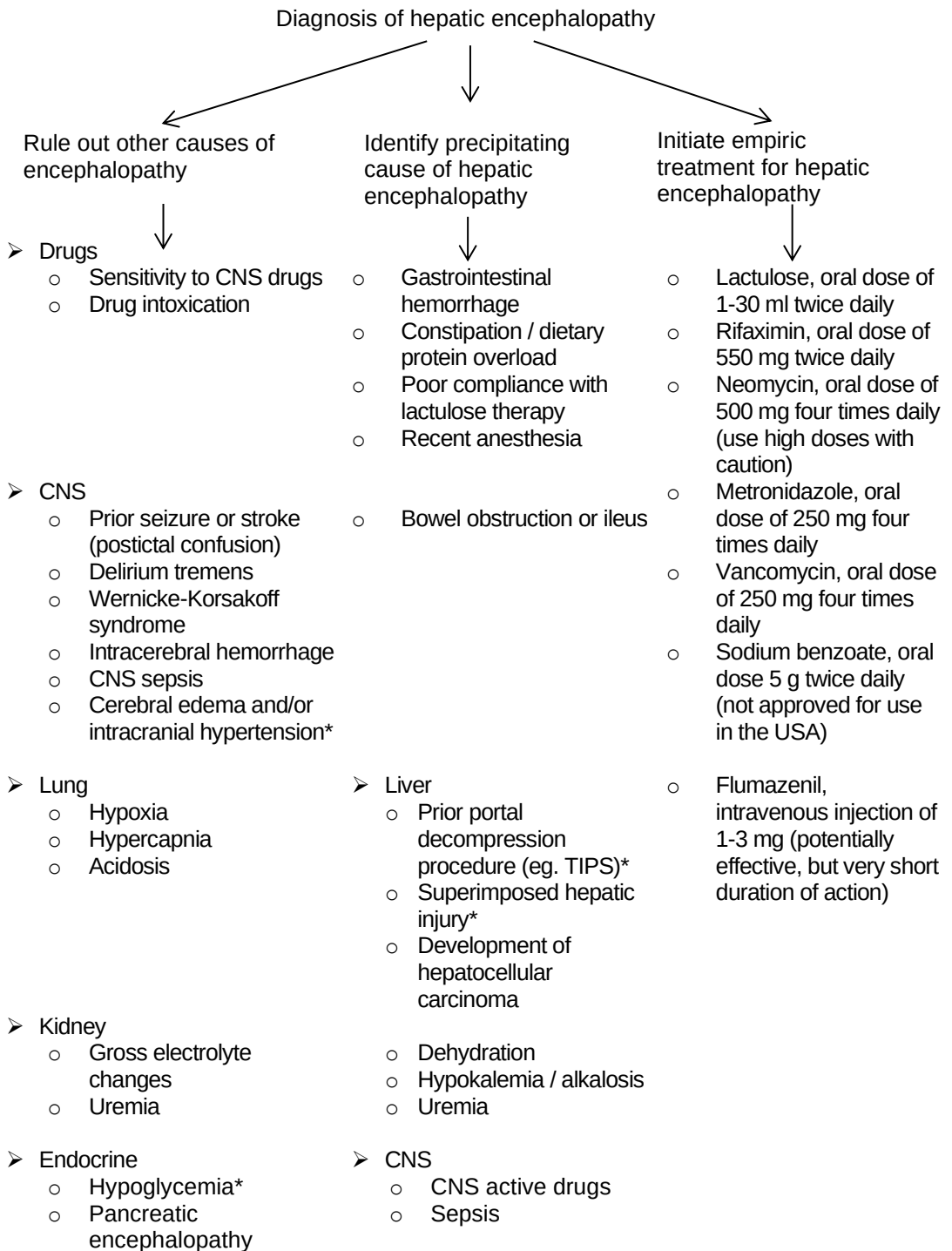
- Vitamin E deficiency is common in patients with cirrhosis (cholestasis $\rightarrow$ $\downarrow$ absorption of fat soluble vitamins $\rightarrow$ vitamin E deficiency)
- The neurological signs of vitamin E deficiency are similar to those of HE (hepatic encephalopathy).
- Don't confuse the two; when in doubt, give vitamin E (tocopherol 1000 IU per day) to the patient with HE.

"We make a living by what we get, we make a life
by what we give."

Winston Churchill



➤ Treatment

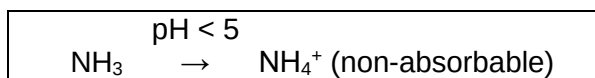


Abbreviation: AB, acid base

*Predominantly observed in patients with acute liver failure



- Treat precipitants
 - Infections eg. SBP, aspirationRTI
 - Increased ammonia production
 - Excessive protein intake
 - Constipation
 - GI bleed (20%)
 - Azotemia (30%)
 - Hypokalemia
 - Increased protein catabolism - surgery, diuretics, arterial hypotension/hypovolemia,
 - Malnutrition
 - Skeletal muscle wasting (less muscle metabolism of NH_3)
 - Treat zinc deficiency
 - Increased diffusion across BBB (alkalosis)
 - Synergistic effects of cytokines – infection (SBP) (10%)
 - Altered brain function – sedative drugs, psychotropics, analgesics, benzodiazepines; hyponatremia; astrocyte swelling
 - Dehydration – fluid restriction, diuretics, excessive paracentesis, vomiting, diarrhea (mechanism unknown)
 - Hypoxia, anemia, fever, sepsis
 - Metabolic:- K^+ ↓ (50%), hyperglycemia, alkalosis; ↓hypoxemia, thyroid, dehydration
 - Drugs (30%) - benzodiazapines, analgesics, interferon, alcohol, NSAIDs, acetaminophen
 - Surgery
 - Shunting, anesthetic, TIPS
 - Liver decompensation
 - HCC, PVT
- Lactulose (beta-galactosidofructose), lacidol beta-galactosidosorbitol (traps NH_3)
 - Enters colon, broken down by colonic bacteria to lactic acid and acetic acid, with acidification of stool $\text{pH} < 5$



- Lactulose enemas (300 mL in 1L of water) in patients who are unable to take lactulose po
- Lactulose 30 mL p.o every 1-2 h until bowel evacuation, then adjust to a dosage that will result in 2-3 formed bowel movements per day (usually 15-30 mL po bid)
- Lactulose can be discontinued once the precipitating factor has resolved
- Hyperosmolar purgation (including lactulose)
 - ↑ stool volume
 - ↑ loss of nitrogen compounds
- Acarbose
 - α-glucosidic inhibitor → ↓ glucose absorption → ↑ SAC charolytic bacteria and ↓ proteolytic urea producing luminal microbiotica → ↓ NH₃
- Antibiotics (pre-, pro- and synbiotics)
 - ↑ lactobacillus spp., ↓ urease-containing bacteria → ↓ NH₃ production
 - ↑ bacterial NH₃ utilization
 - ↓ pro-inflammatory response
 - ↓ gut permeability
 - ↓ bacterial translocation
- L-ornithine-L-aspartate (LOLA)
 - Activate the urea cycle → ↑ NH₃ clearance
 - Improves grade 3 or 4 HE in ~ 25% of patients
- Neurotransmitters: flumazenil (a competitive GABA-benzodiazepine receptor antagonist) or bromocriptine
- Nutrition
 - Treat malnutrition, including EN (enteral nutrition), and TPN (total parental nutrition)
 - Treat associated zinc deficiency
 - Branched chain amino acids
 - Short term (<72h) protein restriction may be considered in severe HE, but is not used for mild to moderate HE



- No long term protein restriction
- Intracranial pressure (ICP) monitoring
 - Transcranial Doppler
 - Jugular venous oximetry
 - 45° elevation of head of bed
 - Moderate hypothermia to
 - ↓ ICP and cerebral blood flow (CBF)
 - ↓ arterial NH_3
 - ↓ cerebral NH_3 uptake
 - IV mannitol
 - ↓ ICP
 - Hyperventilation
 - Vasoconstriction → ↓ CBF
- Manage circulatory effects
 - Fluid management, consider central venous pressure (CVP) monitoring
 - Manage lactic acidosis and sepsis
 - Perform short synacthen test, and give GCS if adrenal insufficiency is present
 - Inotropes: terlipressin (a vasopressin analog) or norepinephrine
 - Albumin
- Extracorporeal liver assist devices (ELADs)
 - MARS (molecular absorbent recirculating system): providing counter-current hemodialysis against albumin and bicarbonate circuits
 - SPAD (single-pass albumin dialysis): counter-current albumin dialysis against high blood flow in a fibre hemodin filter, and continuous veno-venous hemofiltration
 - Prometheus R system, direct albumin adsorption through a specific polysulfur filter
 - Enteral feeding/TPN
- Orthoptic liver transplantation
 - Removes shunted (non-detoxified blood)
 - ↓ production of potentially toxic SCFA (propionate, butyrate, valerate)



Adapted from: Fitz GJ. *Sleisenger & Fordtran's Gastrointestinal and Liver Disease: Pathophysiology/Diagnosis/Management* 2006 pg. 1971-1972.

- Note: osmotic agents (e.g. lactulose) and antibiotics (metronidazole, neomycin, rifaximin) helps symptoms, but do not change in mortality rate
- Sedation (e.g. for EGD and EVL)
 - Propofol safe in cirrhosis with no Δ cognition
 - Midazolam or fentanyl worsens HE
 - NCT (number connecting time), i.e. $\uparrow$ severity of HE score
 - $\uparrow$ agitation
 - Titrate sedation to point where patient's speech is slurred.

Minimal Hepatic Encephalopathy (MHE)

249. Give 4 reasons to treat MHE.

- $\uparrow$ cognitive function
- $\uparrow$ driving performance
- $\uparrow$ performance in workplace
- $\uparrow$ quality of life
- $\uparrow$ sleep
- $\uparrow$ survival
- $\downarrow$ development of overt clinically evident HE

Adapted from: Ortiz M, et al. *J Hepatol* 2005;42 Suppl(1):S45-53.

“We need to move forward our decisions:
we must operationalize.”
Grandad



250. Give 5 management options for MHE.

- Reverse any precipitants (eg. drugs)
- Cathartics: Lactulose
- Antibiotics: Flagyl, vanesmycin, ampicillin, rifamycin
- Probiotics
- High calorie, high protein diet

Adapted from: Holstege A, et al. *Best Practice & Research Clinical Gastroenterology* 2007; 21(3): pg. 541.

➤ Prognosis

251. Give the survival rate and etiological factors for the 3 types of hepatic encephalopathy (acute liver failure, cirrhosis with precipitant, and chronic HE).

Type of HE	Approximate Survival	Etiological factors
○ Acute liver failure	~ 20%	- Viral hepatitis - Alcoholic hepatitis - Drug reactions and overdose
○ Cirrhosis w/precipitant	~ 80%	- Drugs/ Toxins ▪ Diuretics ▪ Alcoholic excess ▪ Sedatives - Infection ▪ Any type, including SBP - Volume loss ▪ Hemorrhage ▪ Paracentesis ▪ Diarrhea/vomiting - Surgery - Constipation
○ Chronic HE	~100%	- Portal-systemic shunting - ↑ Dietary protein intake - Intestinal bacteria



SO YOU WANT TO BE A HEPATOLOGIST!

A patient with cirrhosis develops HE (hepatic encephalopathy) is treated with antibiotics, and their MELD score rises.

- Give the explanation for this deterioration in HE with antibiotics.
 - Antibiotic for HE reduce the intestinal microbiota
 - This ↓ microbiota → ↓ bacterial synthesis of vitamin K
 - With ↓ bacterial vitamin K available for absorption and production of coagulation factors (II, VII, IX, X, protein C), the INR rises
 - ↑ INR contributes points to ↑ MELD score

Pulmonary Complications of Chronic Liver Disease

252. Give 6 potential causes of **increasing dyspnea** in a patient with chronic liver disease.
- Cardiac failure (including cirrhotic cardiomyopathy, and tricuspid valve incompetence)
 - Pulmonary hypertension (portopulmonary hypertension syndrome, PPH)
 - Pleural/pericardial effusions
 - Atelectasis secondary to ascites
 - Pulmonary embolus
 - Pulmonary infection
 - Pulmonary fibrosis (methotrexate)
 - Interstitial lung disease
 - Acidosis
 - Severe anemia
 - Hepatopulmonary syndrome (HPS)
 - Liver disease caused by
 - Cystic fibrosis
 - α_1 – antitrypsin deficiency
 - Pulmonary fibrosis from use of methotrexate

Adapted from: Kim YK, et al. *Radiographics* 2009;29(3):825-37.



253. Give the laboratory/radiological tests for the investigation of the pulmonary complications of cirrhosis.

- CVS
 - ECG
 - Echocardiogram with Doppler
 - Right heart angiogram
- Lung
 - CXR (chest x-ray; normal)
 - CT chest
 - ABG in erect and supine positions, for A-a O₂ gradient
 - Hemoglobin concentration, electrolytes
 - PFT's (pulmonary function tests)
 - Echo bubble (shunting)
- Ascites
 - Pleural tap
 - Radiolabeled ascites scan (technetium – labeled scan)
 - Methylene blue injection of followed by tap of pulmonary fluid

Adapted from: Kew Michael C. *Sleisenger & Fordtran's gastrointestinal and liver disease: Pathophysiology/Diagnosis/Management* 2006: pg. 2009.

254. Give 6 characteristics of pleural fluid in hepatic hydrothorax.

- Cell count <250 polymorphonuclear cells mm³ (uncomplicated)
- Protein <2.5 g/dL
- Pleural fluid/serum total protein ratio <0.5
- Pleural fluid/serum lactate dehydrogenase ratio >0.6
- Pleural fluid/serum albumin gradient >1.1
- Pleural fluid/serum bilirubin ration <0.6
- pH >7.4
- Glucose level similar to that of serum

Printed with permission: Cárdenas A, and Arroyo V. *Best Practice & Research Clinical Gastroenterology* 2007; 21(1): pg. 69.



Hepatopulmonary syndrome (HPS)

➤ Definition

- $\uparrow$ Aa PO₂ (age-corrected alveolar-arterial oxygen) gradient (< 64 years, 15 mm Hg; > 64 years, 20 mm Hg) arising from intrapulmonary vasodilation
- Diagnostic approach if PO₂ from pulse oximeter is < 96, then there is likely moderate severe HRS (Pa O₂ < 70 mm Hg; sensitivity 100%, specificity 88%)
- Diagnosis made by transthoracic echocardiography with contrast (technetium-labeled macroaggregated albumin) to detect > 6% shunt fraction
- Delay of microbubbles reaching the left ventricle on V echo bubble study

Abbreviations: AaPO₂, alveolar-arterial O₂ pressure gradient for oxygen; PaO₂, partial pressure gradient for oxygen; ^{99m}Tc-MAA, perfusion body scan with ^{99m}Technetium-labeled macroaggregated albumin

Printed with permission: Pastor CM, and Schiffer E. *Nature Clinical Practice Gastroenterology & Hepatology* November 2007;4(11): pg 615.

➤ Pathophysiology

- Definition: Intra-pulmonary vasodilation and shunting occurring in the presence of chronic liver disease or pulmonary hypertension, resulting in acute or alveolar-arterial O₂ gradient > 15 mmHg (> 20 mmHg for persons > 64 years)

SO YOU WANT TO BE A HEPATOLOGIST!

About half of patients with cirrhosis have intrapulmonary vasodilation, but only when this is severe does HPS occur. The increased production of nitric oxide (NO) and carbon monoxide are important in the pathophysiology of HPS.

- Give the mechanisms responsible for the increase in NO (nitric oxide) and CO (carbon monoxide) in cirrhosis complicated by hepatorenal syndrome.
 - NO
 - $\uparrow$ production / release of endothelin – 1 $\rightarrow$ $\uparrow$ endothelin – B receptors in pulmonary microvasculature $\rightarrow$ $\uparrow$ eNos (endothelin-1-mediated endothelial NO synthase $\rightarrow$ $\uparrow$ NO
 - $\uparrow$ bacterial translocation in gut $\rightarrow$ $\uparrow$ TNF- α $\rightarrow$ $\uparrow$ macrophages adhering to pulmonary vessels $\rightarrow$ $\uparrow$ iNos (inducible NO synthase) $\rightarrow$ $\uparrow$ NO
 - CO
 - The $\uparrow$ adherence of macrophages to pulmonary vessels $\uparrow$ the production of CO through heme oxygenase-1



- Laboratory
 - $\uparrow$ AaPO₂ and $\downarrow$ PaO₂
 - Orthodeoxia ($\uparrow$ hypoxemia on sitting up)
 - Lung perfusion showing brain uptake > 40% ($\uparrow$ intrapulmonary shunting)
 - Diagnostic imaging
 - Pulmonary vascular dilation at contrast-enhanced echocardiography or ^{99m}Tc-MAA
 - Pulmonary vasodilation on chest CT
 - Tests of pulmonary shunting
 - Using technetium macro-aggregated albumin
 - Pulmonary function testing (PFT)
 - $\downarrow$ diffusion capacity on pulmonary function testing (PFT)
 - Clinical
255. Give the clinical changes which suggest that the patient with cirrhosis has developed HPS (hepatopulmonary syndrome).
- Presence of cirrhosis plus
 - Platypnea ($\uparrow$ SOB on sitting up)
 - Cyanosis (especially distal)
 - Clubbing
 - Permanent telangiectasias of the face (angiomas)
 - Hypoxemia (PaO₂ < 70 mmHg) is usually present, together with cyanosis and clubbing
 - SOBOE, dyspnea worse when sitting up (platypnea from orthodeoxia) and better when lying down (the result of reduction of intra-pulmonary shunting when lying down, with improved oxygenation due to blood going to both lower and upper parts of the lungs)
 - Orthodeoxia (worsening of hypoxemia when person sits up or stands) is due to more blood going to the lower lungs when standing, more intra-pulmonary shunting, and a drop in blood gas arteria PaO₂ decreasing by more than 4 mmHg
 - Orthodeoxia occurs in HPS, ASD and recurrent pulmonary emboli; oxygen deactivation during sleep may occur with orthodeoxia



- Chronic liver disease patients with numerous spider angiomas are more likely to have HPS
- Suspect HPS if alveolar-arterial PaO_2 gradient on room air is > 15 mmHg, and if PaO_2 is < 70 mmHg, or if arterial blood gas PaO_2 falls by more than 4 mmHg on standing
- Seen in 4-24% of persons being evaluated for liver transplantation

SO YOU WANT TO BE A HEPATOLOGIST!

Clubbing is common in persons with liver disease, but when it is associated with distal cyanosis, HPS is suspected. Neither the presence nor the severity of HPS reflect the severity of the associated liver disease and its dysfunction.

- In this setting, give the difference between platypnea and orthodeoxia.
 - Platypnea
 - Dyspnea, which is
 - $\uparrow$ when upright
 - $\downarrow$ when supine
 - Orthodeoxia
 - Hypoxia / hypoxemia, which is
 - $\uparrow$ when upright

➤ Treatment

Therapies for hepatopulmonary syndrome have only been tested in small and uncontrolled trials.

- Oxygen therapy
 - Oxygen therapy (0.5 l/min at rest and 2 l/min during exercise) prevents the deleterious consequences of hypoxemia
 - Treatment for 1 year had a beneficial effect on liver function in two patients (their Child-Pugh score markedly improved (Fukushima et al).
- Transjugular intrahepatic portosystemic shunt
 - The placement of a transjugular intrahepatic portosystemic shunt (TIPS) to relieve portal hypertension that might participate in the pathophysiology of HPS has failed to improve patient outcome.
- Cavoplasty and coil emboli
 - In some patients with Budd-Chiari syndrome (BCS), cavoplasty reversed HPS.
 - The injection of coil emboli that preferentially distribute to dilated vessels might also decrease hypoxemia by obstructing flow to these areas.
- Pentoxifylline



- Pentoxifylline inhibits tumour necrosis factor- α overproduction and is effective in attenuating HPS in rats with ligated common bile ducts. The drug has not been tested in patients with HPS.
- Nitric oxide inhibition
 - $\uparrow$ production of nitric oxide (NO) causes pulmonary vascular dilatation
 - Therapies that reduce pulmonary NO levels or control its effects have been tested.
 - By blocking the NO-induced activation of guanylate cyclase in smooth muscle cells, methylene blue has been shown to improve pulmonary vascular dilatation and hypoxemia.
 - Inhalation of the NO synthase inhibitor N^G-nitro-arginine methyl ester, reduces intrapulmonary vascular dilatation, also improved by the PaO₂ and decreases the associated dyspnea in some patients
 - It is disputed whether there is any benefit from inhibiting the NO-cyclic guanosine monophosphate pathway (Almeida *et al*).
- Liver transplantation
 - O₂, TIPS, liver transplantation
 - Prolonged post-operative mechanical ventilation may be needed, and mortality rate after liver transplantation is high

Printed with permission: Pastor CM, and Schiffer E. *Nature Clinical Practice Gastroenterology & Hepatology* 2007; 4(11): pg. 615.

Portopulmonary Hypertension (PPH)

- Definition
 - Portal hypertension associated with hepatic cirrhosis
- Demography
 - Occurs in 0.25-4.0% of persons with end-stage liver disease, and usually within 4-7 years of the diagnosis of portal hypertension (PHT) (even though there is not a direct correlation between the development of PPH and PHT)
- Pathogenesis
 - Cirrhosis causes $\uparrow$ PA (pulmonary artery) pressure due to
 - Volume overload and $\uparrow$ cardiac output (from $\downarrow$ systemic vascular resistance and hyperdynamic circulation)
 - $\uparrow$ pulmonary vascular resistance in PPH $\rightarrow$
 - $\downarrow$ NO plus $\uparrow$ endothelin-1 $\rightarrow$ PA vasoconstriction



- Obliteration of pulmonary arterioles may occur from intimal proliferation, adventitial fibrosis, and thrombosis of pulmonary vasculature
- $\uparrow$ MPAP > 25 mm Hg
- $\uparrow$ PVR > 240 dynes /s / cm^{-5}
- $\downarrow$ PCWP < 15 mm Hg
- o $\uparrow$ mPAP (mean pulmonary arterial pressure)
 - > 25 mm Hg, at rest
 - > 30 mm Hg, with exercise
- o $\uparrow$ PVR (pulmonary vascular resistance) > 240 dynes / sec / cm^{-5}
- o The presence of
 - PHT (pulmonary hypertension)
 - Portosystemic shunts
 - Hemodynamic abnormalities in portal vein
- o Severity
 - Mild, mPAP of 25 to 35 mm Hg
 - Moderate, mPAP of 35 to 50 mm Hg
 - Severe, mPAP of > 50 mm Hg (prohibitive operative mortality from liver transplantation)

Abbreviations: MPAP, mean pulmonary artery pressure; AVR, pulmonary vascular resistance; PCWP, pulmonary capillary wedge pressure

➤ Clinical

- o Fatigue, SOBOE, orthopnea, hemoptysis, palpitations
- o Hypoxemia and cyanosis are absent
- o PPH is more common in persons with cirrhosis and refractory ascites, and in 12% of persons evaluated for liver transplantation

➤ Differential

256. Give an approach to distinguish between hepatopulmonary syndrome and portopulmonary hypertension.

Clinical	Hepatopulmonary syndrome (HRS: AV shunts)	Portopulmonary hypertension (PPH: constriction of pulmonary vessels)



○ Prevalence in cirrhotics evaluated for LT	- ~ 25%	● 5%
○ Symptomatology	- Progressive dyspnea SOB on sitting up	● Chest pain ● SOB on lying down
○ Pathophysiology	- ↑ VEGF → ↑ angiogenesis ↓ gas exchange – hypoxemia Intrapulmonary vasodilation in precapillary and capillary PA circulation due to vasoactive mediators	● Vasoconstriction ● Remodeling of resistance vessels ● ↑ PAP - Medial proliferation and hypertrophy - Arteriopathy - Thrombosis - ↑ endothelin – 1
○ Production of NO and CO	- ↑ (↑ iNos, ↑ HO-1)	● Normal
○ Clinical examination	- (Platypnea) - Cyanosis - Finger clubbing - Spider angiomas	● No cyanosis ● RV heave ● Pronounced P2 component
○ ECG findings	- None	● RBBB, rightward axis ● RV hypertrophy ● No/mild hypoxemia
○ Arterial blood gas levels	- Moderate-to-severe hypoxemia	
○ Chest radiograph	- Normal	● Cardiomegaly ● Hilar enlargement
Clinical	Hepatopulmonary syndrome (HRS: AV shunts)	Portopulmonary hypertension (PPH: constriction of pulmonary vessels)
○ CEE	- Tri-regurg; Always positive; left atria opacification for >3-6 cardiac cycles after right atrial opacification >6%	● Usually negative. Positive for <3 cardiac cycles; if arterial septal defect or patent foramen ovale



○ ^{99m}Tc MAA shunting index ("bubble study")	- Normal/low PVR	● <6% roatrial opacification ● Elevated PVR ● Normal mPAOP ● Large pulmonary arteries
○ Pulmonary hemodynamics	- Normal/'spongy' appearance (type I)	● Distal arterial pruning
○ Pulmonary angiography	- Discrete arteriovenous communications (type II) (usually lower lobe)	● Only indicated in mild-to-moderate stages
○ OLT	- Always indicated in severe stages	● Late contraindication
○ MELD exception points	- Yes	● No
○ Role of LT	- Reverses HPS in 80%	● Nuclear

Abbreviations: ^{99m}Tc MAA, technetium-99 m-labelled macroaggregated albumin; CEE, contrast enhanced echocardiography; ECG, electrocardiogram; HPS, hepatopulmonary syndrome; OLT, orthotopic liver transplantation; PAOP, mean pulmonary artery occlusion pressure; PAP, pulmonary arterial pressure; PVR, pulmonary vascular resistance; RBBB, right bundle branch block; SOB, shortness of breath (aka dyspnea)

Printed with permission: Herve P, et al. *Best Practice & Research Clinical Gastroenterology* 2007; 21(1): pg. 142.

➤ Treatment of PPH

- Bosentan (anti-endothelin activity) plus sildenafil (a phosphodiesterase – inhibitor) and prostacyclin reduce PA pressure
- Anticoagulation plus long-term O₂ therapy
- Liver transplantation
- Liver transplantation only offered when MPAP > 25 but < 35 mm Hg

Abbreviations: PA, pulmonary artery; PHT, portal hypertension; PPH, portopulmonary hypertension; SOBOE, shortness of breath on exertion

➤ Prognosis



- Median survival for persons with PPH is only 2 years without liver transplantation, but 91% 1 year survival from liver transplantation

MCQ TIPS

“Buzz Word” Associations

- NASH
 - Ballooning hepatocytes
 - Mallory bodies
 - Portal and lobular inflammation
- PBC
 - Chicken-wire fibrosis
 - Florduct lesion
 - Ductopenia
 - Granulomas
- PSC
 - “onion-skinning” obliterative fibrosis
 - Infiltration of limiting plate
 - Interface hepatitis
- Congestive hepatopathy
aka “nutmeg liver”
 - Speckled appearance
 - Dark areas (Dilated hepatic venules filled with blood)
 - Light areas (Normal hepatic parenchyma)
- α -1 AT (alpha-1 antitrypsin deficiency)
 - PAS-positive, diastase resistant globules in the ER (endoplasmic reticulum) of hepatocytes
- HBV “ground glass” hepatocytes
 - HBsAg in ER of hepatocytes giving dull appearance of hepatocytes in chronic HAV.
- The laparoscopic appearance suggestive of peritoneal TB
 - “millet-seed”
 - “violin-string”

Abbreviations: α -1 AT, alpha-1 antitrypsin deficiency; HBV, hepatitis B virus; MCQ, multiple choice questions; NASH, non-alcoholic steatohepatitis; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis

SO YOU WANT TO BE A HEPATOLOGIST!

- Give 3 causes of **ground-glass hepatocytes**.
 - Chronic HBV
 - DILI (drug-induced liver injury)
 - Fibrinogen storage disease
 - Glycogenesis, type IV



Pregnancy and the Liver

➤ Incidence

- 1/200
 - Hyperemesis gravidarum
 - HELLP (hemolysis, elevated LFTs, low platelets)
- 1/1000 ICP (intrahepatic cholestasis of pregnancy)
- 1/10,000 AFLD (acute fatty liver of pregnancy)

➤ Clinical

- Palmar erythema and spider angiomas occur in two thirds of women with normal pregnancies

➤ Laboratory

257. For 8 liver enzymes/ tests of liver function, indicate which increase, decrease, or remain unchanged in normal pregnancy.

➤ Unchanged

- AST, ALT
- INR
- Bilirubin
- GGT

➤ Increased

- Alkaline phosphatase (↑ 2-400%)
- Fibrinogen (↑ 50%)
- α- and β- globulins
- Alpha-fetoprotein*
- Leukocytes
- Ceruloplasmin
- Cholesterol
- Triglycerides

➤ Decreased

- γ- globulin
- Platelets (>50,000)
- Hemoglobin
- Albumin

* Moderate increase, especially with twins

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase

Adapted from Hay E. *Mayo Clinic Board Review* 2008: pg. 419.



Drugs in pregnancy

258. Give 4 physiological mechanisms which contribute to the altered metabolism of some drugs during pregnancy.
- ↑ maternal blood volume (50%)
 - ↓ maternal serum albumin concentration (20%)
 - Progesterone → proliferation of SER
 - Estrogen → proliferation of RER
 - ↑ cytochrome P-450 gene products
 - Increased maternal nitric oxide (NO) release during pregnancy causes maternal vasodilation, ↓ systemic vascular resistance, mean arterial blood pressure, reduced responsiveness to vasoconstrictors, resulting in maternal cardiac output rising 30-50%, sixth activation of the rennin-angiotensin system, and increased GFR as well as renal blood flow.



259. Give the **FDA category** and risk of liver disease-treating drugs during pregnancy and lactation.

Drug	FDA class	Risk in pregnancy	Risk with nursing
○ Adefovir	C	Low risk	+
○ Anti-rejection drugs	C	Not recommended	
○ B blockers	C 1 st trimester	IUGR, fetal brachycardia, hypoglycemia	-
○ Cyclosporine	D		+
○ D-penicillamine (teratogenic in humans; used for Wilson disease)	X	Contraindicate	
○ Interferon	C	Not recommended	+
○ Lamivudine	C	Low risk	-
○ Methotrexate	X	Contraindicated	
○ Metronidazole	B		
○ Octreotide*	B		+
○ Penicillamine	D	Significant embryopathy	-
○ Ribavirin	X	Contraindicated	+
○ Thalidomide (IBD)	X	Contraindicate	
○ Trientine	C	Alternative to penicillamine	-
○ Ursodiol (UDCA)	B	Low risk	+

* Octreotide is useful to stop the bleeding from esophageal varices (EV) in males and in non-pregnant females, but in the setting of a pregnant woman with bleeding EV, infusion of octreotide may result in ischemia of the uterus, and the induction of premature labor, so do **not** use.

Note: Avoid the "X" medications for 6 months before conception.

Printed with permission: Katz PO. 2008 ACG *What's New in Pharmacology Course*: pg. 50.



260. Give 3 medications used in gastroenterology and hepatology which have an FDA (food and drug administration, USA) “X” category of fetal risk.

- Ribavirin (HCV) ○ Thalidomide
- Methotrexate (IBD) ○ Cyclosporine

261. Give the FDA class and risk of liver transplantation-treating drugs during pregnancy and lactation.

Drug	FDA class	Risk in pregnancy	Risk with nursing
○ Antithymocyte globulin	C	Low risk	?
○ Mycophenolate	C	Not recommended	+
○ OKT3	C	Probably low risk	-
○ Sirolimus	C	Not recommended	-
○ Tacrolimus	C	Use if necessary	-

Printed with permission: Katz PO. 2008 ACG *What's New in Pharmacology Course*: pg. 50; and Mahadevan U. *Best Practice & Research Clinical Gastroenterology* 2007; 21(5): pg. 867.

• **Cirrhosis in Pregnancy**

262. Give the complications of cirrhosis in the pregnant patient.

- In the pregnant woman with cirrhosis, the maternal mortality rate is 10%, and there is a 3-25% risk of abortion, premature birth and perinatal death.
- In the pregnant woman with portal hypertension, 18-50% will bleed during pregnancy from esophageal varices

• **Symptomatic Cholelithiasis in Pregnancy**

SO YOU WANT TO BE A HEPATOLOGIST!

- Give the potential **genetic basis** for cholestasis of pregnancy seen in about 15% of cases.
 - About 15% of women with cholestasis of pregnancy have mutations in the MDR3 (ABCB4) gene (a phospholipid flippase that moves PC (phosphatidylcholine) from the inner to the outer surface of the hepatocyte canalicular membrane.
 - More common in women from Chile and Scandinavian countries



263. Give 5 **changes in bile acid metabolism** which occur during pregnancy, and which increase the risk of cholelithiasis.

- ↑ cholesterol
- ↑ supersaturation
- ↑ bile acid pool
- ↑ cholic acid
- ↓ chenodeoxycholic acid (chenic acid)
- ↑ volume of gallbladder (fasting/ fed states)
- ↓ gallbladder contraction

A trick question

- What is the effect of pregnancy on the prevalence of cholelithiasis, and the incidence of acute cholecystitis?
 - Cholelithiasis ↑
 - Acute cholecystitis – no change from non-pregnant state

264. Give 4 factors associated with increased risk of **recurrent cholestasis** of pregnancy.

- Further pregnancies
- Use of OCAs
- Cholecystectomy for increased risk of cholelithiasis, cholecystitis, pancreatitis
- Use of progesterone during subsequent pregnancy
- Use of estrogen
- The increased risk of biliary sludge (10-30%) and cholelithiasis (2-3% of all pregnant women) during pregnancy is due to estrogen-associated with increased transport of cholesterol into bile from the liver, and reduced solubilization of this cholesterol as the result of reduced hepatobiliary transport of bile acids and phospholipids.
- The slowing of gallbladder emptying contributes to the formation of stones.
- The pregnancy-associated increase in estrogens increases the risk of biliary pain in 28% of pregnant women who had pre-existing gallstones



Viral hepatitis may flare in pregnancy, and gallstones form in pregnancy, and both these as well as pre-existing gallstones may become symptomatic.

265. Give an approach to differentiate between viral hepatitis versus symptomatic gallstones in pregnancy.

Findings	Viral Hepatitis (flaring in pregnancy)	Gallstones
○ Nausea/vomiting	Yes	Variable
○ Abdominal pain	Variable	Variable
○ Pre-eclampsia	No	No
○ Cholestasis	Mild to marked	Marked
○ AST/ALT elevation	High	Low
○ Coagulopathy	Rare and late (acute fulminant)	No
○ Hepatic failure	Rare	No
○ U/S	Nonspecific	Dilated bile ducts, stones
○ Management of mother and child	Support HBV – Lamivudine for mother, mT ₃ HBIG at birth for child; immunize child HCV – none; check child at 18 weeks	Support, avoid cholecystectomy if possible

Please see: Swan MG. Chapter 58. In: Therapeutic Choices. Grey J, Ed. 6th Edition, Canadian Pharmacists Association: Ottawa, ON, 2011, Table 4: Cholestatic Liver Disease, page 776-777.



Liver Disorders seen only in Pregnancy

266. Give the trimester of onset and treatment of 4 liver diseases unique to pregnancy.

Liver disease	Onset	Treatment
○ Hyperemesis gravidarum	T1	-Supportive care, rehydration
○ Intrahepatic cholestasis of pregnancy (ICP)	T2-3	-Ursodeoxycholic acid (UDCA) or cholestyramine -Preterm delivery if fetal compromised
○ Pre-eclampsia and eclampsia	T2-3	-Antihypertensive drugs, magnesium sulfate
○ HELLP syndrome	T3	-Induction of delivery
○ Acute fatty liver of pregnancy	T3	-Consider early induction of delivery

HELLP, a syndrome characterized by hemolysis, elevated liver enzymes and a low platelet count; T, trimester

Printed with permission: Keller Jutta, et al. *Nature Clinical Practice Gastroenterology & Hepatology* 2008; 5(8): pg. 437.

- **T1-first trimester**

- **Nausea and vomiting in pregnancy**

- Nausea and vomiting are common in pregnancy, usually beginning by week 4 to 6, and settling by week 20.
- Hyperemesis gravidarum (HG) is severe, persistent vomiting which requires medical therapy
- The PUQE score (pregnancy-unique quantification of nausea and emesis) may be used to assist in directing therapy for HG



267. Give 4 mechanisms for the development of **hyperemesis gravidarum (HG)**, and 4 associated conditions.

➤ Mechanisms

- Gastroparesis – estrogen, progesterone
- Obesity (↑ estrogen)
- Gastric infection –H. pylori
- Hormone changes
 - HCG
 - Estrogen
 - Progesterone
 - Thyroid hormones
 - Leptin

➤ Associations

- Female fetus
- Multiple gestation
- Trophoblastic disease
- Trisomy 21 (Down syndrome)
- Hydrops fetalis
- Personal/ family history

Abbreviation: HCG, human chorionic gonadotropin

• **T2 – Second Trimester**

Intrahepatic cholestasis of pregnancy (ICP)

➤ Demography

- Present in 2% of pregnancies in America, 6% in Chile and Scandinavia
- 10-15% of first degree relatives of women with ICP also develop ICP
- 3rd trimester

➤ Pathophysiology

- Usual cholestatic effects of estrogen in pregnancy, plus



- Genetic predisposition (mutations in canalicular transporters for bile acids, phospholipids and cholesterol [amino phospholipid flippase], as well as FXR, the nuclear regulator of bile acid synthesis)

➤ Risk factors

- Previous ICP (50% recurrence)
- Multiple pregnancies
- Multiple gestations
- Descent
 - Chilean
 - Scandinavian

➤ Clinical

- Usual presentation is painless jaundice and pruritus, possibly due to elevated serum bile acid concentrations
- Generalized pruritus of skin especially on palms & soles but no rash
- Second or third trimester (T₂, T₃)
- Fetal complications
 - Usually occur after 32 weeks and include
 - Intrauterine growth retardation
 - Fetal distress
 - Premature labour
 - Stillbirth (fetal death rates in ICP are two-fold increased, usually occur between 37-40 weeks, are associated with much higher concentrations of serum bile acids, and may be sudden and intrauterine)
 - For this reason the fetus should be delivered early [36-37 weeks of pregnancy]
 - The newborn may have meconium ileus
 - When serum bile acids > 40 µmol / L, ↑ risk of complications
 - Increase risk for
 - Prematurity
 - still birth
 - spontaneous preterm labour and delivery,
 - fetal compromise,
 - fetal cardiac dysrhythmias
 - meconium stained amniotic fluid, and intrauterine fetal death
- Maternal complications
 - Vitamin K deficiency



- Coagulopathy postpartum hemorrhage
- Pruritus and abnormal laboratory tests resolve with delivery
- Recurs 40-60%)with subsequent gestations
- Increased risk for cesarean delivery due to fetal compromise
- Can recur with subsequent use of oral contraceptives (OCAs) and hormonal fluctuations
- Recurrence of ICP (~50%)
- ↑ risk of need for Cesarean section delivery
- ↑ risk of
 - Cholelithiasis
 - Cholestasis with use of OCAs
 - Cholecystitis
 - Pancreatitis

268. Give the clinical presentation and outcomes from intrahepatic cholestasis of pregnancy (ICP).

- Second or third trimester (T₂, T₃)
- Generalized pruritus with no rash
- Marked increases in serum alkaline phosphatase, bilirubin, and serum bile acid levels
- Normal or slight increases in GGT levels
- Mild increases in serum aminotransferase levels

Printed with permission: Schutt VA, and Minuk GY. *Best Practice & Research Clinical Gastroenterology* 2007; 21(5): pg. 778.

➤ Laboratory

- Cholestasis: serum bile acids > 10 µmol/ L
- Jaundice in 20%
- ALT/ AST may be ↑ 20x
- Pruritus & LE/ LFTs fluctuate
- Marked increases in serum alkaline phosphatase, bilirubin, and serum bile acid levels
- Normal or slight increases in GGT levels

➤ Pathology

- Liver biopsy is not necessary, but would show intrahepatic cholestasis, centralobular, with bile plugs in canaliculi and hepatocytes



➤ Prognosis

269. Give the fetal and maternal outcomes of intrahepatic cholestasis of pregnancy.

Maternal outcome	Fetal outcome
- Pruritus and abnormal laboratory tests resolve with delivery - Recurs 40-60%)with subsequent gestations - Increased risk for cesarean delivery due to fetal compromise - Can recur with subsequent use of oral contraceptives (OCAs) and hormonal fluctuations	- Increase risk for ▪ Prematurity ▪ still birth ▪ spontaneous preterm labour and delivery, ▪ fetal compromise, ▪ fetal cardiac dysrhythmias, ▪ meconium stained amniotic fluid, and intrauterine fetal death

270. Give the **medical treatment** of cholestatic disorders during pregnancy

Indication/drug	Fetal risk (FDA category)	Use and safety
➤ Immune-mediated disorders		
○ UDCA	B	Low risk after T1
○ Prednisolone	C	Low risk: increased risk of cleft palate, adrenal insufficiency
○ Azathioprine	D	Low risk
➤ Bacterial cholangitis		
○ Ampicillin	B	Low risk
➤ Sedation and analgesia		
○ Fentanyl	C	Use in low doses
○ Meperidine	B	Use in low doses
○ Midazolam	D	Use in low doses
○ Propofol	B	Avoid in first (and second) trimester

Fetal risk categories (FDA): A – no risk; B – risk in animal studies, but not in humans; C – human risk cannot be excluded; D – risk; X – absolute contraindication.



271. Give 4 benefits of **UDCA** in the management of cholestasis of pregnancy

- ↓ concentration of bile acids in maternal serum and amniotic fluid
- ↑ transport of bile acids in placenta
- ↓ cholestatic potential of progesterone during pregnancy
- ↓ pruritus
- ↓ fetal distress, premature delivery, stillbirth

272. Give the role of **SAM** (S-adenosyl – L- methoionine) in the treatment of cholestasis of pregnancy.

- SAM may enhance the benefit of UDCA (ursodeoxycholic acid) in cholestasis of pregnancy.

273. Give the mechanisms of action of 8 different types of drugs used for the **treatment of pruritus** in patients with cholestatic liver disease.

- Decrease degree of cholestasis: UDCA
- Non-absorbable anion exchange resins: cholestyramine
- Changes in opioidergic neurotransmission : naloxone, naltrexone
- Hepatic enzyme (cP452) inducers: rifampicin, metronidazole, phenobarbital
- Cannabinoid agonist
- Serotonin antagonists: ondansetron
- Changes in threshold to experience nociception: dronabinol
- Antidepressants (SSRIs)
- Sedation (antihistamines)
- Invasive procedures: plasmapheresis, MARS (extracorporeal albumin dialysis), biliary drainage
- IV propofol
- GABAergic changes: gabapentin



- UV light
- Liver transplantation – removes cause of cholestasis

Adapted from: Kremer AE, et al. *Drugs* 2008;68(15):2163-82.

• T3 – Third Trimester

ICP, ALF and HELLP

Acute fatty liver of pregnancy (AFLP), the HELLP syndrome* and intrahepatic cholestasis of pregnancy (ICP) occur only in pregnant women.

274. Give the distinguishing characteristics of ICP, HELLP and AFLD..

	ICP	AFLP	HELLP
➤ Mother			
○ % Pregnancies	0.1–1.0	0.005–0.01	0.2–0.6
○ Time of onset in pregnancy	T3	Second half of pregnancy, or postpartum	Second half of pregnancy, or postpartum
○ Trimester	(2 or) 3	3 or postpartum	3 or postpartum
○ Maternal mortality (%)	0	7–18	1–25
○ Presence of preeclampsia	No	50%	Yes
○ Typical clinical features	Pruritus Elevated serum ALT/AST fasting bile acids	Liver failure with mild jaundice, coagulopathy, encephalopathy, hypoglycemia, DIC	Hemolysis Elevated serum liver tests Thrombocytopenia (often <50,000/μL)
○ Nausea/vomiting	Rare	Yes (80%)	Yes
○ Abdominal pain	Rare	Yes (60%)	Yes (100%)
➤ Laboratory			
○ Cholestasis	Marked	Modest and late	Mild or absent
○ ALT	Mild to 10–20-fold ↑	5–15-fold, ↑ variable	Mild to 10–20-fold ↑



	ICP	AFLP	HELLP
○ Bilirubin	<5 mg/dL (<85 µmol/l)	Often <5 mg/dL (<85 µmol/l)	Mostly <5 mg/dL (<85 µmol/l)
○ Fetal/perinatal mortality (%)	0.4–1.4	9–23	11
○ Recurrence in subsequent pregnancies (%)	45–70	20–70 (carriers of LCHAD mutations) Rare (others)	- 4–19
○ Coagulopathy	No	In severe cases, late	Early: thrombocytopenia Late: DIC
○ Hepatic failure	No	Yes (70% when severe)	Rare
➤ Imaging			
○ U/S	Normal	No change or fatty liver	Areas of necrosis, infarction, or hematoma
➤ Biopsy			
○ Liver biopsy	Cholestasis	Microvesicular fatty infiltration	Periportal patchy, hemorrhagic necrosis, Fibrin deposition Perisinusoidal mild microvesicular fat
➤ Treatment			
○ Management of mother and child	UDCA, vitamin K	Early delivery (cesarian section) increased risk of AFLP in next pregnancy, check LCHAD in fetus(unknown risk of recurrence of AFLD)	Early delivery (cesarian section) for severe uncontrolled pre-eclampsia (hemolysis, seizures)

UDCA low risk after first trimester and effective for cholestasis of pregnancy



Abbreviation: LCHAD: α -subunit, long-chain 3-hydroxyacyl-CoA dehydrogenase; HELLP, hemolysis, elevated serum liver enzymes, low platelets

Adapted from: EASL Clinical Practice Guidelines: Management of cholestatic liver diseases. J Hepatol 2009; 51(2), 237–267 and Myers RP, et al. *First Principles of Gastroenterology* 2005. pg. 652.

HELLP (hemolysis, elevated LFTs, low platelets)

The HELLP (hemolysis, elevated liver enzymes, low platelet) syndrome is a form of pre-eclampsia liver disease.

Danger sign!

A woman in the second trimester of pregnancy with RUQ (right upper quadrant) pain, nausea and vomiting, should be suspected of having HELLP always consider this possibility, rather than focusing just on gallbladder disease.

➤ Demography

- Pre-eclampsia occurs in 5-10% of pregnancies, and accounts for 20% of maternal deaths (Van Dyke 09)
- Preeclampsia occurs in about 4% of pregnancies, and HELLP occurs with about 12% of women with severe eclampsia
- Pre-eclampsia and the HELLP syndrome usually occur in the 3rd trimester, but in 28% HELLP occurs in the early post-partum period.

➤ Pathophysiology

- Pathophysiology relates to the fetal and maternal sides of the placenta
- Even if there are no signs of preeclampsia at the time of delivery, about 30% of cases of HELLP will develop after delivery
- On the maternal side,
 - There is increased release of anti-angiogenic and decreased release of pro-angiogenic factors
 - This leads to maternal vessel vasoconstriction
 - Increased sensitivity to vasoconstrictors, damage to the endothelium of the maternal blood vessels and deposition of fibrin.
 - This in turn leads to ischemic infarcts, including acute hepatic necrosis in 10-20% of pre-eclamptic women.
- In HELLP, there are:



- The usual laboratory findings of hemolysis (H).
- The elevated liver tests (EL) include a wide range of changes in ALT/ AST, further increased in alkaline phosphatase, and jaundice in 5-40% depending on the extent of patchy ischemic necrosis and fibrin deposition, and hemolysis.
- The thrombocytopenia (LP) may be associated with low fibrinogen, increased fibrin degradation products and renal dysfunction.
- Fetal hypoxia may develop quickly, with sudden intrauterine death, so early delivery of the fetus is recommended. Fetal mortality is 3-23%, and maternal mortality is up to 3.5%.

SO YOU WANT TO BE A GASTROENTEROLOGIST!

- Give the maternal and fetal factors implicated in the pathogenesis of HELLP.
 - Mother
 - ↑ sFlt1 (soluble form-like tyrosine kinase 1 (an antagonist of VEGF [vascular endothelial growth factor] and an antagonist of PlGF [placental growth factor]))
 - ↑ sEng (soluble endoglin, which reduces the formation of capillaries)
 - ↑ procoagulant (eg, factor V Leiden, anticardiolipin antibody)
 - ↑ systemic vascular resistance
 - ↓ plasma volume
 - ↓ LCHAD (long-chain 3-hydroxyacyl – CoA dehydrogenase), which when reduced leads to ↓ mitochondrial oxidation of fatty acids)
 - Fetus
 - On the fetal side, the high capacity low resistance placental vessels do not develop, which leads to ↓ blood flow to the fetus from the placenta, fetal ischemia and intrauterine growth retardation
 - ↓ trophoblast invasion of wall of uterus
 - Dilation of spiral arteries
 - ↓ uteroplacental perfusion



Clinical Alert

In the pregnant woman with Wilson disease who develops hemolysis and acute liver disease at the time of delivery, in addition to suspecting the HELLP syndrome, consider and exclude acute Wilson disease.

LCHAD

➤ LCHAD and Liver Disease in Pregnancy

- Both HELLP and AFLP may be associated with maternal defects in the mitochondrial oxidation of fatty acids arising from deficiency of LCHAD (long-chain 3- hydroxyacyl- CoA dehydrogenase).
- ↓ LCHAD in fetus: “AFLP may develop regardless of maternal genotype if the fetus is deficient in LCHAD and carries at least one allele for the G 1528C LCHAD mutation” (*Sleisenger & Fordtran’s gastrointestinal and liver disease* 2010, page 635)...” In cases of AFLP the mother, father and child should be tested for the G1528C LCHAD mutation” (*Sleisenger & Fordtran’s gastrointestinal and liver disease* 2010, page 636)
- ↓ carnitine palmitoyltransferase

275. Give the role of deficiency of the mitochondrial fatty acid oxidation enzyme LCHAD (long-chain 3-hydroxyacyl-coenzyme A dehydrogenase) in AFLD.

- ↓ ability of fetus to oxidize long-chain fatty acids (LCFA), sometimes from a mutation causing ↓ LCHAD activity.
- LCFA from fetus are transferred from fetus to placenta to mother.
- If the mother is heterogeneous for LCHAD, she will accumulate LCFA as microvesicular fat, and will develop
 - Hepatic steatosis
 - HE (hepatic encephalopathy)
 - ALF (acute liver failure)
- If the newborn child has LCHAD deficiency, she / he has ↑ risk of fatal, fasting non-ketotic hypoglycemia over next several months – must check the newborn for their LCHAD levels.

BEWARE: after AFLP, microvesicular steatosis may progress!



➤ Clinical

- Associations
 - Hyperreflexia
 - Peripheral edema
 - DIC (disseminated intravascular coagulation)
 - Abruptio placentae
 - Budd-Chiari syndrome (hepatic vein thrombosis)
- Often associated with preeclampsia
 - ↑ SBP (systolic blood pressure)
 - Proteinuria
 - Peripheral edema
- Mortality rate
 - Mother 20%
 - Fetus 20%
- Recurs
 - 1/3 of future pregnancies
- There is an increased risk of **recurrence** of HELLP in women with severe
 - Hypertension
 - Chronic renal disease
 - Lupus anticoagulant, or
 - Women with a liver transplantation (or other organ transplantation)

➤ Pathology

- The usual patchy hepatic necrosis may lead to confluent necrosis, hepatic hematoma, and even hepatic rupture requiring surgical intervention or hepatic artery embolization.
- Fibrin deposit in sinusoids → focal ischemic necrosis → periportal hemorrhage subcapsular hematoma hepatic rupture.
- Maternal and fetal mortality from a free rupture is 50-100%.

➤ Laboratory

- The extent of laboratory abnormalities does not reflect the severity of HELLP
- Lab' abnormalities
 - Hemolysis (from microangiopathic hemolytic anemia) unconjugated hyperbilirubinemia
 - ↑ LDH
 - ↓ haptoglobin



- ↑ ALT, AST
 - ↓ platelets
 - In keeping with the hemolysis (“H”) in HELLP
 - The peripheral blood smear may show schistocytes
 - There may be increased serum LDH (lactate dehydrogenase)
 - Although transaminases are often increased 6x (median, 249 U/L for serum aspartate aminotransferase), values > 1000 may occur.
- Diagnosis
- Required for diagnosis
 - Hypertension (sustained systolic blood pressure of $\geq 140/90$ after week 20 of pregnancy, in a women whose blood pressure was previously normal)
 - Hypertension-associated end organ damage (eg, liver damage in HELLP syndrome)
 - Proteinuria (≥ 300 mg urinary protein per 24 hr, or 30 mg/dL urine [dipstick #1])
 - While abdominal ultrasound may be reliable to detect intrahepatic complications of HELLP, imaging is not reliable to prove the absence of AFLP (the liver must contain > 30% before the abdominal ultrasound becomes reliably positive for steatosis).

SO YOU WANT TO BE A GASTROENTEROLOGIST!

Using the presence of elevated serum values of AFP (alpha-fetoprotein) is **not** widely recommended as a screening test for hepatocellular cancer (HCC).

- In the setting of a pregnant woman with cirrhosis or chronic HBV infection who has been found to have an increased serum AFP, what are the differential possibilities besides HCC?
 - Mother
 - Physiological (↑ AFP in normal pregnancies)
 - Hydatidiform mole
 - Fetus
 - Down syndrome
 - Neural tube defects



Acute Fatty Liver in Pregnancy

➤ Epidemiology

- Seen in 1/1000 pregnancies
- AFLP accounts for 16-70% of severe liver disease as well as maternal and fetal deaths during pregnancy

➤ Pathophysiology:

- Impaired mitochondrial beta-oxidation or oxidative phosphorylation of fatty acids, resulting in mitochondrial damage, ↓ ATP production, and destruction of hepatocytes
- Associated with pre-eclampsia in 30%, genetic abnormality in LCHAD (long chain 3-hydroxyacyl-CoA-dehydrogenase) in 20%, possibly other as yet unknown genetic mutations, and the use of drugs such as ASA/ NSAIDs
- When mother is LCHAD heterozygote but fetus is homozygote, the risk of AFLP is 43%; when the fetus is a heterozygote or normal, the risk of AFLP is 2.7%

➤ Clinical

- The presentation is that of acute liver failure, including hepatic encephalopathy, coagulopathy, jaundice, ascites, hypoglycemia, renal impairment and pancreatitis
- Intrauterine fetal mortality may be as high as 32%, and maternal mortality rates of 5-26%.

➤ Laboratory

- The level of the altered serum transaminases do not reflect the severity of the liver damage and failure. In addition to an elevated INR, anti-thrombin III levels are often increased as well

“A gem cannot be polished without friction, nor a man perfected without trials.”

Chinese Proverb



➤ Differential

Ticks and Treats

- Overlap - questions are often asked of candidates to distinguish between AFLP (acute fatty liver of pregnancy) and HELLP.
- It is helpful that AFLP does not usually have thrombocytopenia.
- In groups of patients, ALT/AST may be increased in AFLP; although this increase may not be as high as in HELLP, and in the individual patient this relative elevation of differences in ALT/AST is not useful.
- Beware, AFLP is not considered to be a preclampsic liver disease, but about 50% of AFLP may actively have associated pre-eclampsia.
- Both HELLP and AFLP may be associated with inherited defects in the beta oxidation of fatty acids.
- And don't forget: AFLP is associated with severe pericentral (zone 3) microvesicular fat, and HELLP may be associated with fatty liver, albeit not as severe as the pericentral microvesicular fat of AFLP.

➤ Treatment

- Urgent delivery is required; test the mother and infant for LCHAD mutations

Abbreviations: AFLP, acute fatty liver of pregnancy; LCHAD, long chain 3-hydroxyacyl-CoA-dehydrogenase

• **Liver Diseases occurring in Pregnancy which are not unique to pregnancy**

276. Give the cautions to be considered when treating the following liver conditions during pregnancy.

- **HAV**
 - Hepatitis A has low risk in pregnancy
- **HBV**
 - Hepatitis A has low risk in pregnancy
 - Lamivudine is low risk in pregnancy



- **Interferon** and **ribavirin** are contraindicated in pregnancy (use lamivudine, tenofovir if necessary)
 - Adefovir and entecavir have no data in human pregnancy
 - Hepatitis B vaccine has low risk in pregnancy
 - Vertical transmission from mother to child is the commonest route for HBV infection, and depending upon the viral load, may be 80-90%.
 - Babies born to HBV positive mothers should receive HBIG and HB vaccine at birth, and further vaccine at one and six months of age. at 18 months of age, the child born to the HCV positive mother should have HCV RNA testing.
- **HCV**
 - HCV infections are the result of vertical transmission rarely transmitted to fetus
 - Risk of 30% if the mother is both HCV and HIV positive.
 - HCV – don't treat in pregnancy
- **HDV**
 - HDV may be transmitted at the same time as HBV. In contrast, only 5-8%.
- **HEV**
 - HEV hepatitis in pregnant women is associated with a high rate of fulminant hepatic failure, and maternal as well as fetal death. Transmission of HEV is vertical, and the HEV vaccine will soon be available.
 - HEV – often fatal in Africa and Asia
 - Underlying chronic liver disease
 - Rare to become pregnant
 - Prognosis variable
 - Stillbirths increased
 - High bilirubin → kernicterus
- **HSV**
 - The risk of herpes simplex hepatitis is increased during pregnancy, and may present with markedly elevated transaminases or with fulminant hepatic failure.



- **AIH**

- Maintenance medications for autoimmune hepatitis (AIH) should not be stopped during pregnancy, and even with these being continued, there is an increased risk of spontaneous abortion (12%) and perinatal deaths (7%)

- **Wilson disease**

- Penicillamine should be avoided, or dose adjusted
- If necessary, switch to oral zinc, or trientine
- The woman of child bearing potential who has Wilson disease is usually not able to conceive because of associated amenorrhea and infertility.

277. Were the patient with WD to become pregnant, give the reason why copper-lowering therapy should be continued when D-penicillamine is teratogenic in humans.

- When therapy for Wilson disease is stopped during pregnancy, the sudden release of copper causes RBC hemolysis, with possible acute liver failure and death.
- If a woman with Wilson disease is planning/ hoping to become pregnant, switch her from D-penicillamine to trientine (not teratogenic in humans).
- PBC/PSC/ICP
 - UDCA low risk after first trimester and is effective for cholestasis of pregnancy
- Portal hypertension
 - Propranolol -avoid after first trimester (fetal cardiotoxicity)
 - Nadolol has a long half-life- should be avoided

“We get too soon old and too late smart.”

Grandad



Jaundice / Hyperbilirubinemia

➤ Pathophysiology

278. Give the pathophysiology of the development of hyperbilirubinemia and jaundice.

- RBC heme is broken down by RE (reticuloendothelial system), largely in the spleen.
- Heme oxygenase converts heme to biliverdin.
- Biliverdin reductase converts biliverdin to bilirubin.
- Lipid soluble unconjugated bilirubin (UB) is made water soluble by the binding of UB to albumin (albumin – UB complex).
- The albumin-UB complex passes through the fenestrations in the endothelium of the hepatic sinusoids and into the space of Disse.
- In the space of Disse the UB dissociates from the albumin.
- UB is transported by OATP (organic anion transport protein) across the SM (sinusoidal membrane) of the hepatocyte.
- In the cytosol of the hepatocytes, UB binds to glutathione S- transferase.
- UDP – GT (uridine – 5' – diphosphate glucuronyl transferase) in the ER.
 - Binds to UB to prevent its back flux across the SM and into portal blood
 - Conjugates UB to glucuronic acid
- The CB (conjugated bilirubin) is a mono- and diglucuronic
- The CB is transported across the CM of the hepatocyte by ATP-dependent MRP2 (multiple drug resistance-associated protein 2)
- CB enters the bile, and passes along the length of the small intestine and into the colon.
- The bacteria in the liver of the distal ileum and colon contain B-glucuronidases bacterial B-glucuronidases hydrolyze CB to UB.
- UB is reduced further by intestinal bacteria to urobilinogen.
- The fate of urobilinogen includes
 - Passed in stool
 - Oxidized to urobilin and passed in urine
 - Absorbed in the distal, ileum and colon, to be re-secreted
 - By liver into bile
 - By renal glomerulus into urine
 - CB is water soluble, and when the bilirubin level is high in serum and bile, not all CB is hydrolyzed to UB.



- CB tea-coloured urine occurs only in conjugated hyperbilirubinemia urine. Urine turns to colour of tea.
- In unconjugated hyperbilirubinemia, all UB is bound to albumin and does not enter the urine so the urine is not tea-coloured.

279. Give the clinical processes which contribute to the development of hyperbilirubinemia.

- Increased bilirubin production (indirect hyperbilirubinemia; AP/ALT often normal)
 - Destruction of transfused erythrocytes
 - Hemolysis secondary to pre-existing hemolytic conditions (eg: G6PD deficiency, hemoglobinopathies)
 - Hemolysis secondary to mechanical heart valve prostheses
 - Reabsorption of hematomas
 - Multiple blood transfusions
- Hepatocellular Injury (predominant serum ALT elevation with or without hyperbilirubinemia)
 - Inhalational anesthetics-halothane, others
 - Ischemic hepatitis (shock liver)
 - Hepatic artery thrombosis
 - Other drugs-antihypertensives (eg: labetalol), heparin
 - Acute post-transfusion hepatitis
 - Unrecognized previous chronic liver disease-NASH, HCV etc
 - Hepatic allograft rejection
- Cholestatic Jaundice (elevated serum alkaline phosphatase, GGT, direct hyperbilirubinemia)
 - Benign postoperative cholestasis
 - Cardiac bypass of prolonged duration
 - Sepsis
 - Acalculous cholecystitis
 - Common bile duct obstruction-gallstones, pancreatitis
 - Cholangitis



- Bile duct injury-post-cholecystectomy, post-liver transplantation
- Microlithiasis (biliary sludge)
- Prolonged total parenteral nutrition
- Hemobilia
- Drugs-amoxicillin-clavulanate, chlorpromazine, erythromycin, teletromycin, trimethoprim-sulfamethoxazole, warfarin, others

Adapted from: Stevens WE. *Sleisenger & Fordtran's gastrointestinal and liver disease: Pathophysiology/Diagnosis/Management* 2006: pg. 1856 and Faust TW, et al. *Clin Liver Dis* 2004;8(1):151-66.

➤ Differential diagnosis

280. Give 10 major intrahepatic and extrahepatic causes of cholestasis leading to jaundice.

➤ Intrahepatic

- Drugs
- Alcoholic hepatitis ± cirrhosis
- PBC
- Viral hepatitis
- Chronic hepatitis ± cirrhosis
- Cholestasis of pregnancy
- Sepsis
- TPN

➤ Extrahepatic

- Common bile duct stone(s)
- Pancreatic/periampullary cancer
- Benign biliary stricture
- PSC, SSC (secondary sclerosing cholangitis)
- Bile duct carcinoma
- Benign pancreatic disease
- Extrinsic duct compression

Adapted from: Heathcote J. *First Principles of Gastroenterology* 2005: pg. 590.



281. Give 5 factors contributing to **physiological jaundice** in the neonate.

- Absence of placental bilirubin metabolism
- Reduced hepatic blood flow via ductus venosus shunting
- Decreased red blood cell survival
- Proportionally increased red blood cell mass
- Reduced enteric bacterial flora
- Presence of intestinal β -glucuronidase
- Immature liver function
- Delayed oral feeding

Printed with permission: Machida H. *First Principles of Gastroenterology* 2005: pg. 725.

282. Give 10 causes of **unconjugated** hyperbilirubinemia in the neonate.

- Increased bilirubin production (hemolytic disease)
 - Blood group incompatibility (Rh, ABO, minor groups)
 - Membrane defects (spherocytosis, elliptocytosis, infantile pyknocytosis)
 - Enzyme deficits (G6-PD, hexokinase, pyruvate kinase)
 - Drugs (oxytocin, vitamin K)
- Increased RBC breakdown
 - Infection
- Hematoma, Extrahepatic biliary obstruction
 - Bile duct ligation/injury
 - Choledocholithiasis
 - Acalculous cholecystitis
 - Post cholecystectomy, post liver transplantation
 - Microlithias (biliary sludge)
 - Postoperative pancreatitis
 - Extrinsic compression of common bile duct or common hepatic duct
 - Hemobilia
- Pre-existing Abnormalities in Bilirubin Metabolism/Excretion
 - Chronic liver disease
 - Gilbert's syndrome
 - Swallowed maternal blood



- Increased RBC mass
 - Polycythemia (maternal diabetes, delayed cord clamping, small for gestational age, high altitude)
- Decreased bilirubin metabolism
 - Reduced uptake
 - Portacaval shunt, hypoxia, sepsis, acidosis, congenital heart disease
 - Decreased conjugation (unconjugated)
 - Crigler-Najjar type I, II
 - Gilbert syndrome
 - Lucey-Driscoll syndrome
 - Hypothyroidism
 - Panhypopituitarism
- Altered enterohepatic circulation
 - Breastfeeding
 - Free fatty acids, steroids, breast milk β -glucuronidase
 - Intestinal hypomotility
 - Retained meconium
 - Reduced intestinal flora
 - Newborn antibiotic use

“Challenges are what make life interesting and
overcoming them is what makes life meaningful.”

Joshua J. Marine



Congenital Syndromes of Conjugated Hyperbilirubinemia

283. Give a comparison of four congenital syndromes of conjugated **hyperbilirubinemia** (Gilbert's, Crigler-Najjar types 1 & 2 [CN-T₁, CN-T₂], Dubin-Johnson (DJ), and Rotor's syndrome) in terms of their prevalence, autosomal inheritance, serum bilirubin concentration, diagnostic features, prognosis and treatment.

Name	Defects
○ Gilbert syndrome	- "a mutation in the TATAA element in the 5' promoter region of the UDP glucuronyl transferase gene" ¹ - Activity of UDP-GT is ~ 30% of normal.
○ Crigler-Najjar – type II	- ↓UDP-GT activity < 10% of normal
○ Crigler-Najjar – type I	- UDP-GT is zero (risk of kernicterus)
Name	Defects

- Conjugated hyperbilirubinemias (> 15% of total bilirubin is conjugated)
- Dubin – Johnson syndrome
 - Defect in MRP₂ gene
 - Rotor syndrome
 - Defect unknown

¹Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier, Philadelphia, 2010, page 1228.

"The pain you feel today is the strength you feel tomorrow. For every challenge encountered there is opportunity for growth."

Unknown



284. Give the variables to differentiate between Gilbert syndrome, Crigler-Najjar type-1 and -2, Dubin Johnson (DJ) syndrome, and Rotor syndrome.

Variables	Gilbert	CN-T1	CN-T2
○ Prevalence	7% of population	Very rare	Uncommon
○ Inheritance (all autosomal)	Dominant	Recessive	Dominant
○ Serum bilirubin concentration	<100 $\mu\text{mol/L}$ (all conjugated)	>400 $\mu\text{mol/L}$ (all conjugated)	<100 $\mu\text{mol/L}$ (about half conjugated)
○ Diagnostic features	Bilirubin conc' ↑ with fasting ↓ with phenobarbital	Bilirubin conc'- no response to phenobarbital	Bilirubin conc' ↓ with phenobarbital
○ Prognosis	Normal	Early death from kernicterus	Usually normal

Dubin Johnson (DJ) and Rotor Syndrome

Treatment	None needed	Liver graft	Phenobarbital
○ Prevalence	Uncommon		Rare
○ Inheritance (all autosomal)	Recessive		Recessive
○ Serum bilirubin concentration ($\mu\text{mol/L}$)	<100 (about half conjugated)		<100 (about half conjugated)
○ Diagnostic features	Coproporphyrin excretion (>80% isomer !) Pigment in centrolubular hepatocytes		Normal gallbladder visualization at oral cholecystography
○ Prognosis	Normal		Normal
○ Treatment	Avoid estrogen		None available

"Be an advocate, seek something good for everyone: seek justice and love."

Grandad



285. Give 5 categories of causes of **conjugated** hyperbilirubinemia in the neonate, and for each give 5 examples.

- Infection
 - Bacterial urinary tract infection/sepsis
 - Cytomegalovirus
 - HSV, type 6
 - Rubella
 - Syphilis
 - Toxoplasmosis
 - Other viruses: adenovirus, Coxsackie virus, echovirus, parvovirus B19
- Metabolic
 - Bile acid synthesis disorders
 - Cystic fibrosis
 - Endocrine disorders: hypopituitarism, hypothyroidism
 - Fructosemia
 - Galactosemia
 - Neonatal hemochromatosis
 - Niemann-Pick disease
 - Peroxisomal disorders
 - Progressive familial intrahepatic cholestasis
 - Tyrosemia
 - α_1 -antitrypsin deficiency
- Bile duct disorders
 - Extrahepatic
 - Bile duct perforation, stenosis
 - Biliary atresia
 - Choledochal cyst
 - Cholelithiasis
 - Inspissated bile/bile plug
 - Intra/extrahepatic masses
 - Neonatal sclerosing cholangitis
 - Intrahepatic
 - Alagille syndrome
 - Byler disease (familial progressive disorder)
 - Nonsyndromic bile duct paucity



- Miscellaneous
 - Parenteral nutrition
 - Intestinal obstruction
 - Shock
 - Trisomy 21

Printed with permission: Robertson M, and Martin SR. *Principles of Gastroenterology* 2005: pg. 728.

286. Give 10 causes of **jaundice in patients with lymphoma**.

- Related to lymphoma
 - Hepatic infiltration
 - Jaundice without infiltration
 - Intrahepatic cholestasis
 - Rare
 - Hodgkin's disease
 - Stauffer's syndrome-like [renal cell Ca]
 - Extrahepatic obstruction
 - Usually hilar
 - Usually non-Hodgkin's lymphoma
 - Autoimmune hemolytic anemia, DIC
 - Hepatic artery clots
- Related to therapy
 - Chemotherapy (can cause acute liver failure)
 - Hepatic irradiation
 - Infection
 - Post-transfusion HCV
 - HBV reactivation
 - Opportunistic infections

Adapted from: Sherlock S, and Dolley J. *Diseases of the Liver and Biliary System* (Eleventh Edition) 2002: pg. 60.



Cirrhotic Cardiomyopathy

➤ Definition

287. Define cirrhotic cardiomyopathy, and give the criteria that help to make or support the diagnosis.

- A cardiac dysfunction in patients with cirrhosis characterized by impaired contractile responsiveness to stress and/or altered diastolic relaxation with electrophysiological abnormalities in the absence of other known cardiac disease.

➤ Pathophysiology

- Hyperdynamic circulation from arterial vasodilation causes heart ↑ rate and cardiac output, and ↓ systemic vascular resistance and arterial blood pressure, with ↑ peripheral but not central intravascular volume

➤ Diagnosis

• Diagnostic criteria

- Systolic dysfunction
 - Blunted increase in cardiac output on exercise, volume challenge or pharmacological stimuli
 - Resting ejection fraction <55%
- Diastolic dysfunction
 - E/A ratio <1.0 (age-corrected)
 - Prolonged deceleration time (>200 ms)
 - Prolonged isovolumetric relaxation time (>80 ms)

• Supportive criteria

- Electrophysiological abnormalities
- Abnormal chronotropic response
- Electromechanical uncoupling/dys-synchrony
- Prolonged Q-T_c interval
- Seen in 60% of persons with cirrhosis correlates with the severity of the liver disease, and predisposes the person to ventricular arrhythmias
- Enlarged left atrium



- Increased myocardial mass
- Increased BNP and pro-BNP
- Increased troponin I

Abbreviations: BNP, brain natriuretic peptide; E/A ratio, ratio of early to late (arterial) phases of ventricular filling

Printed with permission: Møller S, and Henriksen JH. *Gut* 2008; 58: 274.

- Diagnostic tools in the assessment of systolic and diastolic dysfunction in persons suspected of having cirrhotic cardiomyopathy.

➤ Systolic function

- Echocardiography/MRI:
 - Volumes
 - Fractional shortening
 - Velocity of fractional shortening
 - Ejection fraction (planimetry)
 - Response to stress (dobutamine)
 - Wall motion
- Exercise ECG
 - Exercise capacity
 - Oxygen consumption*
 - Pressure x heart rate product
- Radionuclide angiography (MUGA)
 - Ejection fraction
 - Cardiac volumes
 - Pattern of contractility
- Myocardial perfusion imaging with gating
 - Regional myocardial perfusion
 - Cardiac volumes
 - Ejection fraction
 - Wall motion and wall thickening



➤ Diastolic function

- Echocardiography/MRI/MUGA
 - E/A ratio
 - Deceleration time
 - A and E waves
 - Relaxation times

Printed with permission: Møller S, and Henriksen JH. *GUT* 2008; 58: pg. 276.
training program in gastroenterology.

➤ Treatment

- Left heart failure is rare because of the reduced systemic vascular resistance not afterload reduction
- Treatment requires preload reduction (O₂ diuretics, sodium restriction)

288. Give 3 hepatic conditions associated with cardiac abnormalities, such as arrhythmias and heart failure (HF).

- HH (hereditary hemochromatosis)
- Alcoholic cardiomyopathy
- Cardiac cirrhosis from right-sided HF
- Drugs, e.g. amiodarone toxicity

"Knowledge speaks, but wisdom listens."

Jimi Hendrix



Hepatic Tumors

289. Give a classification of hepatic masses seen on abdominal ultrasound.

➤ Tumours

- Primary and secondary metastases

➤ Benign lesions (usually require no further treatment)

- Cavernous hemangioma
- Focal fatty liver areas
- Focal nodular hyperplasia (reaction to an arterial malformation; the telangiectatic subtype of FNH is associated with estrogen use; 10% multiple, 20% associated with cavernous hemangioma)
- Simple liver cysts
- Hepatic adenoma (associated with the use of OCA; require further follow-up)

➤ Malignant lesions

- Cholangiocarcinoma (CA 19.9)
- Cystadenocarcinoma
- Epithelioid angiomyolipoma
- Hemangioendotheliomatosis
- Liver metastases
- Lymphomas
- Mixed epithelial and stromal tumours
- Mixed hepatocellular-cholangiocarcinoma
- Primary hepatocellular carcinoma
- Sarcomas

➤ Abscesses

- Amebic liver abscess
- Biliary cystadenoma
- Echinococcal cysts
- Granulomatous abscesses



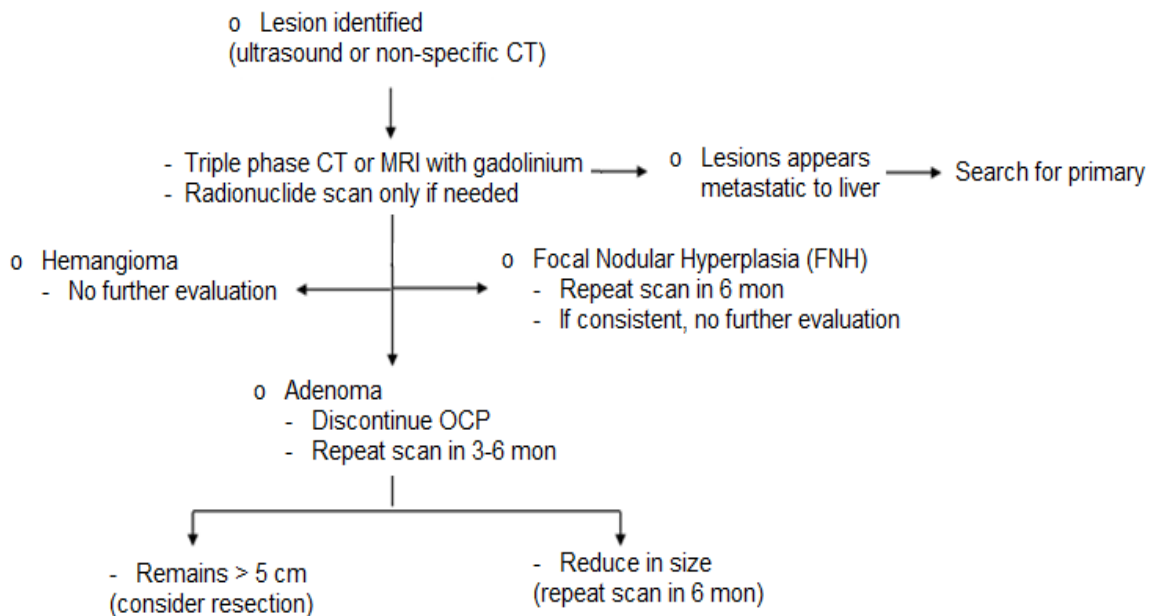
- Inflammatory pseudotumour
- Nodular regenerative hyperplasia
- Pyogenic liver abscess

Abbreviation: OCA, oral contraceptive agent

Adapted from: Roberts LR. 2008 AGA Annual Postgraduate Course Syllabus: pg 245.

- When a mass is identified in the liver of a person with or without chronic liver disease, a triple phase CT or MRI with gadolinium is performed
- Nuclear scintigraphy with sulphur colloid is taken up by the Kupffer cells; uptake is increased with metastatic lesions (thyroid, breast, lung, pancreas, colon), hemangioma or cysts, and is reduced with hepatic adenomas and HCC
- Radionuclide scanning with RBC identifies an hepatic mass as an hemangioma

290. Give an **algorithm** for evaluation of hepatic mass in a patient without chronic liver disease.



Hepatic Cysts

291. Give a classification of hepatic cysts.

- Simple hepatic cysts
- < 5 cm, and up to 3 cysts before PCLD (polycystic liver disease) needs to be considered
- Polycystic liver disease
- ADPKD (autosomal dominant polycystic kidney disease)
- Biliary microhamartomas
- Caroli disease (type V choledochal cyst)
- Congenital hepatic fibrosis
- Type IV choledochal cysts

292. Give 6 features on diagnostic imaging which may help to differentiate the nature of the hepatic tumor / cyst.

- Cysts containing daughter cysts (hydatid)
- Partly cystic and partly solid
 - Biliary
 - Cystadenoma
 - Cystadenocarcinoma
- Hyperechoic lesion with interspersed hypoechoic areas
 - Areas of
 - Necrosis
 - Hemorrhage
 - Fat
- Vascular
 - Hemangiomas
 - Metastasis from NET (neuroendocrine tumor)

“Be Modest-
There is always a taller mountain.”

Grandad



Peliosis Hepatis

- Definition
 - Multiple blood-filled cavities distributed randomly throughout the parenchyma of the liver
- Types
 - Parenchymal
 - Cavities lined by hepatocytes
 - Phlebectatica
 - Cavities lined by hepatocytes
 - May progress to
 - Fibrosis
 - Regenerative nodules
 - Cirrhosis
 - Tumors
- Clinical associations
 - Anabolic steroids
 - Bartonella infection in HIV-immunosuppressed patients
 - Azathioprine
 - OCA (oral contraceptive agent)
 - Vitamin A
 - Hydroxyurea
 - About 1/3 of patients with severe disease will have a symptomatic, harmless ↑ ALT.
- **Cavernous hemangioma**
 - Common congenital malformation of the liver vasculature, with
 - Ectatic blood vessels with no malignant potential and not affected by oral contraceptive hormones.
 - Because of tortuous vessels and stasis, thrombosis and pain may occur
 - Caused by
 - Congenital malformation, or
 - Hamartomatous change
 - Enlarges under influence of estrogens / pregnancy
 - The increased vascularity is of capillary origin



- Diagnostic imaging
 - Abdominal ultrasound echogenic
 - Bolus-enhanced CT with sequential scans
 - These show
 - Periphery – enhanced
 - Margin – corrugated
 - Centre – hypodense
 - SPECT (single photon emission computed tomography) with colloid ^{99m}Tc –labelled red blood cells

Note: Enhance slowly with dynamic studies because the increased vascularity is from capillaries

- MRI may show pathognomic changes
- Ring – or C-shaped configuration
- Centre – fibrous, with no uptake (avascular)

You are sensible and don't want to perform a percutaneous biopsy in a patient with a large hypoechoic liver lesion on abdominal ultrasound / suggestive of a cavernous hemangioma.

293. Give the findings of diagnostic imaging tests which suggest that a hepatic mass is a cavernous hemangioma.

- CT or MRI contrast enhanced
 - Centipetal filling of contrast (from the periphery to the center)
 - well circumscribes
- RBC nuclear scan with technetium
 - ↑ Uptake of labelled RBC on the venous phase
 - ↑ retention on delayed films

SO ho-ho-ho, YOU WANT TO BE A HEPATOLOGIST!

In the context of a large hemangioma, give the meaning of the **Kasabach-Merritt** syndrome.

- The Kasabach-Merritt syndrome is a large hemangioma, DIC (disseminated intravascular coagulopathy) and thrombocytopenia resulting from platelets being sequestered and destroyed in the hemangioma.



Adenoma

- Demography
 - Usually seen in 1/ 10⁶ women in their childbearing years, and especially if they are on OCA (3 x increased risk)
 - Premalignant, with risk of malignancy increasing with size of adenoma
- Pathology
 - 90% single, 10% multiple
 - Circumscribed, but not encapsulated
 - Vascular channels of various sizes
 - Thrombi in vascular channels
 - Mast cells within hemangiomas
 - Sclerosis
 - Sheets of normal or near normal looking hepatocytes
 - No triads, central vein or bile ducts
 - Adenomatosis may occur
 - May undergo malignant transformation
- Clinical
 - Estrogen and/or progesterone oral contraceptive drugs
 - Anabolic steroids
 - Type I glucagon storage disease
 - Clinical course
 - May enlarge
 - When ≥ 5 cm may
 - Bleed
 - Undergo malignant degeneration
 - Associated with use of OCA (oral contraceptive agent)
 - Large, subcapsular lesions may rupture and bleed
 - Resect if > 5 cm
 - No malignant potential
- Genetic alterations
 - HNF 1α inactivation ,through biallelic mutations of the TCF1 gene
 - B-catenin activation
 - Acute inflammation



- Diagnostic imaging
 - Multiphase, helical CT or MRI
 - Definite margin (pseudocapsule)
 - Vessels enter adenoma at the periphery and pass in a spoke-wheel manner to the centre
 - Focal avascular areas
 - Technitium sulfur colloid scan
 - Features on triphasic CT or gadolinium enhanced MRI may be difficult to distinguish from HCC
 - A technitium sulfur colloid scan may be needed to show the typical cold lesions (no sulfur colloid uptake)
 - Serum AFP may become positive when hepatic adenomas becomes malignant

Focal Nodular Hyperplasia (FNH)

- Definition
 - "Focal nodular hyperplasia is a circumscribed, usually solitary lesion [of the liver] composed of nodules of benign hyperplastic hepatocytes surrounding a central stellate scar" (Feldman M., et al. *Sleisenger and Fordtran's Gastrointestinal and Liver Disease*. 9th Edition. *Saunders/Elsevier* 2010, page 1587).
- Demography
 - 2nd only to hemangiomas as a cause of a benign tumor of the liver.
- Pathology
 - Common congenital malformation of the liver vasculature, with hyperplasia of hepatocytes around the vascular abnormality, leading to a central scar
 - Hyperplastic regenerative nodules separated by fibrosis septae.
- Cause / associations
 - Adenomas
 - Cavernous hemangiomas (20%)
 - HHT (hereditary hemorrhagic telangiectasia)
 - Epithelial hemangioendothelioma



- Not caused by OCA (oral contraceptive agents), but may enlarge under the influence of OCA

➤ Diagnostic Imaging

- Contrast-enhanced CT (triphasic)
 - Hypodense
 - Arterial phase
 - Enhanced
 - Single lesion
 - Subcapsular
 - Enhancement of mass during arterial phase
 - Fibrous septa
 - Centre
 - No enhancement
 - Central stellate scar
 - Hemorrhage / necrosis

➤ Differential

294. Give an approach to **distinguish** between **focal nodular hyperplasia (FNH)** and **hepatic adenoma (HA)**.

Characteristic	FNH	Adenoma
○ Gender	Female	Female
○ Hormone therapy	-*	+++
○ Symptoms	Rare	Occasional
○ Multiple	About 30%	12-30%
○ Pathological associations	Hemangiomas	Glycogenoses androgens, peliosis
○ Central arterial scar	Yes Static	No; If stimulated (estrogens, OCA)
○ Treatment	Conservative	Resection if symptomatic
○ Malignant potential	-	+

*the telangiectatic subtype of FNA is associated with estrogen use



295. Give the diagnostic features, on 4 types of diagnostic imaging, which help to distinguish between hepatic hemangioma, focal nodular hyperplasia, and adenoma.

	Hemangioma	Focal nodular hyperplasia	Adenoma
➤ Ultrasound	○ Hyperechoic ○ Well defined borders	- Variable appearance well defined borders	- Non diagnostic
➤ Triple phase CT	○ Pre contrast: hypodense ○ Centripital globular enhancement ○ Retained contrast in delayed images	- Pre contrast: Hypo or isodense - Homogenous arterial enhancement - Hypodense central scar - Isodense in delayed imaging	- Pre contrast: Hypo or isodense - Irregular enhancement - Delayed peripheral arterial enhancement during venous phase
➤ MRI	○ T1: well circumscribed low signal ○ T2: Hyperintense signal	- T1: low signal - T2: Hyperintense signal with central scar	- T1: Low signal intensity with well defined capsule - T2: Heterogenous enhancement
➤ Gadolinium enhanced MRI	○ Progressive enhancement ○ Delayed washout on venous phase	- Homogenous arterial enhancement - Hypodense central scar - Contrast accumulates in scar on delayed T1	- Irregular enhancement with delayed washout
➤ Radionuclide scan (tagged RBC)	○ ↑ uptake during venous phase ○ Delayed emptying	- Equal or ↑ uptake compared to surrounding liver	- ↓ uptake compared to surrounding liver

Source: Shiffman ML. 2009 ACG Annual Postgraduate Course:167-171.

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296. Give 6 clinical, laboratory and diagnostic imaging **differences** between **FNH and FLHCC** (fibrolamellar hepatocellular cancer)

Feature	FLHCC	FNH
○ Associated with cirrhosis	-	-
○ Normal hepatic synthetic function	+	-
○ Treated by surgical resection	+	Depends
○ Diagnostic imaging		
- Central scar	+	+
- Calcification	+	-
- ↓ Intensity (dark, hypointense) on T2-images of MRI	+	-
- Progressive enlargement	+	-
○ Histology		
- Large, granular cells	+	-
- Pale bodies	+	-
- Bands of fibrosis	+	-
○ Bile duct proliferation	-	+
○ Malformed blood vessels in central scan	-	+
➤ Treatment		
○ No malignant potential		
○ No treatment needed		

Nodular Regenerative Hyperplasia (NRH)

- Definition
 - Regenerative nodules without fibrosis
- Pathology
 - Injury to the hepatic vasculature from
 - Autoimmune disorders
 - Myeloproliferative syndromes
 - Antineoplastic medications → remodeling of surrounding liver tissue into a nodule around portal triads, which contains liver tissue and no fibrosis



➤ Clinical

- The nodules of regenerative liver tissue may
 - Compress adjacent hepatic vasculature, leading to non-cirrhotic portal hypertension
 - Compress bile ducts, leading to jaundice
- Associated conditions
 - Hematological
 - Hypercoagulable states
 - Myeloproliferative disorders
 - Lymphoproliferative disorders
 - Drugs
 - Azathioprine
 - Chemotherapeutic agents

➤ Diagnosis

- MRI is the best diagnostic imaging test to distinguish HCC from a large cirrhotic nodule

Abbreviation: NRH, nodular regenerative hyperplasia

➤ Treatment

- Stop offending drug
- Treat associated hematological disorders

Focal Fatty Liver

- Abdominal ultrasound
 - Hyperechoic lesion
 - CT
 - Hypodense lesion
 - MRI
 - T1-weighted images positive
 - Note:
 - No distortion of surrounding architecture



Polycystic Liver Disease

- Definition
 - PCLD alone, or PCLD plus ADPKD (autosomal dominant polycystic kidney disease), or PCLD plus cysts in pancreas or spleen, arise from ductal plate malformation
- Pathology
 - May transform to squamous cell carcinoma
- Clinical associations
 - CNS
 - Berry aneurysms
 - CVS
 - Mitral valve prolapse
 - Biliary tree
 - Biliary microhamartomas
 - Liver
 - Congenital hepatic fibrosis
 - Colon
 - Colonic diverticulosis
 - Inguinal hernias
- Diagnostic Imaging
 - MRI
 - T2 – weighted image – bright fluid-filled cysts

Biliary Microhamartomas (aka Von Meyenburg Complexes)

- Definition
 - Malformation of ductal plate leading to “cystically dilated intra- and interlobular bile ducts embedded in a fibrous stroma” in or near portal tracts

(Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier 2010, page 1590)



➤ Clinical

- Associations
 - Congenital hepatic fibrosis
 - Caroli disease
 - Autosomal dominant polycystic kidney disease (ADPKD); aka PCLD, polycystic liver disease
- May undergo malignant degeneration to cholangiocarcinoma

Caroli Disease

Intrauterine malformation of ductal plate

- Dilated ducts associated with
 - Congenital hepatic fibrosis
 - Medullary sponge kidney
 - Choledochal cysts, type V
- Stones form in dilated ducts
 - Cholangitis (~33%)
 - Cholangiocarcinoma (10%)

Please see Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier 2010, Figure 94.10, for Algorithm's to use to Approach the Patient with a Hepatic Mass Lesion without or with associated cirrhosis

Hepatocellular Cancer (HCC)

➤ Epidemiology

- Hepatocellular carcinoma (HCC) is one of the most common malignant tumours worldwide and its incidence is increased in industrialized countries
- M:F 2:1-4:1; increased BMI, androgenic hormones
- 70-90% of HCC occur against the background of hepatic fibrosis grades 3 to 4, or cirrhosis, 1-4% per year (El-Serag HB, Rudolph KL. *Gastroenterology* 2007:2557-2576); the remainder are associated with HBV and hemochromatosis (HCV in Japan)



➤ Causes / risk factors

- 70-90% of HCC occur against the background of hepatic fibrosis grades 3 to 4, or cirrhosis, 1-4% per year (El-Serag HB, Rudolph KL. *Gastroenterology* 2007:2557-2576); the remainder are associated with HBV and hemochromatosis (HCV in Japan)

297. Give 15 risk factors for developing hepatocellular cancer (HCC).

- Patient
 - M:F 2:1 – 4.1
 - Africans > 20 years (HBV⁺)
 - Asian males > 40 years (HBV⁺)
 - Asian females > 50 years (HBV⁺)
 - Family history of HCC
 - Dietary aflatoxin exposure
 - Obesity
 - Tobacco, marijuana smoking
 - Oral contraceptive pill
 - Androgenic hormones
- Without cirrhosis
 - Chronic HBV infection (even without cirrhosis)
 - Chronic HCV infection (Japan; all others, HCV cirrhosis)
 - Hepatic adenoma
 - Hemochromatosis
 - Aflatoxin B1
 - Congenital/familial
 - Previously resected HCC
- With cirrhosis
 - HCV
 - HCV +ALD + obesity (accelerated)
 - EtOH
 - Hemochromatosis- dietary Fe overload in persons of African ancestry; hereditary hemochromatosis
 - PBC
 - Alpha-1-antitrypsin deficiency
 - NASH
 - Autoimmune hepatitis
 - Wilson disease



- Type 1 hereditary tyrosinemia
- Type 1 and type 2 glycogen storage disease
- Hypercitrulinemia
- Ataxia-telangiectasia
- o Medications
 - Exposure to OCAs (oral contraceptives)

Abbreviations: ALD, alcoholic liver disease; FH, family history; NASH, non-alcoholic steatohepatitis; PBC, primary biliary cirrhosis

Adapted from: Gores GJ. *AGA Institute Postgraduate Course Book* 2006: pg. 257.; Lai S-W, et al. *Am J Gastroenterol* 2012; 107: 46-52; and Kew MC. *Sleisenger & Fordtran's Gastrointestinal and Liver Disease: Pathophysiology/Diagnosis/Management* 2006: pg.2014; and 2010: pg. 1575.

Major Etiologies

- o Chronic hepatitis B, C or D
- o Toxins (e.g. alcohol, tobacco, aflatoxins)
- o Hereditary metabolic liver diseases (e.g. hemochromatosis, α 1-antitrypsin deficiency)
- o Autoimmune hepatitis
- o Obesity (males)
- o Diabetes mellitus
- o Nonalcoholic steatohepatitis (NASH)
- o Nonalcoholic fatty liver disease (NAFLD)

Printed with permission: Macmillan Publishers Ltd: Spangenberg et al, *Nat.Rev. Gastroenterol Hepatol* 2009;6: 423-432.

298. Give the **mechanism** for the $\uparrow$ risk of HCC in HBV, even without the presence of cirrhosis.

- There is $\uparrow$ risk of HCC with HBV infection. The mechanisms include:
 - o HBV is incorporated into cellular DNA (in 90% of HCC patients)
 - o Chromosomal insertion is random
 - o HBV is indirectly and directly carcinogenic
 - Cis-activation of cellular genes
 - Transcriptional activation of HBV x protein



- Viral mutations
- Activation of
 - MAP (mitogen-activated protein kinase)
 - JAK/STAT pathways (Janus kinase-signal transducer and activator of transcription)
- Risk of developing HCC
 - HBV ~ 4/100 patient years

299. Give the risk factors for HCC in HBV.

- Patient
 - Presence of cirrhosis
 - Young age of acquisition
 - Asian or African race
 - Male gender
 - Older age of HCV onset and diagnosis
 - Family history of HCC
 - Exposure to aflatoxin, alcohol, and tobacco
 - Long duration of HCV
 - Hepatitis B co-infection with HBV, HIV
 - Heavy alcohol intake (> 50 g/day)
 - Obesity +/- NASH
- Liver
 - Degree of hepatic fibrosis
 - Associated iron overload (hereditary hemochromatosis)
- Infection
 - HCV infection for > 25 years
 - Failure of HCV to respond to IFN (interferon)
 - Absence of previous HCV treatment
 - Co-infection with HCV, HDV, and possibly HIV
 - Active replication of HBV



- Genotype C
- Long duration of active disease

Adapted from: Gores GJ. *AGA Institute Post Graduate course book* 2006: pg. 251-2.

➤ Clinical

- Usually seen in the patient with cirrhosis
- Also occurs in non-cirrhotic
- HBV
- HCV (in Japan)
- Hereditary hemochromatosis
- α -AT deficiency
- NAFLD / NASH
- Hemochromatosis

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Auscultating an arterial bruit in the RUQ of a patient with cirrhosis suggests HCC.

- Give the significance of auscultating a **friction rub**.

A friction rub auscultated in the RUQ of the abdomen suggests

- HCC (hepatocellular cancer)
- Liver metastasis
- Liver abscess

“Doing the best at this moment puts you in the best place for the next moment.”

Oprah Winfrey



300. Give 10 **paraneoplastic syndromes** associated with hepatocellular carcinoma (HCC).

- CNS
 - Neuropathy
- Endocrine
 - Sexual changes- isosexual precocity, gynecomastia, feminization
 - Hypoglycemia
 - Hypercalcemia
 - Thyrotoxicosis
- MSK
 - Carcinoid syndrome
 - Hypertrophic osteoarthropathy
 - Osteoporosis
 - Polymyositis
 - Thrombophlebitis migrans
- CVS
 - Systemic arterial hypertension
- Skin
 - Porphyria
- GI
 - Watery diarrhea syndrome
- Hematology
 - Polycythemia (erythrocytosis)

Adapted from: *Sleisenger and Fordtran's Gastrointestinal and Liver Disease: Pathophysiology/ Diagnosis/ Management*. 9th edition, 2010, Table 94.2: page 1571.

“Happiness cannot be traveled to, owned, earned,
or worn. It is the spiritual experience of living every
minute with love, grace and gratitude.”

Denis Waitley



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Paraneoplastic syndromes are common in HCC.

- Give the name of the **substances secreted** by the HCC tumor, which result in the following 3 paraneoplastic syndromes.

Syndrome	HCC-secreted substance
○ Hypoglycemia	– Pre-IGF II (insulin-like growth factor)
○ Polycythemia	– Erythropoietin (or erythropoietin-like substance)
○ Hypercalcemia	– PTHrP (parathyroid hormone related peptide)

➤ Please see

- Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. *Saunders/Elsevier* 2010, Table 94.4, Risk Factors for Hepatocellular Carcinoma
- Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. *Saunders/Elsevier* 2010, Table 94.6, Treatment Option for Hepatocellular Carcinoma
- AASLD practice guideline (Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. *Saunders/Elsevier* 2010, Table 94.7), High-risk Groups for Whom Surveillance for Hepatocellular Carcinoma is Recommended.

301. Give the **screening for HCC**.

- Hepatitis B carriers
 - African >20 years
 - Asian males >40
 - Asian females >50
 - Family history of HCC
 - All patients with cirrhosis
- Non HBV non-cirrhosis
 - Hepatitis C (in Japan)
 - Hereditary hemochromatosis
 - Alpha 1 antitrypsin deficiency
 - NASH
 - Autoimmune hepatitis

Adapted from: El-serag H.B. 2009 ACG Annual Postgraduate Course: 39-43.



➤ Laboratory

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- Give the circumstances when an elevated AFP (alfa fetoprotein) > 200 mg/mL is considered by AASLD guidelines to be diagnostic of HCC.
 - In the presence of cirrhosis or a mass in the liver (especially when > 2 cm)
- In the presence of a liver mass in a person with cirrhosis and an AFP > 500 mg/mL, HCC is likely
 - Hepatic regenerative activity ↑AFP
- Only 1/3 of HCC patients have AFP > 100 mg/ml, but values > 200 mg/ml are highly specific for HCC, 10.9 mg/ml, sensitivity 66% (Marrero JA, et al. *Gastroenterology* 2009.)
- Diagnosis in a cirrhotic is usually made by diagnostic imaging, without liver biopsy (risk of seeding of tumor)
- A non-invasive diagnosis of HCC in a cirrhotic is suggested by
 - Nodule > 2 cm
 - AFP > 400 ng/mL
 - Diagnostic imaging
 - 1 of 2 tests, if AFP > 400 ng/mL
 - 2 of 2 tests, regardless of AFP

➤ Pathology

- Risk of seeding from tumour biopsy ~ 3%

* Note: Not necessary to biopsy liver to diagnose HCC



302. Give the pathology of hepatocellular (HCC).

- Gross
 - Nodules
 - Large circumscribed mass
 - Diffuse infiltration
- Microscopic
 - Well-differentiated
 - Trabecular form (thick trabeculae)
 - Hepatocytes – polygonal
 - Cytoplasm - ↓ eosinophilia
 - Nuclei
 - Large
 - Hyperdramatic
 - Nucleoli – prominent
 - Bile production
 - Acinar (pseudoglandular) form
 - Gland-like structures around a bile canaliculus
 - Bile canaliculus contains bile
 - Moderately differentiated
 - Pleomorphic, multinucleated giant cells
 - Cell nests
 - Central ischemic necrosis
 - Little bile connective tissue
 - Differentiated
 - Pleomorphic cells and nuclei
 - Bizz are giant cells
 - Globular hyaline
 - Mallory hyaline
- Prognosis / risk stratification / staging



303. Give the prognostic factors in HCC.

- Patient
 - ECOG classification
 - Presence of symptoms
- Liver function
 - Child-Pugh class
 - Serum bilirubin
 - Albumin levels
 - Presence/absence of portal hypertension
- Tumour status
 - Number and size of nodules
 - Presence/absence of macrovascular invasion
 - Presence/absence of extrahepatic spread

Abbreviation: ECOG, Eastern Cooperative Oncology Group.

SO YOU WANT TO BE A HEPATOLOGIST!

- In approximately what proportion of patients with HCC or pancreatic cancer in whom investigations suggest that the primary lesion is resectable will the tumor turn out to be non-resectable as defined by diagnostic laparoscopy and laparoscopic ultrasound?
 - About one third of patient's with HCC or pancreatic cancer will have their respectability status down-graded to non-resectable by diagnostic laparoscopy and laparoscopic ultrasonography.



Useful background: The **Okuda staging system of HCC**.

Criterion	Cut-off
○ Tumour size	>50% (largest cross-sectional area of tumour to largest cross-sectional area of liver) = positive <50% = negative
○ Ascites	Clinically detectable = positive Undetectable = negative
○ Serum albumin	<3g/dL = positive >3g/dL = negative
○ Serum bilirubin	<3g/dL = positive >3g/dL = negative
○ Stage	
- I	No positive criterion
- II	positive criteria
- III	Three positive criteria

Printed with permission: Nguyen MH, and Keeffe EB. *Best Practice & Research Clinical Gastroenterology* 2005;19(1):164.

Accurate staging at the time of diagnosis, based on the Barcelona Clinic Liver Cancer classification (BCLC), is central to the choice of the appropriate therapeutic strategy

304. Give the components of **BCLC** staging classification for HCC.

- Tumor size and spread
- Patient performance status
- Child-Pugh class

See Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. *Saunders/Elsevier* 2010, Figure 94.4, page 1576.



Fibrolamellar HCC

➤ Pathology

- Hepatocytes
 - Large
 - Eosinophilic
- Cytoplasm
 - Large mitochondria
 - Hyaline bodies
- Fibrous stroma
 - Forming trabeculae or nodules
- Stain for cytokeratin 19 to determine if the HCC is the even more aggressive progenitor cell variety arising from stem cells near the canals of Hering

305. Give the non-pathological characteristics with differentiate FLM (fibrolamellae HCC) from HCC.

- Younger persons
- Not associated with
 - Cirrhosis
 - HBV, HCV
- No AFP secreted
- Better prognosis

"We learn something from everyone who passes through our lives. Some lessons are painful, some are painless... but, all are priceless."

Unknown



306. Give the diagnostic workup of a liver mass in a patient with chronic liver disease.

➤ Mass <1 cm	○ Diagnosis ○ Follow up	- Low likelihood of being HCC, therefore no specific diagnostic tests - Repeat imaging study every 3 months - If no growth in 1-2 years, no HCC; continue screening every 6 months - If growth, treat as HCC	
➤ Mass 1-2 cm	○ Diagnosis ○ Follow up after biopsy	- Two dynamic imaging studies (US, CT scan, or MRI) - Biopsy confirms HCC - Non diagnostic biopsy	• Both with typical vascular pattern • One typical and the other atypical • Both atypical • Treat as HCC • Repeat imaging study every 3 months: • If no growth in 1-2 years- no HCC • If growth, treat as HCC ○ Treat as HCC ○ Consider biopsy of mass ○ Consider biopsy of mass vs. close follow up
➤ Mass >2 cm	○ Diagnosis ○ Follow up after biopsy	- One dynamic imaging study (US, CT scan, or MRI) - Biopsy confirms HCC ○ Non diagnostic biopsy	• Typical vascular pattern • Atypical vascular pattern • Treat as HCC • Repeat imaging study every 3 months: ○ If no growth in 1-2 years- no HCC ○ If growth, treat as HCC ○ Treat as HCC ○ Biopsy of mass



- The contrast enhanced imaging studies of computed tomography (CT) and magnetic resonance imaging (MRI) use the unique dynamic radiological behaviour of hepatocellular carcinoma (hypervascular on the arterial phase and washout on the delayed venous phase).
- The sequence of events needed to make the radiological diagnosis depends on the size.

Abbreviations: CT, computerized tomography; HCC, hepatocellular carcinoma; MRI, magnetic resonance imaging; US, ultrasound

Printed with permission: Garcia Tsao, et al. *The American Journal of Gastroenterology* 2009; 104:1822.

307. Give the diagnostic imaging characteristics on CT/MRI/PET scan/nuclear medicine of hemangioma, focal nodular hyperplasia (FNH), adenoma, HCC, and metastases.

- Hemangioma – nodular, no washout at periphery; RBC scan, triphasic CT scan (arterial phase); MRI
- Focal nodular hyperplasia
 - Central vessel
 - Stellate central scar
 - Homogenous
- Adenoma
 - Heterogeneous
 - Hemorrhage
 - Fat
 - Necrosis
 - Impaired arteriole (no bile duct) “feeding” lesion
- HCC
 - Tumour thrombus in vessel
 - Fat
 - Cirrhosis
 - Capsule heterogeneous
 - Bile production
 - Extrahepatic involvement
- Metastases
 - Washout at periphery
 - Ring enhancing



- Fat
- Blood
- Calcification
- New or increasing size – may be hyper/hypo-vascular

Adapted from: Hussain SM, and Semelka RC. *Magn Reson Imaging Clin N Am* 2005;13(2):255-75.

308. Give the **imaging criteria** applied for confirming HCC in patients with cirrhosis and a nodule detected by ultrasound.

➤ Ultrasound

- Lesion has nodular configuration
- Lesion is at least 1 cm in longest diameter*
- Lesion shows arterial hypervascularization:
 - Hyper enhanced nodule in the arterial phase by two imaging techniques**
 - Hyper enhanced nodule in the arterial phase and as hypo enhanced nodule in the portal venous or delayed phase by one imaging technique**

➤ CT

- Arterial enhancement (hypervascular, supplied by hepatic artery) and washout, for HCC, sensitivity is 90% and specificity is 95%

➤ MRI

- Similar performance characteristics as CT, but size of HCC is a factor, with accuracy of > 90% for > 20 mm lesion seen on MRI, but 30% for lesion < 20 mm
- Biopsy under radiological guidance

Test	Sensitivity	Specificity
US	90%	91%
CT	92%	98%

- For hyper-enhanced nodule > 1 cm, suspect HCC

*apply to lesions emerged during Us surveillance. For lesions detected at first imaging examination, lesion diameter should be at least 2 cm to allow non-invasive diagnosis of HCC.

**imaging techniques include: contrast-enhanced US, contrast-enhanced spiral CT, and gadolinium enhanced MRI.

Source: El-serag H.B. 2009 ACG Annual Postgraduate Course: 39-43.



- Abdominal ultrasound
 - In general terms, abdominal ultrasound has a sensitivity of 48% and a specificity of 97% for detection of HCC.

Algorithm for mass / nodule in cirrhotic liver on abdominal ultrasound (US) in persons at risk for HCC

Diameter	Follow-up
< 1 cm	US every 4 months for 1 year, then every 6 months longterm
> 1 cm	4-phase CT / dynamic contrast enhanced MRI

➤ Screening / surveillance

309. Give the category of patients with chronic liver disease who are recommended for surveillance for HCC.

- Non-cirrhotic
 - HBV carriers with
 - Active hepatitis
 - Family history of HCC
 - HCV chronic hepatitis plus fibrosis
- Cirrhotic
 - C-P A and B
 - C-P C awaiting liver transplantation

Abbreviation: C-P, Child-Pugh

310. Give the risk of cirrhosis, hepatocellular carcinoma (HCC) and mortality in hepatitis B and hepatitis C virus (HBV/HCV) monoinfected and coinfecting patients

	Cirrhosis ¹	HCC (OR) ²	Mortality (SMR) ³
HBV monoinfection	~ 22%	16-23	1.4-5.3
HCV monoinfection	~ 30%	8-17	2.4-3.1
HBV/HCV coinfection	~ 50%	36-165	5.6-49

Abbreviations: HBV, hepatitis B; HCC, hepatocellular carcinoma; HCV, hepatitis C; OR, odds ratio; SMR, standard mortality ratio

¹Zarski et al, 1998

²Shi et al, 2005 Donato et al, 1998

³Amin et al, 2006 Di Marco et al, 1999

Printed with permission: Wurstthorn, et al. *Best Practice Res Clin Gastroenterol* 2008;22:1063-1079.



311. Give 3 precursor lesions of HCC (hepatocellular cancer) in the patient with hereditary hemochromatosis.
- Males with iron overload and advanced fibrosis
 - Dysplastic lesions
 - Proliferative lesions
 - Increased number of iron free foci (IFF, >50% at risk to develop HCC)

Adapted from: Hytioglou P, et al. *Gastroenterol Clin North Am* 2007;36(4):867-87.

SO YOU WANT TO BE A HEPATOLOGIST!

Multiphase, dynamic, helical CT is the imaging technique of choice for the diagnosis of HCC. The most helpful features are enhanced arterial phase in the involved area, washout (loss of central nodule enhancement composed with uninvolved liver), and enhancement of the capsule in the porto-venous and delayed phase. When the lesion is > 2 cm these diagnostic imaging changes.

- Give the reasons why the classical CT changes of HCC may disappear as the HCC enlarges
 - Arterial enhancement (neoangiogenesis causing hypervascularity)
 - Shift of blood from primarily portal artery

➤ Diagnostic imaging

312. Give the differential of **hypervascularity** on ultrasound, in addition to HCC.
- Arterial portal shunts
 - Atypical hemangiomas
 - Aberrant venous drainage
 - Dysplastic nodules
 - Confluent fibrosis
 - The most sensitive and specific imaging technique for the diagnosis of HCC is Gad-MR (gadolinium magnetic resonance). Other methods include contrast-enhanced ultrasonography, helical-computed tomography, and superparamagnetic iron oxide magnetic resonance (Lesni et al., *AJC* 2010; 105: 599-609).



- Hepatic nodules smaller than 2 cm in diameter may still contain a focus of HCC.

Abbreviation: LT, liver transplantation; RFA, radiofrequency ablation; TACE, transarterial chemoembolization; TACI, transarterial chemotherapy infusion

- Non-invasive criteria have been established by American and European groups (AASLD and EASL), and provide a similar sensitivity of about 80% in making a diagnosis of what turns out to be HCC.
- CT
 - ↓ HA, PV supply
 - Arterial neovascularization
 - Venous washout
- Hypervascularization in the arterial phase, followed by washout in the venous phase, suggestive of malignancy.
- Dynamic MRI
 - Dynamic MRI using gadolinium contrast agents may be used in association with dynamic CT if the hepatic mass is 1 to 2 cm in size. The findings on the arterial phase of high signal intensity on T2-weighted images, on the venous and delayed phases finding central washout if contrast and capsular enhancement, have a sensitivity and specificity for HCC of 81% and 85%.
- MRI super-paramagnetic MRI
 - Iron oxide taken up by Kupffer cells, which are missing in HCC
 - Slows up as dark HCC on this test
 - Art phase gives sensitivity
 - Venous phase gives specificity

313. Give 4 non-histological diagnostic criteria for HCC (hepatocellular cancer).

- Hepatic mass on ultrasound in cirrhotic
- Focal lesion > 2 cm with evidence of cirrhosis (if <2 cm, on 2 imaging modalities – CT angiogram Arterial hypervascularization and venous washout MRI (contrast enhanced ultrasound; MRI – triphasic (hyper T₂, 150-T₁))



- AFP > 200 ng/ml (normal AFP does not R/o HCC)
- Sulphur colloid scan – old (Kupffer cells positive in FNH)
- Non-cirrhotic HBV, HCV (Japan), hemochromatosis, α AT deficiency

Adapted from: Talwalkar JA, and Gores GJ. *Gastroenterology* 2004;127(5 Suppl 1):S126-32.

- Every 6 months AFP (alpha-fetoprotein) and abdominal ultrasound over 5 years improves survival from HCC in HBV-positive patients in China (42-5). Most of the detected HCC in the screened group were detected at an early stage; with 3 year survival rates after HCC resection of 53% in the screened group versus none in the non-screened group
- Improved survival from HCC screening depends of course on the availability of effective therapy for the early detected lesions
- HCC screening in persons awaiting liver transplantation is cost-effective

Abbreviation: AFP, alpha-fetoprotein; HCC, hepatocellular cancer

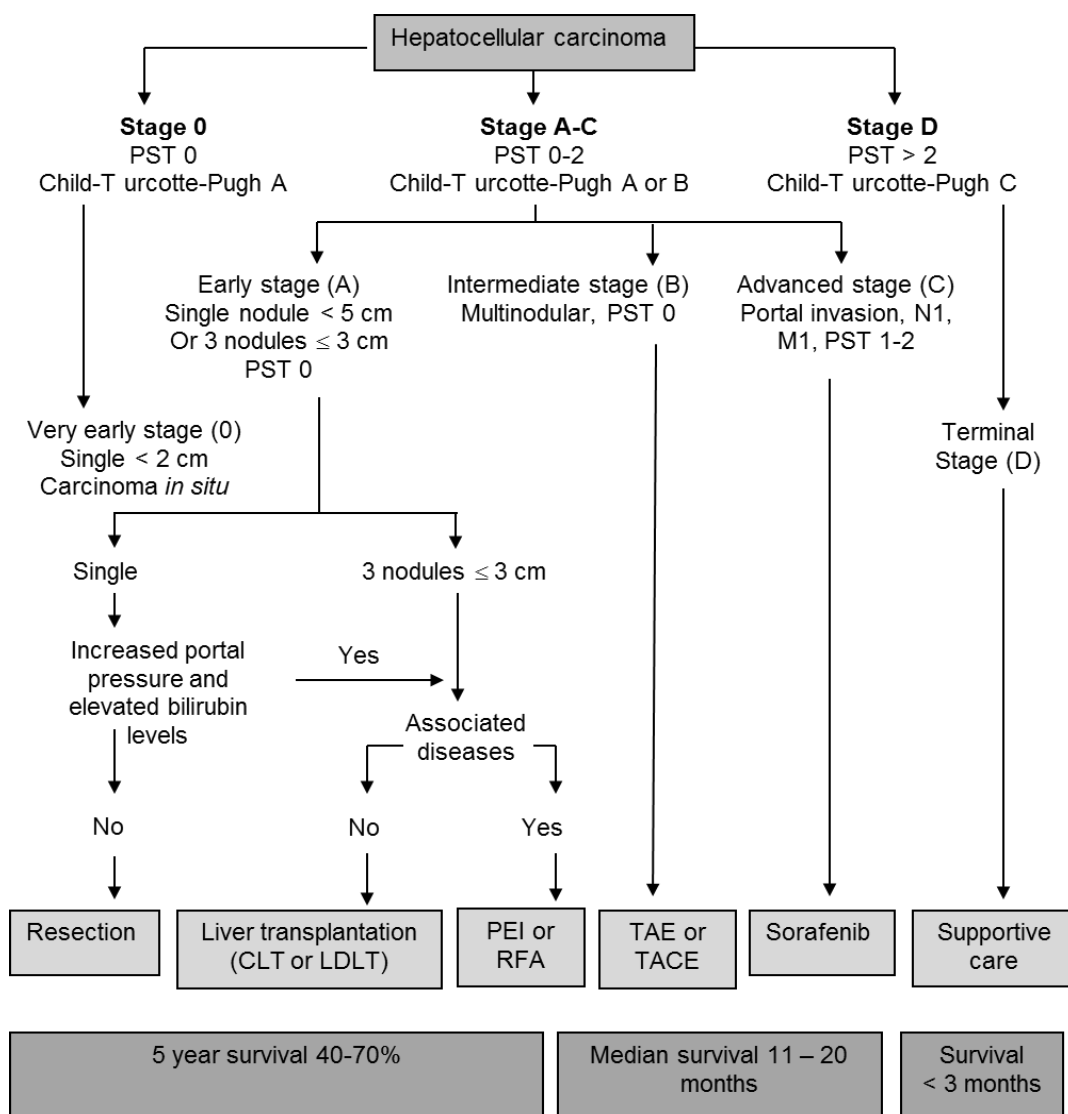
➤ Treatment

Reminder

- Accurate staging at the time of diagnosis, based on the Barcelona Clinic Liver Cancer classification, is central to the choice of the appropriate therapeutic strategy
- Accurate staging at the time of diagnosis, based on the Barcelona Clinic Liver Cancer classification, is central to the choice of the appropriate therapeutic strategy
- Therapeutic options for advanced HCC have improved considerably during the past few years and now include targeted therapy with sorafenib, an inhibitor of multiple tyrosine kinases
- Novel therapeutic strategies are needed that will further improve survival of patients with HCC, especially for those who present with advanced disease at the time of diagnosis
- Clinical trials should follow guidelines that define meaningful primary and secondary end points and should be coordinated by centers with expertise in the care of patients with HCC
- Sorafenib, a mixed kinase inhibitor, prolongs survival in persons with metastatic HCC



314. **Algorithm** for staging and treating patients diagnosed as having hepatocellular carcinoma. This algorithm is based on the Barcelona Clinic Liver Cancer (BCLC) guidelines.



Abbreviations: CLT, cadaveric liver transplantation; LDLT, live donor liver transplantation; PEI, percutaneous ethanol injection; PST, performance status test; RFA, radiofrequency ablation; TACE; transarterial chemoembolization; TAE, transarterial embolization.

Printed by permission: Cabibbo et al. *Nature Clinical Practice Gastroenterology and Hepatology* 2009;6(3): 159-169, Figure 1, page 160. and Bruix J, Sherman M. Management of hepatocellular carcinoma: An update. *Hepatology*. 2011; 53(3): Figure 2, 1020–1022.



SO YOU WANT TO BE A GASTROENTEROLOGIST!

- Give the management of the “**post-embolization syndrome**” (abdominal pain, nausea / vomiting, fever) associated with hepatic arterial embolization and chemoembolization for hepatic tumor (e.g. HCC, metastatic GIST).
 - Just provide supportive care.

315. Give 6 **treatment options** for the patient with HCC.

- Staging, MRI – Barcelona criteria, Child’s stage
- Surgical resection
- Partial hepatectomy (HBV) satisfying Milan criteria:
 - 1 tumour, < 5 cm
 - 3 tumours, each < 3 cm
 - Edmonton volume criteria <115 mm³
 - no distant metastasis
 - no portal vein distension
- Liver transplantation (LT)
- Chemotherapy: po, iv, transarterial (TA) chemoembolization (TACE), TA chemotherapy infusion (TACI); drug eluting beads
- Percutaneous hepatic injection: ethanol or acetic acid injection
- Energy-mediated ablation: cryoablation, microwave or radiofrequency ablation (RFA), for < 2 cms potentially curative
- Radiotherapy: internal, external
- Palliative care
- Investigational: somatostatin, immune modulation, gene therapy, PDT
- Mixed tyrosine kinase inhibitors (sorafenib)

Adapted from: Nguyen MH, and Keeffe EB. *Best Practice & Research Clinical Gastroenterology* 2005;19(1): pg 164.; and Tranberg KG. *Best Practice & Research Clinical Gastroenterology* 2004;18(1): 127.



316. Compare and contrast the prevention and treatment of HCC in persons with HBV and HCV infection.

	HBV	HCV
○ New infection	– Neonatal vaccination	▪ General infection control
○ Existing infection	– Antiviral therapy (suppression)	▪ Antiviral therapy (eradication)
	– Nucleos (t) ide analogues	▪ Interferon plus ribavirin; role of proteinase inhibitors under study
○ Treatment	– Early diagnosis and curative treatment	
○ Prevent recurrence	– Transplantation	
	– Antiviral therapy (?)	
	– Molecular targeting drug	

Abbreviations: HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus

Printed with permission: Masuzaki, et al. *Best Prac Res Clin Gastroenterol* 2008:1137-1151.

317. Give the likely explanation for the severe and unfortunate adverse effect of TACE in a person with a portal vein (PV) thrombosis.

- The TACE catheter is inserted into the HA (hepatic artery) which is the main source of blood supply to the liver, along with the PV (portal vein).
- If the patient had a PV thrombosis associated with the HCC, the only residual blood supply to the liver is the HA, in which flow may have been partially compromised by TACE.



318. Give the management strategy of HCC based on CTP class, size and performance status (PS)

➤ CTP A, PS-0	Single HCC <2cm	HVPG <10mm Hg and bilirubin < 1.5 mg/dl	Surgical resection
		Varices/collaterals or HVPG >10 mm Hg or bilirubin >1.5mg/dl	Live transplant evaluation RFA/PEI
➤ CTP A- B, PS, 0-2	Single HCC 2-5 cm	HVPG <10mm Hg and bilirubin <1.5 mg/dl	Surgical resection
		Varices/collaterals or HVPG	Liver transplant evaluation
		>10 mm Hg or bilirubin >1.5mg/dl	RFA/PEI
	2 or 3 HCC masses <3 cm (the largest)		Liver transplant evaluation
	Intermediate stage (multinodular, PS,O)		Radiofrequency ablation
	Advanced stage (portal invasion, metastases)		Transarterial chemoembolization
			Sorafenib
➤ CTP C, PS>2	Terminal stage		Symptomatic treatment

Abbreviations: CTP, Child-Turcotte- Pugh; HCC, hepatocellular carcinoma; HVPG, hepatic venous pressure gradient; PEI, percutaneous ethanol injection; PS, performance status; RFA, radiofrequency ablation.

Printed with permission: Garcia Tsao et al. *Am J Gastroenterol* 2009; 104:1802-1829.

- The BCLC staging system for HCC. M, metastasis classification; N, node classification; PS, performance status; RFA, radiofrequency ablation; TACE, transarterial chemoembolization.
- A cirrhotic patient with HCC has good hepatic reserve, and TACE (transarterial chemoembolization) is undertaken for downstaging of the tumor prior to liver transplantation (LT), as well as a bridge to LT. Unfortunately, hepatic decompensation may occur rapidly after TACE.



Cholangiocarcinoma

➤ Demography

- Prevalence in North America, $1/10^5$
- Cholangiocarcinoma is the second most common hepatic malignant tumour.

➤ Causes / associations

319. Give 5 factors / associations which increase the risk of cholangiocarcinoma.

- Infection
 - HCV-associated cirrhosis
 - *Clonorchis viverrini* and *sinensis*
- Developmental
 - Caroli disease
 - Choledochal cyst
- Cholelithiasis, intrahepatic
 - PSC (primary sclerosing cholangitis)
 - Caroli disease
 - Choledochal cyst
 - Thorotrast contrast dye

➤ Laboratory tests

320. Give 5 tests used to diagnose cholangiocarcinoma.

- Diagnosis
 - Serology CA 19-9, CEA, CA 19-9 + CEA, CA-125
- Tumor marker CA 19-9
 - False positives
 - Cancer
 - Stomach
 - Pancreas
 - Colon
 - Gynecologic
 - Acute bacterial cholangitis
 - False negative
 - Lewis blood group-negative
 - With PSC – CA 19-9 > 129 U/ml; sensitivity 79%; specificity 98%
 - Without PSCs > 100 U/ml; sensitivity, 53%; specificity 89%



CA 19-19	Sensitivity	NPV	Specificity
○ CA 19-9, biliary obstruction	53%	72 to 92%	
– Without PSC	38% to 89%		50% to 98%
– With PSC			

➤ Pathology

- Few cells (paucicellular)
- Brush cytology
- FNA (fine-needle aspiration)
- Desmoplastic reaction
- FISH (fluorescence hybridization)
- Cytology
 - Acinar or tubular structures
 - Absent bile secretion
 - Desmoplastic reaction
 - Prominent colonization of stroma
 - May be difficult to distinguish from metastatic adenocarcinoma
- Subtypes
 - Intrahepatic
 - Extrahepatic
 - Hilar (Klatskin tumor)
 - Distal bile duct
 - Four types, by bismuth - Corlette Classification (Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease, 9th Edition. Saunders / Elsevier, Philadelphia, 2010, Table 69.3, page 1173 for details of Diagnostic Criteria for Cholangiocarcinoma.
- Perihilar cholangiocarcinoma is extrahepatic in location, but the ICD classification considers that this an intrahepatic tumor

➤ Diagnostic Imaging

- Locations
 - Hepatic bifurcation (Klatskin tumour)
 - Distal CBD
 - Intrahepatic (5-15%)



- MRI
 - MRI “... is currently the imaging technique for cholangiocarcinoma” (Feldman M., et al. Sleisenger and Fordtran’s Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier, Philadelphia, 2010, page 1174).
 - IDUS high frequency intraductal ultrasound
 - CT/ PET; sensitivity / specificity; intrahepatic, 93% and 80%, but extrahepatic, 53% and 33%, respectively.
- MRCP –
 - T1 –weighted, hypodense lesion
 - T2 –weighted, intense lesion
 - Variable fibrosis and necrosis
 - Atrophy
 - Capsular retraction
 - Biliary duct dilation
 - Hypovascular (progressive, delayed hyperenhancement)
- Endoscopy
 - ERCP + cytology
 - Choledochoenteroscopy
 - ERCP + choledoscopy (for dominant stricture; sensitivity 92%)

Note: See Feldman M., et al. Sleisenger and Fordtran’s Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier, Philadelphia, 2010, Table 69.3, page 1173 for details of Diagnostic Criteria for Cholangiocarcinoma.

- Cytology

	Sensitivity
– Cytology	30%
– Cytology, brushings and biopsies	40% to 70%

➤ Treatment

321. Give the 4 criteria for surgical resection of cholangiocarcinoma.

- No extrahepatic metastases
- No encasement or invasion of
- No involvement of both segmental bile duct
- No contralateral lobular atrophy



- Prognosis
 - When not a surgical candidate, survival rate
 - 1 year 28%
 - 5 year 5%
 - 5 year 29% to 36%
 - Liver transplantation combined with radiation, brachytherapy and chemosensitization
 - 5 year 82% survival rate

Liver Transplantation (LT)

- Prognosis (survival rate [SR])
 - 92% 5 yr SR
 - 80% 10 yr SR

322. Give the prognostic significance of a person requiring hemodialysis before LT.

- "...return of adequate renal function is unlikely after transplantation of dialysis has been required for more than one month prior to liver transplantation" (Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier 2010, page 1597); combined liver-kidney transplantation may need to be considered.

- Clinical
 - Causes of death Post-LT
 - "natural" causes
 - Malignancy 21% } - 2X ↑ Risk non-skin solid organ cancers
- 30X ↑ lymphoproliferative disorders
 - Infection
 - Recurrent liver disease
 - "de-novo malignancy post-liver transplant (L-Tx)"



➤ Assessment

The **UNOS listing criteria** for status 1, 2A, 2B and 3 for liver transplantation.

Status 1

- Fulminant hepatic failure. Onset within 8 weeks of initial symptoms and one of the following:
 - Stage 2 encephalopathy
 - Bilirubin > 15 mg/dl
 - INR > 2.5
 - Hypoglycemia (glucose level < 50 mg/dl)
- Primary non-function of graft transplanted within 7 days
- Hepatic artery thrombosis occurring within 7 days of transplantation
- Acute decompensated Wilson disease

Status 2A

- Patient with chronic liver failure and a Child-Pugh score ≥ 10 , in the critical care unit, with a life expectancy without a liver transplant of less than 7 days, with at least one of the following criteria:
 - Unresponsiveness active variceal hemorrhage with failure or contraindication of surgical or transjugular intra-hepatic shunt
 - Hepatorenal syndrome
 - Refractory ascites/hepatorenal syndrome (hydrothorax)
 - Stage 3-4 encephalopathy unresponsive to therapy
- Contraindications to status 2A listing:
 - Extrahepatic sepsis unresponsive to antimicrobial therapy
 - Requirement for high dose or two or more pressor agents to maintain an adequate blood pressure
 - Severe, irreversible multi-organ failure

Status 2B

- Patients with chronic liver disease and a Child-Pugh score ≥ 10 , or ≥ 7 and one or more of the following clinical considerations:
 - Unresponsive variceal hemorrhage
 - Hepatorenal syndrome
 - Spontaneous bacterial peritonitis
 - Refractory ascites/hepatorenal syndrome (hydrothorax)



- Liver transplant candidates with hepatocellular carcinoma can be registered as status 2B if they meet the following criteria:
 - Thorough assessment has excluded metastatic disease
 - Recipient has one nodule ≤ 5 cm or three or fewer nodules all ≤ 3 cm
 - Patient is not a resection candidate

Status 3

- Patients with chronic liver disease and a Child-Pugh score ≥ 7

Adapted from: United Network Organ Sharing. *UNOS policy* 3.6 June 23, 2009.

➤ Indications

323. Give the indications for liver transplantation.

- Acute liver failure (ALF; fulminant hepatic failure; King's College criteria)
- Complications of cirrhosis
 - Ascites
 - Encephalopathy
 - Synthetic dysfunction
 - Liver cancer
 - Refractory variceal hemorrhage
 - Chronic gastrointestinal blood loss due to portal hypertensive gastropathy
 - INR
 - Na
 - HCC
 - DILI
 - Cr
 - MELD >13
 - PSE
 - Ascites
 - Hepatorenal syndrome
 - Vascular
 - Weber Rendir (intractable bleed)
 - GAVE; Budd-Chiari
- Systemic complications of chronic liver disease
 - Hepatopulmonary syndrome
 - Portopulmonary hypertension



- Liver-based metabolic conditions causing systemic disease, and which may also cause liver disease
 - Primary oxaluria
 - Familial Amyloidosis
- Inherited liver diseases
 - α_1 -antitrypsin deficiency
 - Wilson disease
 - Urea cycle enzyme deficiencies
 - Glycogen storage disease
 - Tyrosemia

Adapted from: Lilly LB, Girgrah N, and Levy GA. *First Principles of Gastroenterology* 2005: pg. 634.

SO YOU WANT TO BE A HEPATOLOGIST!

There are many indications for liver transplantation (LT) (Please see, Feldman M., et al. *Sleisenger and Fordtran's Gastrointestinal and Liver Disease*. 9th Edition. Saunders/Elsevier 2010, Table 95.1, page 1594, Indications for Liver Transplantation). In adults,

- In adults, give the commonest diseases of the liver for which transplantation is performed include
 - HBC, 33%
 - Cholestatic disorders, 14%
 - ALD (alcoholic liver disease), 12%
 - NASH, 9%
 - HCC, 6%
 - HBV, 4%

Adapted from: Martin P, et al. *Sleisenger & Fordtran's gastrointestinal and liver disease: Pathophysiology/Diagnosis/Management* 2006: pg. 2037; and 2010, pg. 1594.

- Give the major indications for liver transplant (LT) in children.
 - Biliary atresia
 - Failed portoenterostomy (Kasai procedure) for biliary atresia.



➤ **Contraindications**

○ **Definition of the word “Contraindications”**

- Definition: Absolute contraindication – “...a clinical circumstance in which the likelihood of a successful outcome is so remote that liver transplantation should not be offered (Feldman M., et al. Sleisenger and Fordtran’s Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier 2010, page 1596),
- While there are many “absolute” contraindications to LT (please see (Feldman M., et al. Sleisenger and Fordtran’s Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier 2010, Table 95.2, page 1596 and Table 95.4, page 1600), there are many “shades of grey”

Please see, Feldman M., et al. Sleisenger and Fordtran’s Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier 2010, Table 95.4, page 1600, regarding Factors Associated with Severe Hepatitis C Virus Recurrence Following Liver Transplantation.

324. Give 15 possible “relative” **contraindications** to liver transplantation.

○ **Patient**

- Ongoing alcohol or drug abuse
- Non-adherence
- Lack of social support
- Serious underlying symptomatic illness
- Advanced cardio-pulmonary disease
- Sepsis
- Marked psychiatric impairment
- HIV/ AIDS
- Diabetes mellitus
- Advanced age
- Obesity
- Multi-organ failure
- Increased intracranial pressure
- Jehovah Witness
- Non-adherence



- Anatomy
 - Metastatic cancer
 - Anatomical abnormalities
 - PV thrombosis (large size)
 - Outside Milan criteria for HCC (1 lesion <5 cm, 3 lesions <3 cm)
 - Cholangiocarcinoma
- Liver
 - Mild liver disease (Child <7, or MELD <9)
- Co-morbidity
 - Pulmonary hypertension
 - Right heart dysfunction
 - Extrahepatic cancer

Adapted from: Hay J. *Mayo Clinic Gastroenterology and Hepatology Board Review* 2008: pg. 433.

325. Give 4 medical methods introduced recently to **increase the availability** or to extend the fair allocation of livers for transplantation.

- MELD (Model for End-Stage Liver Disease)
 - Equitable organ allocation
- MELD score and retransplantation
 - The MELD score has helped to equitably allocate donor livers for transplantation, with the sick patients with higher MELD scores moving to “...the head of the line [waiting list]”. When patients undergo retransplantation, then probability of survival is about 20% lower than their outcome expected following the initial transplantation.
 - Maximal utility is achieved with MELD score for

HCV	21
Non-HCV	24
- Modified MELD
 - Hyponatremia (dilutional)
 - HCC
 - HPC (hepatopulmonary syndrome)
 - Polycystic disease
- LDLT (liver-donor liver transplantation)
- Split decreased-donor grafts
- Marginal / extended criteria grafts



326. Outline the **protocol for evaluation** of potential living-related liver donors.

- Stage 1
 - Complete history and physical examination
 - Laboratory blood tests: liver biochemical test, blood chemistry, hematology, coagulation profile, urinalysis, alpha-fetoprotein, carcinoembryonic antigen, and serologic tests for hepatitis A, B, and C, cytomegalovirus, Epstein-Barr virus, and human immunodeficiency virus
 - Stage 2
 - Imaging studies: abdominal ultrasound examination, chest x-ray
 - Complete psychiatric and social evaluation
 - Imaging studies: computed tomography scan of the abdomen
 - Other studies: pulmonary function tests, echocardiography
 - Stage 3
 - Histology: liver biopsy
 - Imaging studies: celiac and superior mesenteric angiography with portal phase
 - Stage 4
 - Imaging studies: magnetic resonance cholangiogram Informed consent
- Printed with permission: Ghobrial RM, et al. *Clin Liver Dis* 2000; 4: 553.

➤ Complications

327. Give 20 early and/or late **non-pharmaceutical complications** arising after liver transplantation.

- Surgery-related
 - Non-specific
 - Cannot get off of ventilator
 - Dehiscence
 - Ileus
 - DVT
 - Atelectasis
- Metabolic
 - Hypertension
 - Hypercholesterolemia
 - Diabetes mellitus
 - Obesity



- Sexual dysfunction
- Abdominal bleeding
 - Anastomoses (immediate)
 - Site of implantation (immediate)
- Vascular complications
 - Suprahepatic/infrahepatic vena caval obstruction (immediate)
 - Hepatic artery thrombosis (early)
 - Portal vein thrombosis (early)
 - Hepatic artery stenosis (late)
- Biliary complications
 - T-tube insertion (early)
 - Anastomosis (early)
 - Stenosis of papilla Vateri (early)
 - T-tube removal (late)
 - Anastomosis, extrahepatic (late)
 - Multiple strictures, intra-hepatic, abscesses
- Renal failure (adverse effects of treatment)
- Vascular
 - Coronary artery disease (dyslipoproteinemia)
 - Cerebrovascular
 - Peripheral vascular
- CNS/PNS
 - Depression
 - Neuropathy
 - Seizures
- Malignancy
 - Lymphoma
 - EBV-PTLD (Ebstein-Barr virus – post transplant lymphoproliferative disorder)
 - Pre-existing malignancies (within 5 years)
 - Acquired donor malignancy



- Increased risk of all malignancies
 - Skin cancers (non melanoma)
 - Non-skin solid tumors
 - Head and neck
 - Esophagus
 - Kaposi sarcoma
 - Cervical (HPV)
 - Prostate
 - Lung
 - Breast
 - Colon
- Infections
 - Viral (HSV, CMV, EBV)
 - Bacterial (lines, wound)
 - Fungal (PCP, Candida - catheters)
- Drug reactions
- 1° graft failure
- Rejection
- Recurrence of disease
- Death

Adapted from: Mueller AR, Platz KP, and Kremer B. *Best Practice & Research Clinical Gastroenterology* 2004;18(5): 882

"If opportunity doesn't knock, build a door."

Milton Berle



➤ Non-GI adverse effects of immune suppression

328. Give the most common **adverse effects** of immune-suppressive drugs frequently used after orthotopic liver transplantation.

Adverse effect	Cyclosporin	Tacrolimus	Glucocorticoids	Azathioprine	Mycophenolate Mofetil	mTOR Inhibitors
Alopecia	-	+	-	+	+	-
Arterial hypertension	+++	++	+++	-	-	+
Bone marrow suppression	+	+	-	+++	+++	++
Dermatitis	-	+(rash, pruritus)	+	-	-	++ (oral ulcers, acne)
Gastrointestinal** Toxicity	+	+	+	+	+++ (gastritis and/or diarrhea)	++
Hirsutism and/or gingival hyperplasia	+	-	-	-	-	-
Hyperglycemia and diabetes mellitus	-(?)	+	+++	-	-	-
Hyperlipidemia	++	+	++	-	-	+++
Impaired wound healing	-	-	+	+	+	++
Lymphoma malignancy	++	++	-	?	?	-
Myalgia arthralgia	-	-	+	+	-	++
Nephrotoxicity	+++ (K ⁺ , Mg ²⁺)	+++ (K ⁺ , Mg ²⁺)	-	-	-	+ proteinuria
Neurotoxicity ^a	++	++	+	-	+	-
			psychiatric		headache	
Osteoporosis	+	+	+++	-	-	-
Pneumonitis	-	-	-	-	-	+



It should be noted that each agent has other specific adverse effects in addition to those listed in the table. ^aNeurotoxicity includes mainly peripheral neuropathy, headaches, tremor, convulsions, akinetic mutism, and insomnia.

? , Incidence unknown; - not reported; + rarely reported; ++ commonly reported; +++ very frequently reported adverse effect limiting usage of the drug.

Printed with permission: Benten D, et al. *Nature Clinical Practice Gastroenterology and Hepatology* 2009;6:1:23-36.

**please see separate table of GI complications of immunosuppression associated with liver transplantation.

329. Give 10 **gastrointestinal complications** of transplant immunosuppression.

- Infections
 - Viral: CMV (especially for MMF), HSV
 - Fungal: *Candida albicans*, *Candida tropicalis*
 - Bacterial: *versinia enterocolitica*, *Clostridium difficile*
 - Parasites: microspordia, *Strongyloides*, *H. pylori* (70% in renal transplant recipients, and 60% in hemodialysis patients)
- Mucosal injury and ulceration
 - Diarrhea, constipation dyspepsia (especially tacrolimus and MMF)
 - Ulcerations: stress/NSAID ulcers
 - Giant gastric ulcers (>3cm, lung transplant recipients)
 - Diverticular disease: complicated diverticulitis (perforation, abscess, Phlegmon, fistula); especially with polycystic kidney disease
 - Perforations: early, late (especially from diverticulitis or CMV colitis)
- Biliary tract disease
 - Cholecystectomy (often as an emergency, high mortality [MR])
 - Cholelithiasis
- Pancreatitis
 - 5% in liver, Tx, MR 64%



- Liver
 - Acute cellular rejection
 - Acute early cellular rejection of graft occurs in the first few weeks after liver transplantation, especially for REC and AH
 - Chronic rejection occurs in 10% of liver transplant recipients, especially in HCV or AH
 - Recurrence of initial condition / retransplantation
 - Post liver transplantation steatosis
 - Steatosis occurs in as many as a third of persons following a liver transplantation (LT), with a histological diagnosis of NASH occurring in about 10% of these persons.
- Post-transplant diabetes and cardiovascular disease
 - Early after liver transplantation, transient hyperglycemia occurs in 40% of patients, and 9-21% have persistent hyperglycemia (new onset diabetes)
 - Hyperlipidemia occurs in 20-50% of liver transplant patient, with a 2.6 fold higher risk of coronary artery disease (CAD) and 20% of deaths occurring 3 years after liver transplantation coming from CAD

Abbreviation: CAD, coronary artery disease

330. Give 7 factors which predict the risk for **post-LT steatosis**.

- Post-LT obesity
- Diabetes mellitus
- Hyperlipidemia
- Arterial hypertension
- Tacrolimus-based immunosuppression regimen
- Alcoholic cirrhosis as the primary indication for LT (Dumortier et al., AJG 2010; 105: 613-620).
- The more of these risk factors that are present, the higher their rate for steatosis: for example; 3 factors, 30% risk; 4-66%; 5-82%; 6 risk factors, 100% ped LT steatosis.



331. Give the three types of **hepatic rejection** after transplantation.

○ **Hyperacute rejection**

- Hyperacute rejection (also known as massive hemorrhagic necrosis) seldom occurs, but when it does it results in rapid graft destruction with coagulative parenchymal necrosis owing to widespread endothelial dysfunction.
- Endothelial cells are primarily targeted by a pre-existing anti-donor humoral immune response that leads to the deposition of antibodies, platelets, fibrin and erythrocytes within the portal venules and hepatic sinusoids.
- Lymphocytes are usually absent and bile ducts unaffected.
- This form of rejection is seen more commonly in recipients with ABO incompatible grafts.

○ **Acute rejection**

- Acute rejection (also known as cellular rejection) is more common than hyperacute rejection, and usually occurs in the first 3 months post-transplantation.
- It is characterized by portal tracts that are heavily infiltrated with lymphocytes, bile duct damage and venular inflammation.
- Early acute rejection (within the first 3 months post-transplantation) generally responds well to increased doses of immunosuppressive agents, with resolution of biliary inflammation and stable long-term allograft function.
- The degree of inflammation and graft damage does not correlate with either the response to increased immunosuppression or with long-term outcome.
- By contrast, late acute rejection, recurrent rejection and steroid-resistant rejection are more likely to develop into chronic rejection.

○ **Chronic rejection**

- Chronic rejection (also known as ductopenic rejection or vanishing bile duct syndrome) affects a small minority of liver allograft patients and may lead to graft loss.
- A central late feature of chronic rejection is a loss of bile ducts (ductopenia), and pruning of the distal branches of the portal venous system owing to persistent inflammation and arterial foam cell infiltration and the presence of arterial foam cells.
- Vanishing bile duct syndrome eventually ensues, with progressive cholestasis and liver dysfunction and, ultimately, graft failure.

Printed with permission: Eksteen and Neuberger. *Nature Clinical Practice Gastroenterology & Hepatology* April 2008;5(4): pg 210.



➤ Pathology

332. Give the pathological features of acute cellular rejection after Liver Transplantation (LT).

- Portal tract
 - Inflammation, with lymphocytes eosinophils and plasma cell
 - Extension of inflammation into periportal area
- Bile ducts
 - Extension of inflammation into bile ducts
- Central vein
 - Lymphocytic infiltration around central vein, representing endothelitis

➤ GI malignancy

- Lymphomas, Kaposi sarcomas, skin cancer
- Gastric MALT lymphomas; may be associated with *H. pylori*
- Colorectal cancer (liver Tx, RR, CRC 12.5)
- Colorectal Cancer (CRC) in UC (ulcerative colitis) plus primary sclerosing cholangitis (PSC)
 - In patients given a liver transplant for PSC in the setting of associated UC, the incidence of CRC is 1% per year, with a cumulative risk of colonic mucosal dysplasia of 15% at 5 years and 21% at 8 years
- Post transplantation Lymphoproliferative disorder (PTLD) (10% of Tx pts; acute perforation, obstruction, bleeding; associated with EBV)

Printed with permission: Helderman JH, and Goral S. *J Am Soc Nephrol* 2002; 13: 277-287.

➤ **Non-skin solid organ tumors**

- 10% per year
- Squamous cell and basal cell skin cancer is 12-90 times more common in transplanted patient
- Risk 2x > general population
 - Head/neck Ca
 - Esophageal Ca
 - Kaposi sarcoma
- Non-melanoma skin cancer (NMSC)
 - Alcohol L-Tx for ALD ↑ risk
 - CRC
 - IBD/PSC
 - 10% at 10 yrs
 - 22% at 20 yrs



Post-Transplant Lymphoproliferative Disorder (PTLD)

- Demography
 - There is a 10-fold increased risk of non-Hodgkins lymphoma (B-cell related to EBV) after liver transplantation, giving a relative risk of 3%
 - Most commonly first 18 month post LT
 - More immune suppression in heart Tx patients, so more PTLD.
 - 5 year survival rate, 50%
- Cause
 - EBV-associated latent infection in B-cells
 - ↑ LDH, ↑ EBV viral load
- Pathology
 - Extranodal, high grade, poor prognosis
 - B cells originate from recipient, not from donor cells
 - May occur in GI tract (e.g. colon)
- Management
 - ↓ immune suppression (↓ by 25% to 50%)
 - Short-term, 70% effective
 - EBV treatment
 - Multi-gent chemo (CHOP), radiation, surgery, rituximab
 - Rituximab 50% remission rate (for CD20+ PTLD)

Biliary Obstruction

- Usually 1 month post L-Tx
- Strictures of biliary tree occur in 20-35% of patients post liver transplantation, especially at the duct-to-duct anastomosis, or at the Roux-en-Y
- Post transplant biliary strictures result from hepatic artery occlusion, chronic allograft rejection, or prolonged cold ischemia time
- Common bile duct (CBD)
 - Stone
 - Stricture
 - Bile duct injury and cholestasis in both post-LT HCV and with acute rejection cholestatic syndrome have a serious prognosis.
- Ischemic stricture of CBD post L-Tx, above anastomosis
- Chronic rejection
- Post L-Tx, can see anastomosis on ERCP



Recurrence of Liver Disease Leading to Need for Liver Transplantation

333. Give 7 examples of liver disorders which may recur in the liver **following liver transplant** (recurrence rates in brackets).

- HBV (100%)
- HCV (more virulent; cholestatic type often fatal)
- Alcoholic liver disease (~50%)
- NASH
- PBC, AIH, PSC (20%)
- Hemochromatosis (late)
- 2° amyloid
- HCC
- Autoimmune hepatitis (AIH)

Adapted from: Lilly LB, Girgrah N, and Levy G.A. *First Principles of Gastroenterology* 2005: pg. 642.

Sexual Function and Pregnancy

- Decreased libido in 25% of men and women after liver transplantation
- Erectile dysfunction in 30% of men after liver transplantation
- Post-transplant, pregnancy is associated with
 - ↑ fetal loss (18%)
 - Low birth weight (31%)
 - Premature delivery (39%)
 - Pre-eclampsia (21%)
 - The need for caesarian section (47%)
 - Allograft rejection occurs in 10-20% of women during pregnancy



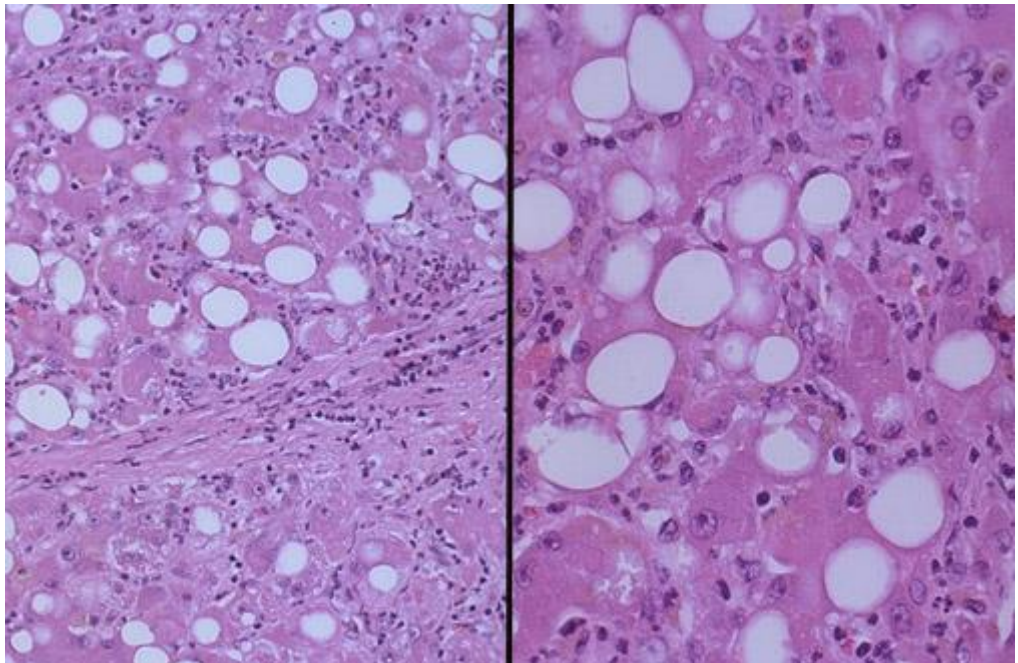
Case Self Test Studies in Hepatic Histopathology

Alcoholic Liver Disease i

Case 1. Clinical vignette: A 55-year-old sales executive presents for a physical examination pertaining to an insurance policy application. He has consumed 4 bottles of beer a day for 30 years. Past history, symptoms review, and physical examination is non-contributory. You suspect Alcoholic Liver Disease.

- Give the typical pathological features of Alcoholic Liver Disease.
 - Hepatocyte swelling and necrosis
 - Macrovesicular fatty change in centrilobular area
 - Mallory hyaline
 - Neutrophils, portal lymphocytes and macrophages
 - Sclerosing hyaline fibrosis

Identify these features on the following slides.



Reference: Colombat M, et al. Portal lymphocytic infiltrate in alcoholic liver disease. *Hum Pathol.* 2002;33;1170-4.

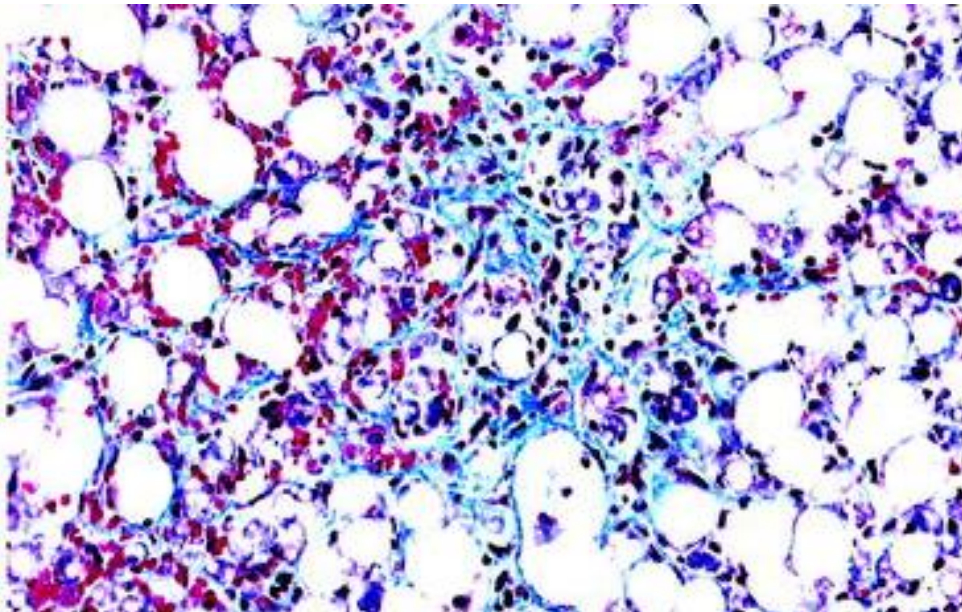


Non-alcoholic steatohepatitis.

Case 2. Clinical vignette: A 45-year-old type II diabetic with a BMI of 35 from Brandon, Manitoba presents with 2 x normal increased AST. There is no alcohol intake. This is a routine follow-up for mild hypertension, and she is otherwise well except for hypercholesterolemia. You suspect non-alcoholic steatohepatitis.

- Give the typical pathological features of non-alcoholic steatohepatitis.
 - Micro- and macrovesicular steatosis, zone 3
 - Lobular plasma cell and lymphocyte infiltrate
 - Ballooning degeneration of hepatocytes
 - “Chicken-wire” fibrosis

- Identify these features on the following slide.

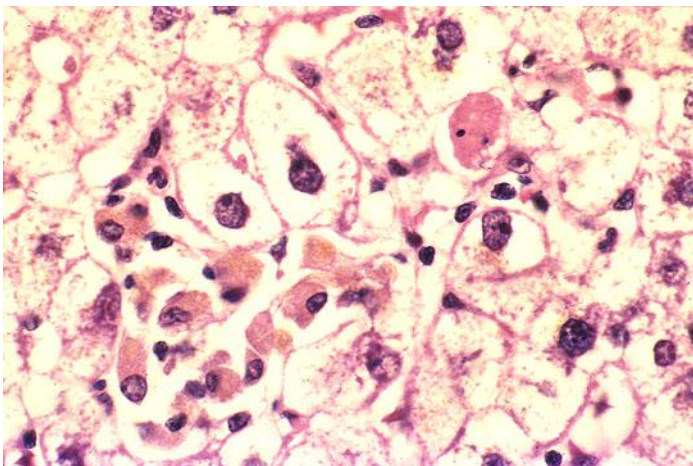
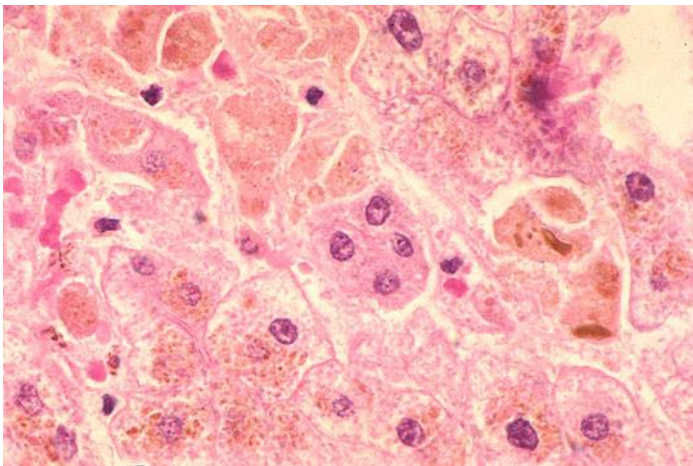


Hepatitis A

Case 3. Clinical vignette: A 19-year-old young man from White Rock, BC, traveling in SE Asia presents with fatigue and jaundice. You suspect hepatitis A.

- Give the typical pathological features of Hepatitis A.
 - Portal and periportal inflammation
 - Ballooning degeneration
 - Relative sparing of centrilobular hepatocytes
 - Acidophil bodies or cytolysis (hydropic degeneration)
 - Bridging necrosis
 - Interface hepatitis

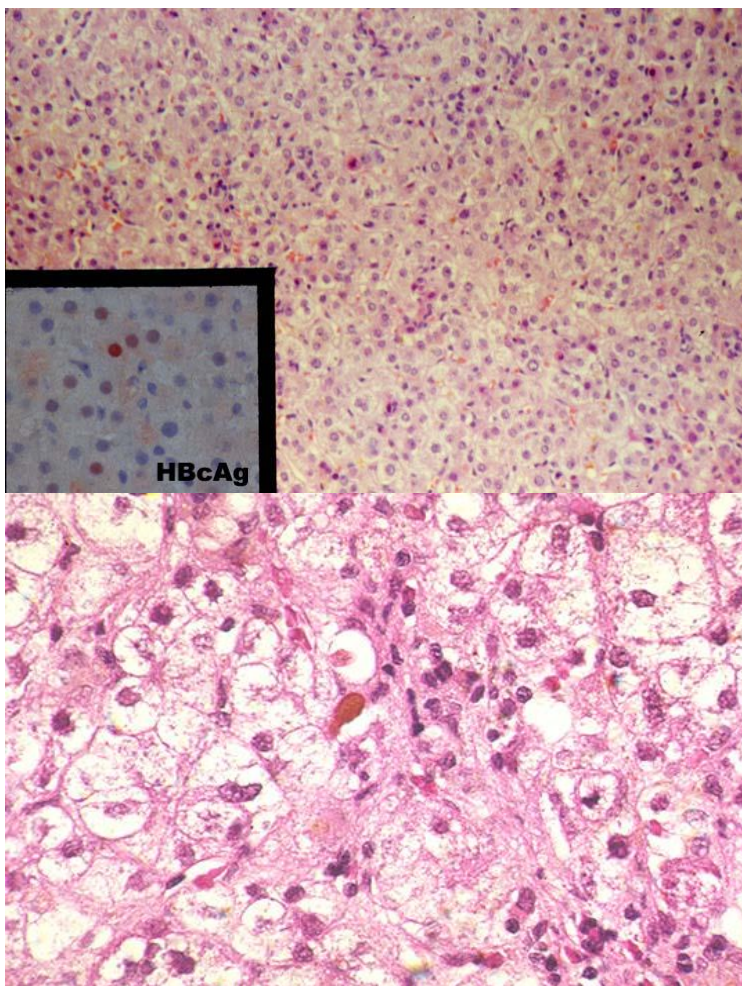
Identify these features on the following slides.



Hepatitis B

Case 4. Clinical vignette: A 62-year-old businessman from Elk Point, AB, presents with recent onset of malaise and transaminitis. He denies alcohol intake. His younger brother died from HCC. You suspect Hepatitis B.

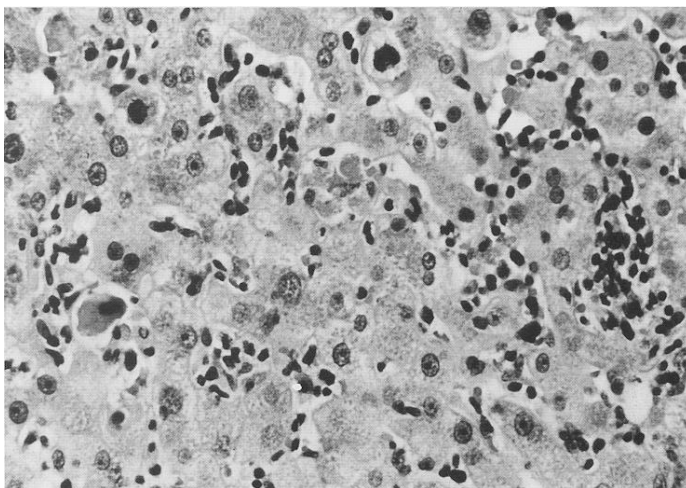
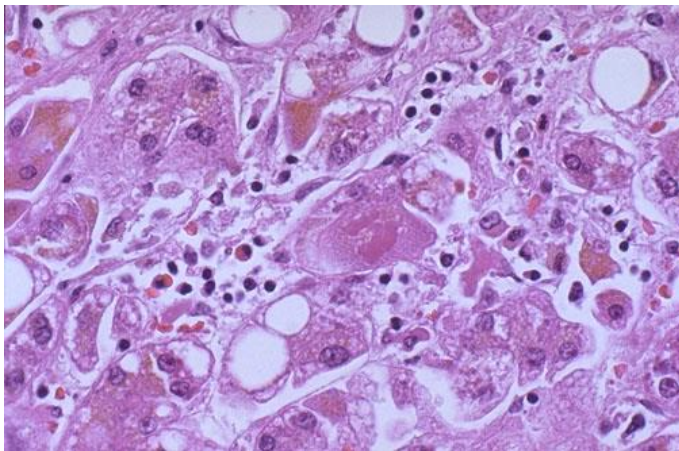
- Give the typical pathological features of Hepatitis B.
 - Piecemeal necrosis
 - Ground glass hepatocytes
 - Identify these features on the following slides.



Hepatitis C

Case 5. A 39-year-old hemophiliac physician from Brookville, ON, presents with fatigue and mild jaundice. You suspect Hepatitis C.

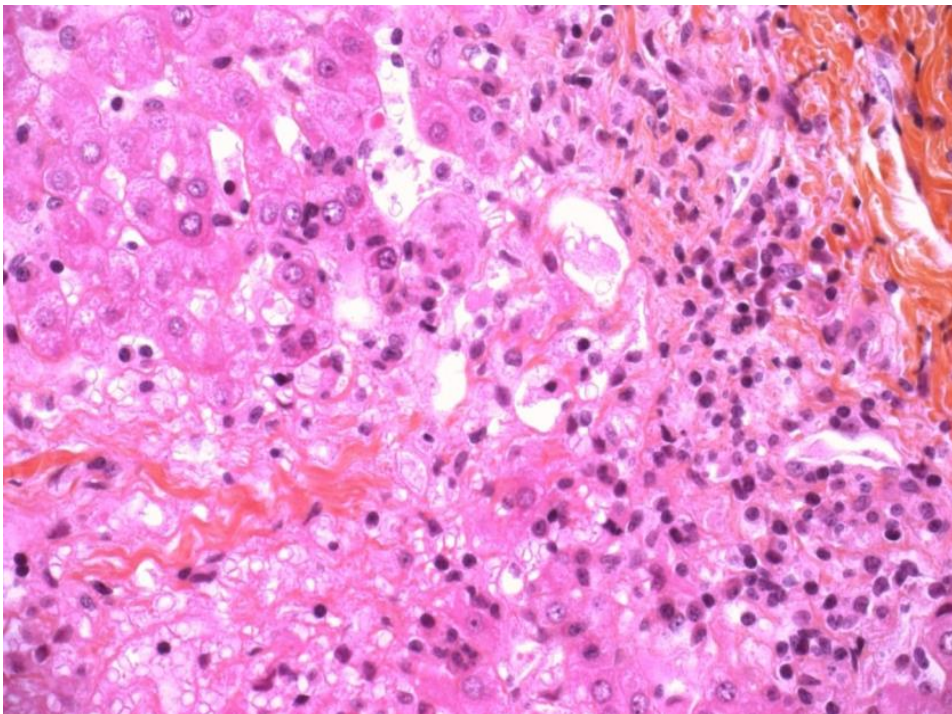
- Give the typical pathological features of Hepatitis C.
 - Sinusoidal lymphocytic infiltrate
 - Mallory hyaline
 - Macrovesicular steatosis
 - No/minimal plasma cells or eosinophils
 - Identify these features on the following slides.



Autoimmune Hepatitis

Case 6. Clinical vignette: A 45-year-old high school principal from Trois-Riviera, QC, with treated hypertension presents with a 6 month history of pruritus. The GGT and AP are increased twice normal. You suspect Autoimmune Hepatitis.

- Give the typical pathological features of Autoimmune Hepatitis.
 - Portal infiltrate with abundance of plasma cells
 - Bridging necrosis
 - Central necrosis with plasma cells
 - Identify these features on the following slide.



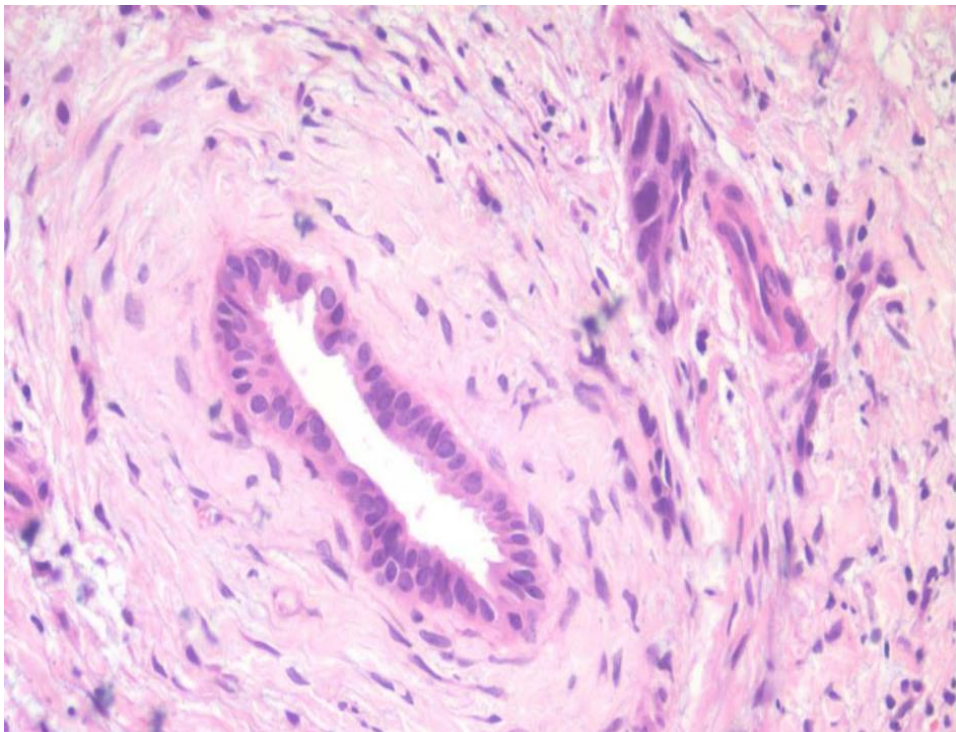
Reference: Khettry U, et al. Liver transplantation for primary sclerosing cholangitis: a long-term clinicopathologic study. *Hum Pathol.* 2003;34: 1127-36.



Case 7. Clinical vignette: A 24-year-old male nurse from Red Earth, SK, with a 10 year history of ulcerative colitis presents with abnormal LFTs. You suspect Primary Sclerosing Cholangitis (PSC).

- Give the typical pathological features of PSC.
 - “Onion skin” fibrosis

Identify this feature on the following slide.



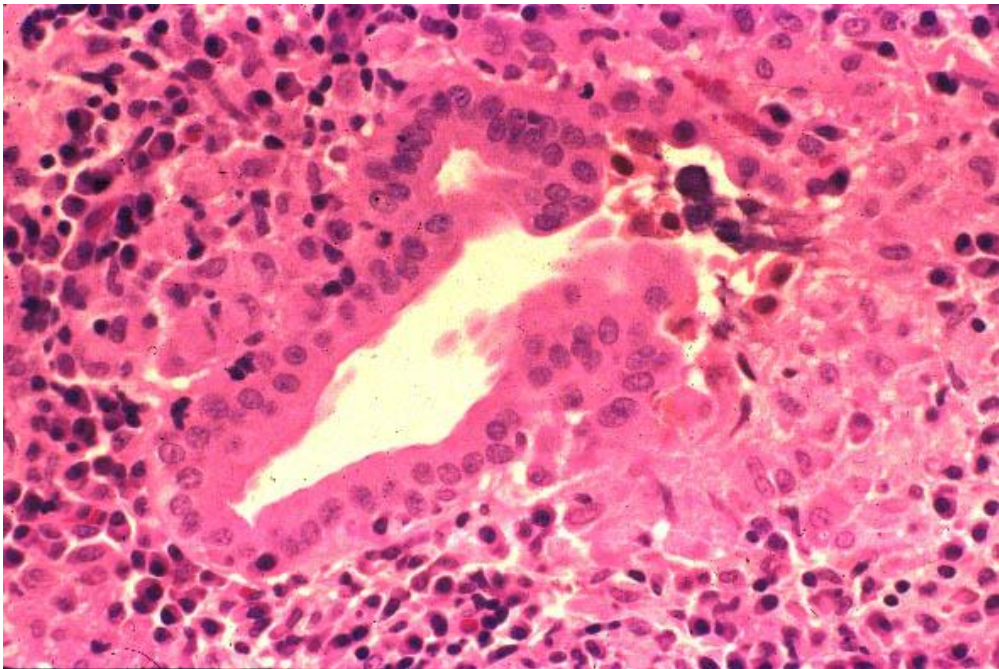
Reference: Khettry U, et al. Liver transplantation for primary sclerosing cholangitis: a long-term clinicopathologic study. *Hum Pathol.* 2003;34:1127-36.



Primary Biliary Cirrhosis (PBC)

Case 8. Clinical vignette: A 50-year-old woman from Halifax, NS, presents with an asymptomatic elevation in her GGT and AP at the time of routine follow up of her dyslipoproteinemia. You suspect Primary Biliary Cirrhosis (PBC).

- Give the typical pathological features of PBC.
 - Dense lymphocytic infiltrate in portal tracts
 - Minimal neutrophils
 - Granulomatous destruction and loss of medium-sized interlobular bile ducts
 - Destruction of bile ductules within the liver
 - Identify these features on the following slide.



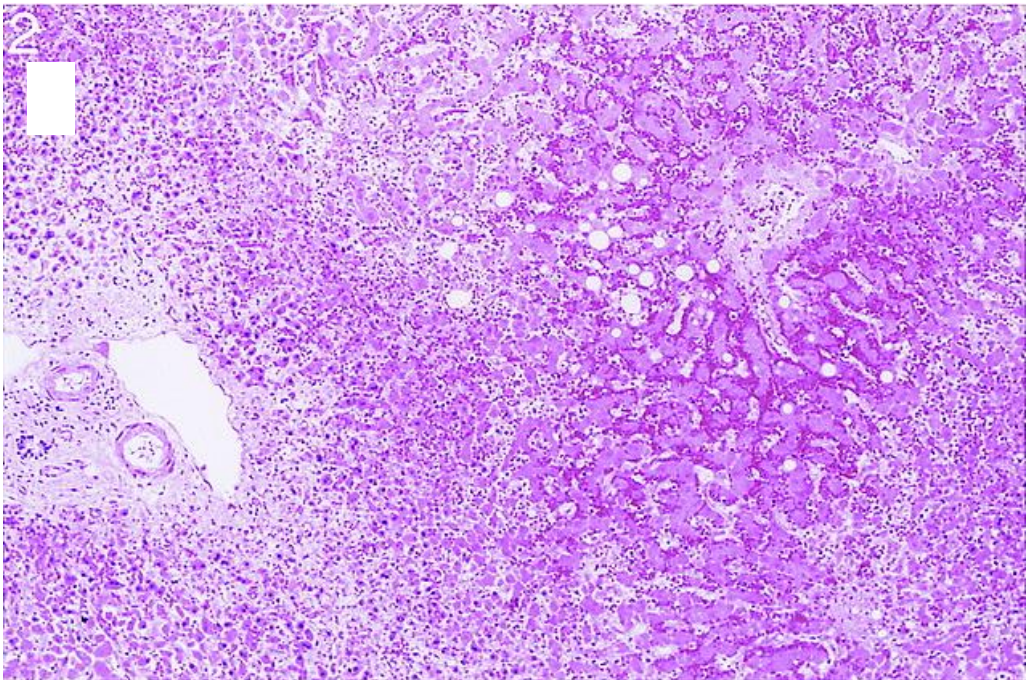
Reference: Khettry U, et al. Liver transplantation for primary sclerosing cholangitis: a long-term clinicopathologic study. *Hum Pathol.* 2003;34:1127-36.



Massive Hepatic Necrosis (MHN)

Case 9. A distraught 19-year-old student from Mitchell, ON, consumed a bottle of unknown OTC pills, and presents to the ER with confusion and jaundice. You suspect Massive Hepatic Necrosis (MHN).

- Give the typical pathological features of MHN.
 - Massive necrosis of hepatocytes in all zones
 - Reticulin collapse
 - Minimal inflammatory reaction
- Identify these features on the following slide.



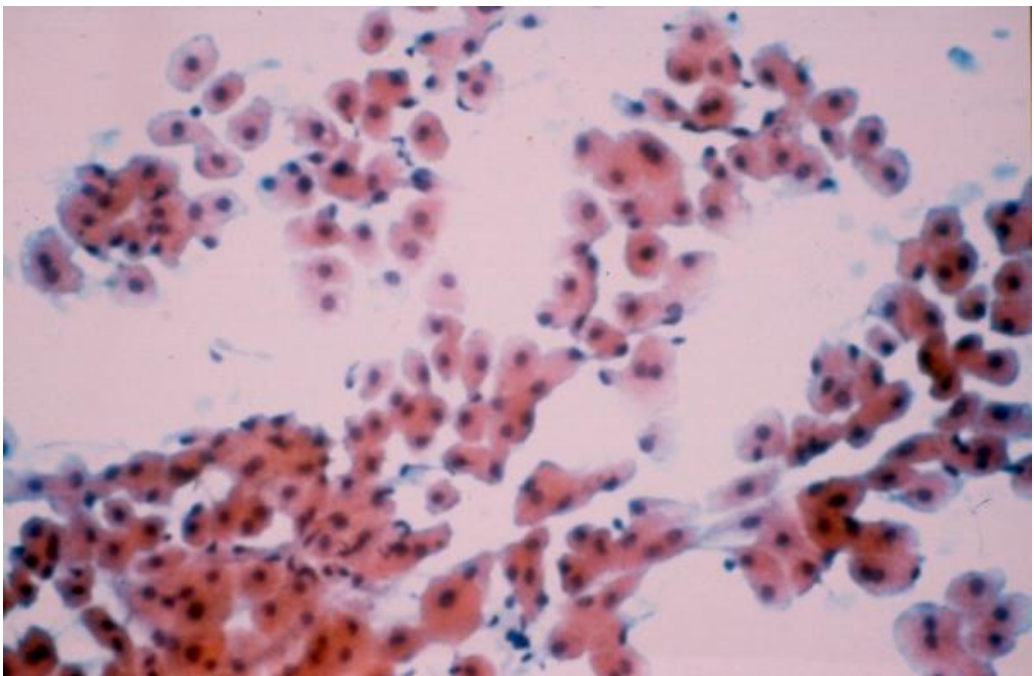
Reference: Khettry U, et al. Liver transplantation for primary sclerosing cholangitis: a long-term clinicopathologic study. *Hum Pathol.* 2003;34:1127-36.



Nodular Hyperplasia (FNH)

Case 10. A 30 year old woman presents with abnormal liver enzymes. You suspect Focal Nodular Hyperplasia (FNH).

- Give the typical pathological features of FNH.
 - Hepatocyte nodules surrounded by fibrous septa
 - Foci of intense lymphocytic infiltrates
- Identify these features on the following slide.

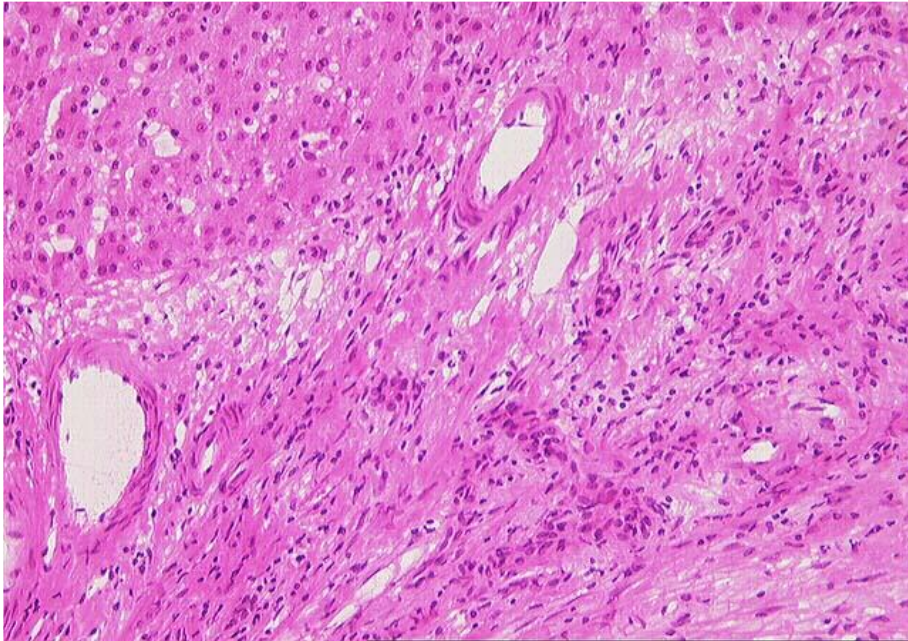


Reference: Gräntzdörffer I, et al. Angiotensin I-converting enzyme (CD143) is down-regulated in focal nodular hyperplasia of the liver. *Am J Surg Pathol* 2004;28(1):84-8; Wanless IR. Epithelioid hemangioendothelioma, multiple focal nodular hyperplasias, and cavernous hemangiomas of the liver. *Arch Pathol Lab Med* 2000;124(8):1105-7.



Hepatocellular carcinoma (HCC)

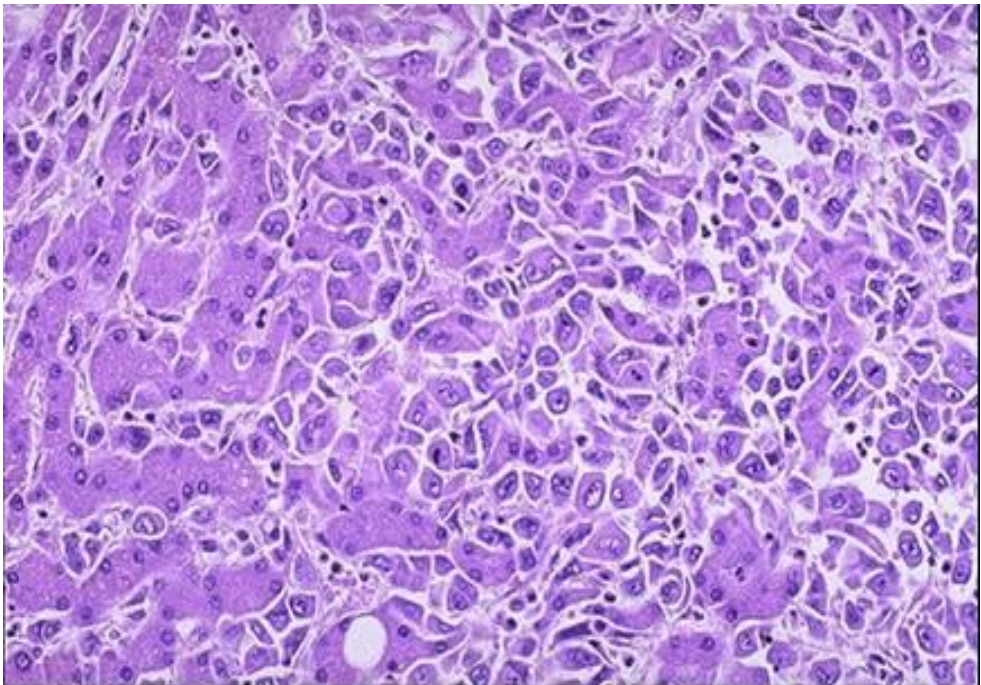
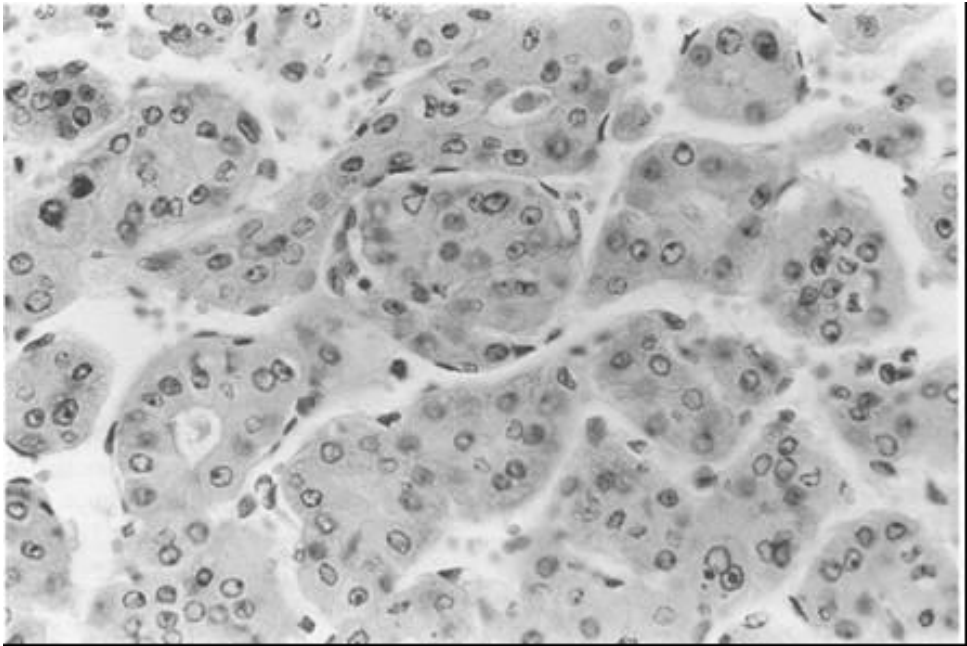
Case 11. Clinical vignette: A patient with known HIV and HBV from Calgary, AB, presents with worsening ascites and cachexia. You suspect hepatocellular carcinoma (HCC).



- Give the typical pathological features of HCC.
 - Well differentiated to bizarre pattern
 - Trabecular patterns
 - Sarcomatoid and clear cell patterns
 - Pseudoglandular
 - Cells surrounded by layer of flattened endothelial cells
 - Giant cells
 - Sinusoidal vessels surrounding tumour cells
 - Vascular invasion
 - Scanty stroma
 - Polygonal cells with distinct cell membranes
 - Higher N/C ratio
 - Granular eosinophilic cytoplasm
 - Round nuclei with coarse chromatin and thickened nuclear membrane

Reference: Fan Z, et al. Hep par 1 antibody stain for the differential diagnosis of hepatocellular carcinoma: 676 tumours tested using tissue microarrays and conventional tissue sections. *Mod Pathol* 2003;16:137-44; Itoh T, et al., Immunohistochemical detection of hepatocellular carcinoma in the setting of ongoing necrosis after radiofrequency ablation. *Mod Pathol* 2002;15:110-5. Identify these features on the following slides.

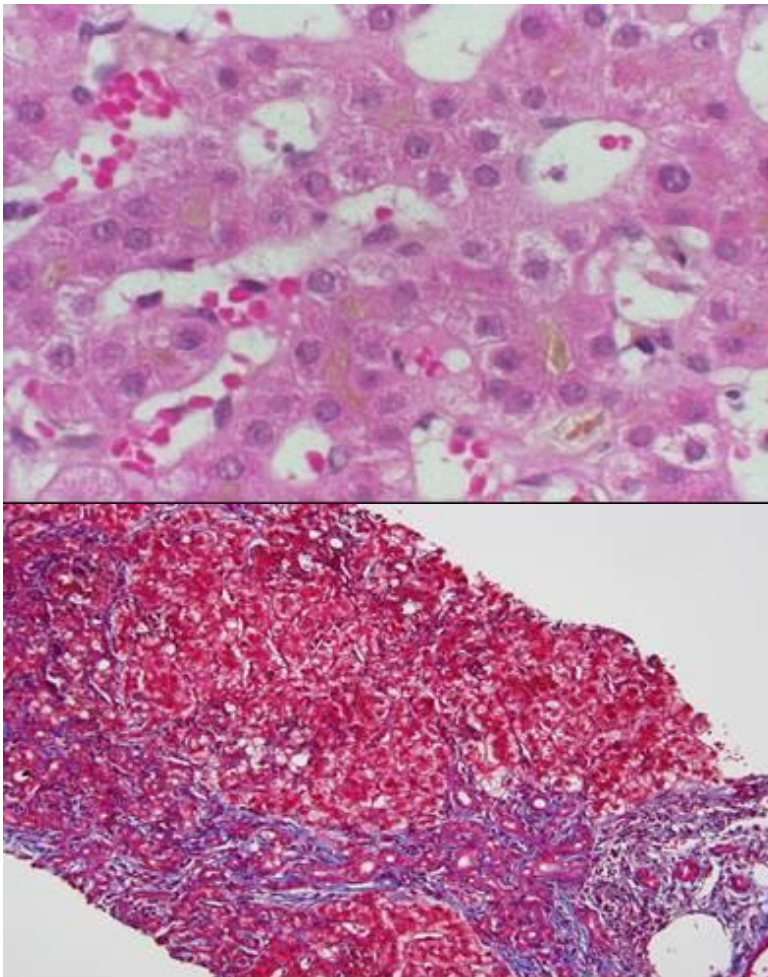




Cholestasis syndrome

Case 12. Clinical vignette: On a Royal College OSCE exam, this slide was presented for interpretation, with the only history being “jaundice of unknown origin.” You suspect Cholestasis syndrome.

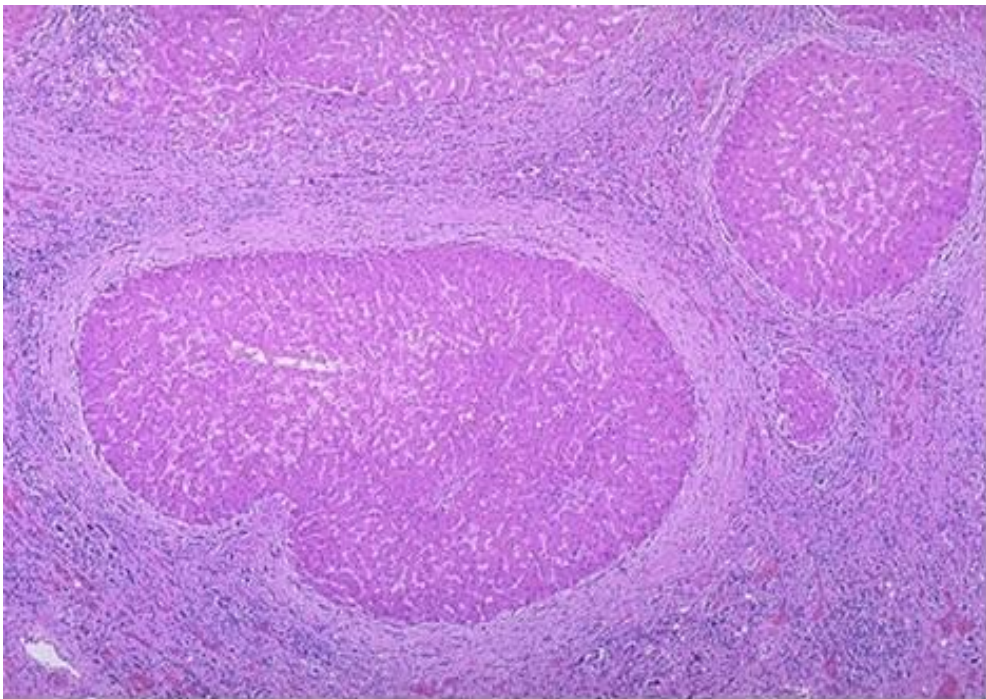
- Give the pathological features of Cholestasis syndrome include:
 - Bile plugs
 - Canalicular cholestasis
 - Ductular cholestasis
 - Cholangiolar proliferation
 - Identify these features on the following slides.



Cirrhosis

Case 13. Clinical vignette: A 58-year-old man from P.E.I. with known alcoholic liver disease presents with recent onset abdominal distension and confusion. You suspect Cirrhosis.

- Give the typical pathological features of Cirrhosis include:
 - Disruption in architecture of entire liver
 - Bridging fibrous septa
 - Rounded parenchymal nodules of regenerating hepatocytes without central veins
 - Identify these features on the following slide.



BILIARY TREE AND GALLBLADDER



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Anatomical Overview of Bile ducts and Gallbladder (from small to large)

- Canaliculus
 - Channels between hepatocytes
 - Terminal channels (aka canals of Hering)
 - Perilobular (aka intralobular) ducts
 - Zone 3 to zone 1
 - Interlobular ducts
 - Hepatic ducts (right and left)
 - Common hepatic duct
 - Cystic duct
 - Gallbladder
 - Neck
 - Infundibulum
 - Hartmann pouch
 - Body
 - Fundus
 - Common bile duct
 - Ampulla of Vater
1. In the context of the anatomy of the gallbladder, give what is the **Hartmann pouch**, and what is its clinical significance?
- A. “Hartmann pouch is a bulging of the inferior surface of the infundibulum that lies close to the neck of the gallbladder” (Feldman M., et al. *Sleisenger and Fordtran’s Gastrointestinal and Liver Disease*. 9th Edition. *Saunders/Elsevier*, Philadelphia, 2010, page 1049).
 - Gallstones may become impacted in the Hartmann pouch, which blocks the cystic duct, and leads to cholecystitis.

“All our dreams can come true – if we have the
courage to pursue them.”

Walt Disney



Stones

- Stones in the biliary tree usually arise from cholelithiasis.
- However, multiple stones in the biliary tree, especially in the left hepatic system, suggests recurrent pyogenic cholangitis (RPC), aka “oriental cholangitis”.
 - RPC may be caused by infections, such as *Clonorchis sinensis* and *Ascaris lumbricoides*
 - Because of the recurrent episodes of cholangitis, strictures may occur in biliary tract

After a liver biopsy a patient develops abdominal pain, hypertension and dropping hemoglobin concentration.

2. **Give the findings on NG tube aspiration which may help to determine if the above scenario is likely due to acute bleeding from hemobilia.**

NG tube shows	Likelihood of acute bleeding
No blood, but bile	< 5%
No blood, no bile	< 15%
-- Blood	> 95%

3. Give 3 causes of pneumobilia.

- Sphincterotomy
- Gallstone ileus
- Anaerobic infection of portal tract with *Clostridium perfringens*

“Harsh words are heavy and often fall with a big thud,
but a kind word will bounce on and on...”

Anonymous



Strictures and Stents

The commonest places for an injured biliary tract / duct are cystic duct and duct of Luschka.

4. Give the features in favour of using a plastic versus a metal stent for the management of a Hilar bile duct tumor.

	Feature	Plastic	Metal
➤ Stricture	○ Size	3 mm	10 mm
	○ Duration	< 6 mon (temporary)	6 mon ("permanent")
➤ Stent	○ Cost	~ \$ 300	~ \$ 1500
	○ Covered	No	Yes

- Plastic stent can be inserted through a larger metal stent (3mm → 10 mm)

5. Give the anatomical sites which favour the use of covered versus uncovered metal stents.

- Covered
 - Head of pancreas (HOP) (↑ risk of migration)
- Uncovered
 - Intrahepatic duct

Benign Biliary Strictures

- Types

6. Give the **Bismuth classification** for benign biliary strictures.

Classification	Location
I	> 2 cm distal to hepatic confluence
II	< 2 cm distal to hepatic confluence
III	Hilar stricture, hepatic confluence is preserved
IV	Involves the hepatic confluence, bile ducts are separated

Source: Zepeda-Gomez S and Baron TH. Nat Rev Gastro Hep 2011; 8: 573-581.



➤ Causes

7. Give 10 causes of benign biliary strictures.

- Biliary duct
 - Postsurgical
 - Cholecystectomy (open or laparoscopic)
 - Biliary anastomosis (orthotopic liver transplantation or biliary reconstruction)
 - Biliary-enteric anastomosis
 - Trauma
 - Post-endoscopic biliary sphincterotomy
 - Post-ERCP
 - Primary sclerosing cholangitis
 - Post-radiation therapy
 - Infections (tuberculosis, histoplasmosis, viral, parasitic)
 - Choledocholithiasis
 - Autoimmune cholangiopathy
 - Inflammatory
 - Ischemia
 - Hypotension
 - Intrahepatic infusion of chemotherapy agents
 - Hepatic artery thrombosis
- Sphincter of Oddi
 - Sphincter of Oddi dysfunction
 - Vasculitis
- Pancreas
 - Chronic pancreatitis

Abbreviation: BBS, benign biliary strictures

Adapted from: Zepeda-Gomez S and Baron TH. Nat Rev Gastro Hep 2011; 8: 573-581, Box 1

“Challenges are what make life interesting and overcoming them is what makes life meaningful.”

Joshua J. Marine



Sphincter of Oddi Dysfunction (SOD)

- Basic mechanisms
 - Stenosis
 - Dyskinesia

SOD is usually suspected in the setting of biliary-like pain with or without a gallbladder (without stones), or idiopathic recurrent pancreatitis. The cause of SOD is unknown.

- Causes / associations

8. Give 3 conditions associated with SOD.

- Post liver transplantation
- Hyperlipidemia
- AIDS (acquired immunodeficiency syndrome)
- Chronic use of opium

- Clinical
 - Biliary-type pain after cholecystectomy
 - Biliary-type pain with intact gallbladder and no stones
 - Recurrent idiopathic pancreatitis (↑ ALT, ↑ AP, CBD > 10 mm)

- Diagnosis
 - Scintigraphy
 - Fatty meal ultrasonography
 - Morphine + neostigmine low sensitivity / specificity (Nardi test)
 - SOM (sphincter of Oddi manometry) may show ↑ SOD (sphincter of Oddi) (> 35 to 40 mm Hg)

- Sphincter of Oddi Manometry (SOM)
 - SOM, done at time of ERCP
 - The insertion of the manometry of catheter may cause spasm)
 - SOM - specific, not sensitive



- SOD patients have a high complication rate
 - Post-ERCP
 - Post-ERCP placement of the stent

Measurement of SOM (sphincter of Oddi manometry) is performed at the time of ERCP.

9. Give 2 non-invasive tests for biliary or pancreatic SOD, as well as their performance characteristics.
 - Biliary scintigraphy (ultrasound) after
 - Fatty meal (stimulated ultrasound testing of diameter of biliary duct)
 - CCK injection (for biliary SOD)
 - Secretin injection (for pancreatic SOD)

	For Biliary SOD	For pancreatic SOD
	Fatty meal	Secretin
Sensitivity	21%	88%
Specificity	97%	82%

➤ Classification

10. Give the modified **Milwaukee Classification** for Biliary Sphincter of Oddi Dysfunction (SOD).

Type	Biliary-type pain	↑ LEs	DBD (> 10 mm)	↑ SO pressure
I	+	+	+	65% to 85%
II	+	Either ↑ LEs or DBD	+ / -	55%
III	+	-	-	28%

Abbreviations: DBD, dilated bile duct; LE, liver enzymes (ALT, AST, AP [alkaline phosphatase])

Adapted from: Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. *Saunders/Elsevier* 2010, Table 63.1, page 1068.



The Milwaukee Classification for biliary SOB is applied to biliary-type pain. However, SOD dysfunction may be a cause of recurrent idiopathic pancreatitis.

11. Give the way in which the Milwaukee classification for possible pancreatic SOD differ from biliary SOD?

	Pancreatic SOD	Biliary SOD
Laboratory tests	↑ Lipase or amylase	↑ ALT, AST, AP
Duct diameter	Bile duct > 10 mm	Pancreatic duct > 6 mm in the head, > 5 mm in the body of pancreas

➤ Treatment

- When sphincter pressure > 40 mmHg, response to sphincterotomy, 91% (vs 25% with sham sphincterotomy)
- When sphincter pressure < 40 mmHg, response to sphincterotomy is only 42% (sham, 33%)

Success of sphincterotomy	ABN SOM	Relief (%)
		N-SOM
I	90-95	90-95
II	85	35-42
III	55-60	< 10% high risk of complication

- Because of the technical difficulties with SOM and its sometimes unreliable results, the test is not always done to diagnose SOD.
- However, with type II or III disease, if the SOM is normal, the response to ERCP plus sphincterotomy is much lower (see below), and it could be argued that in type II or III patients, SOM should be obtained.
- SOD are diagnosed with the modified Milwaukee criteria rather than an abnormal SOM (i.e. SOD which is not manometrically proven).

12. List 4 possible causes for failure to achieve pain relief after biliary sphincterotomy for presumed sphincter of Oddi dysfunction (SOD).

- Sphincter
 - Inadequate initial sphincterotomy (remaining ↑ SOD pressure)
 - Restenosis



- Pancreatitis
 - Chronic pancreatitis with a normal pancreatogram
 - Nonpancreaticobiliary pain (beware functional gastrointestinal disease)

Source: Elta, Grace H. *Sleisenger & Fordtran's gastrointestinal and liver disease: Pathophysiology/Diagnosis/Management* 2006: pg. 1365.

! Caution Alert!

- For reasons which are unclear, the risk of post-ERCP pancreatitis is ↑ 3x (>25%) when the indication for the ERCP is SOD.
 - For this reason a stent may be placed after ERCP to ↓ risk of post-ERCP pancreatitis in persons who turn to have SOD.
- When SOD is diagnosed, and the patient is not post-liver transplant, does not have hyperlipidemia, does not have HIV/AIDs or is not a chronic opium user (conditions associated with ↑ SOM and thereby SOD), watch out for a possible intra-ampullary neoplasm mimicking SOD.

Cholelithiasis

SO YOU HAVE NOW GIVEN UP – ON BEING A (PEDIATRIC) GASTROENTEROLOGIST!

Congenital abnormalities of the biliary tree include choledochal cysts, Caroli disease and Caroli syndrome.

- Explain why biliary atresia is sometimes not included in this list of congenital abnormalities of the biliary tree.
 - Injury to biliary tract occurs after birth
 - There is some evidence for an in utero infection (e.g., HSV, retrovirus, Rhesus rotavirus).



➤ Types of gallstones

- Composition
 - Cholesterol
 - Crystals of cholesterol monohydrate
 - Calcium bilirubinate
 - Calcium carbonate / phosphate
 - Pigment
 - Calcium bilirubinate
 - Mixed
 - Rare
 - Calcium carbonate
 - Calcium-fatty acids
- Site
 - Intrahepatic
 - Brown pigment
 - Gallbladder
 - Cholesterol >> black pigment
 - Bile duct
 - Mixed
- Physical state of cholesterol
 - Low concentrations
 - Monomers of bile acids (BA)
 - CMC (critical micellar concentration)
 - Simple micelles are spontaneously formed with BA monomers
 - Small (~ 3 nm diameter)
 - Disk-like macromolecular aggregates
 - Solubilize and incorporate
 - Cholesterol
 - Phospholipids (mostly lecithin, with some phosphatidylethanolamines and sphingomyelin) to form mixed micelles (~ 4-8 nm diameter)
 - Biliary vesicles
 - Secreted by hepatocytes
 - Composed of cholesterol monohydrate crystals and phospholipids
 - Large (40-100 nm diameter)
 - Multilamellar spherical structures
 - As the gallbladder (GB) absorbs H₂O, the GB bile becomes concentrated



- Phase diagram and triangular co-ordinates
- The stability of the biliary vesicles determines the stability of bile molecular rearrangements such that
- In high concentrations of BA, there are the biliary vesicles may transform into mixed micelles
- The maximal solubility of cholesterol is determined by the relative molar percentages of cholesterol, phospholipids and bile acids
- This allows for the quantification of the degree of saturation of bile with cholesterol
- This quantification of cholesterol saturation is the CSI (cholesterol saturation index), aka the lithogenic index
- Examples of CSI
 - < 1 unsaturated
 - 1 saturated
 - > 1 supersaturated (↑ risk of forming gallstones)

Pigmental gallstones are seen in patients with chronic hemolytic anemia, liver disease, and with TPN.

“Happiness cannot come from without. It must come from within.”

Helen Keller



17. Give 5 differences, (besides their colour) between black versus brown pigmented stones.

Characteristics	Black	Brown
○ Site	GP	GB, HBT
○ Infected bile	No	Yes
○ Association with chronic hemolytic anemia	Yes	Yes
○ Composition of stones	Polymers of calcium bilirubinate	Monomers of calcium bilirubinate plus cholesterol, fatty acids, bile salts, phospholipids
○ B-glucuronidase forming unconjugated bilirubin glucuronide	Endogenous	Exogenous (E. Coli, roundworms, Clonorchis sinensis)
○ Reduced acidification of bile	Yes	-
○ Gallbladder dysfunction	No	No

Abbreviations: GB, gallbladder; HBT, hepatobiliary tree

➤ Genetics

There are over a dozen genes and gene predicts that have been identified (please refer to Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier, Philadelphia, 2010, Table 65.1, page 1103, for a lot of Human Cholesterol Gallstone [LH] gene and gene Products).

18. Give 3 clinical observations which suggest that there may be **genetic factors** leading to the formation of gallstones ↑ risk of gallstones.

- Siblings
- Monozygotic twins
- Relatives of index person with gallstones



➤ Pathophysiology

19. Give the pathophysiology of the formation of gallstones.

There are 5 primary defects which lead to the production of gallstones:

- ↑ hepatic secretion of cholesterol
 - ↑ hepatic uptake of HDL-C
 - CETP (cholesterol ester transfer protein)
 - ↑intestinal CH absorption and ↑ hepatic VLDL synthesis
 - Apolipoprotein (APO) E and APOB genes polymorphisms
 - 7α-hydroxylase (CYP7A1) gene variant
 - ↓ conversion of CH (cholesterol) to BA (bile acids) in the “neural” pathway
 - ↓ PL secretion
 - ABC B4 (aka MDR3 [multidrug resistant gene 3]) missense mutation of phosphatidylcholine (PC) transporter in hepatocyte CM
 - ↓ CYP7A1
 - ↑ HMG-CoA reductase
 - ↓ bile PC
 - ↑ bile CH
 - ↑ CH secretion
 - Variant of ABCG5/-G8 on CM of the hepatocytes
 - Aberrant splicing of CCK-IR (cholecystokinin-1 receptor)
 - ↓ gallbladder motility

Abbreviations: CH, cholesterol (free); PC, phosphatidylcholine

- The lithogenicity of bile is finally determined by the molar % of cholesterol (CH), phospholipids and bile acids.
- The amount of CH available for transport across the CM of the hepatocyte is determined by a balance between entry of CH across SM, exit across the SM (the sinusoidal membrane), metabolism in hepatocyte cytosol, and exit across the CM (canalicular membrane).
- ↓ cholesterol nucleation and crystallization
- ↓ gallbladder motility
- Intestinal factors



- After cholecystitis, give 3 conditions / circumstances when it is appropriate to perform early laparoscopic cholecystectomy
 - Pregnancy
 - Severe acute cholecystitis
 - Gallstone pancreatitis
 - Intractable pancreatitis

20. Give the **mechanisms** by which the gallbladder, small intestine and liver contribute to the formation of cholesterol gallstones.

- Gallbladder
 - Fasting period
 - 7α -hydroxylation of CH to BA (bile acids) by
 - $\uparrow$ volume
 - $\uparrow$ cholesterol absorption ("loss of capacity for selective absorption of biliary cholesterol and phospholipids") by GB
 - $\uparrow$ stiff sarcoplasmic membranes
 - $\downarrow$ activation of G-proteins in muscularis propria
 - $\uparrow$ storage of CE
 - $\downarrow$ motility
 - $\uparrow$ inflammation and proliferation
 - Postprandial
 - $\downarrow$ binding of CCK to CCK-1 receptors
 - $\downarrow$ emptying continued BG bile supersaturation
 - $\uparrow$ post-emptying (residual) volume
 - Interdigestive period
 - $\downarrow$ filling
 - $\uparrow$ lithogenic hepatic bile enters duodenum
 - $\downarrow$ cholesterol solubilisation
 - $\uparrow$ mucin glycoproteins
 - Binds chol, PL, BA
 - $\uparrow$ nucleation factors
 - $\downarrow$ antinucleation factors
 - $\uparrow$ vesicles fusion / aggregation
 - $\uparrow$ mucin in lithogenic bile



- ↓ motility
 - Contractile of gallbladder (GB)
 - ↑ parasympathetic
 - ↓ sympathetic
 - ↑ fasting residual GB volumes
 - ↓ response to CKK
 - Likely important in CF, pancreatic insufficiency
- GB sludge
 - Cholesterol monohydrate crystals, Ca bilirubinate, mucin
 - Radiolucent cholesterol stones
 - Black stones – hypersecretion of bilirubin conjugates into bile
 - Hemolysis
 - Cirrhosis
 - Pigmental gallstones are seen in patients with chronic hemolytic anemia, liver disease, and with TPN.

Useful Quotes

“..... for the average patient, early operation [for acute cholecystitis] is preferable because

- The total length of hospitalization [is] reduced
- Costs are reduced
- Morbidity is less, and
- Deaths related to progressive acute cholecystectomy are prevented”

Feldman M, et al. Sleisenger and Fordtran’s Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier 2010, page 1130.

➤ Small intestine

21. Give 3 small intestinal factors contributing to the formation of gallstones.

- ↑ intake
 - ↑ parasympathetic
 - Diet of cholesterol
 - Supersaturated bile



- ↑cholesterol absorption
 - 1° ↑inefficiency of uptake
 - 2° ↑ dietary intake
- ↓ transit
 - ↑ gram + anaerobic bacteria → ↑ 7α-dehydroxylase activity
 - ↑ conversion of 1° cholic acid to 2° deoxycholic acid
 - ↑deoxycholic → ↑ lithogenicity of bile
- Dysfunction / resection of the terminal ileum → ↓ bile acid absorption → if hepatic synthetic reserve is associated from ileal loss → supersaturation of bile → stone formation

➤ Liver

22. Give the role of the hepatocyte in the **metabolism** of cholesterol (CH).

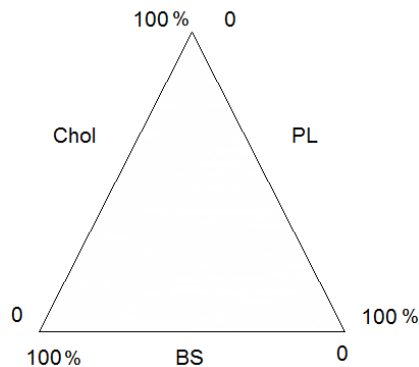
Cholesterol handling by the hepatocyte is determined by the following:

- CH uptake across the SM from LDL, HDL, CMR secretion of
 - CH across SM in VLDL back into portal blood
 - As CH in N-HDL (nascent HDL), using ABCA1
- Metabolism
 - De Novo synthesis of CH from acetate, through HMG-CoAR
 - Esterification of CH to CE (cholesterol ester) by way of ACAT
 - 7α-hydroxylation of CH to BA (bile acids) by
 - CYP7A1
 - CYP27A1
- Transfer of CH across CM by ABCG5/-G8
- If cholesterol saturation index (CSI) is > 1, bile is saturated, and cholesterol precipitates and form crystals

Abbreviations: ACAT, acyl-coenzyme A: cholesterol acyltransferase; CM, canalicular membrane of hepatocytes; CMR, chylomicron remnants; CYP27A, 27-hydroxylase ("acidic" pathway); CYP7A1, cholesterol 7α-hydroxylase ("neutral" pathway); HDL-L, high-density lipoprotein; HMG CoAR, 3-hydroxyl-3-methyl glutaryl-coenzyme A reductase; LDL, low-density lipoprotein; SM, sinusoidal membrane of hepatocytes; VLDL, very-low-density lipoprotein



➤ Liver “phase diaphragm”



- If cholesterol saturation index (CSI) > 1, bile is saturated, and cholesterol can precipitate and form crystals

Abbreviations: BS, bile salts; chol, cholesterol; PL, phospholipids

- Note: This figure is also referred to as “triangular co-ordinates”

➤ Risk factors

23. Give clinical risk factors for the development of gallstones.

- Hereditary
- Classical “4 Fs”
 - Female
 - Fertile
 - Forty
 - “fat” (obesity)
- Diet
 - ↑ calories
 - ↑ carbohydrates (refined)
 - ↑ saturated fats
- Origin
 - Sweden
 - Chile
- Gastric bypass surgery
 - TPN
 - Cholelithiasis
 - Acalculous cholecystitis



- Dyslipidemias
 - ↓ HDL-cholesterol
 - ↑ triglycerides
- Drugs
 - Estrogen / OCP (oral contraceptive pill)
 - Clofibrate
 - Octreotide
 - Ceftriazone
- Diabetes
- Loss of ileal function
- Spinal cord injuries

Contraceptive estrogens and conjugated estrogens, the lipid-lowering clofibrate, the somatostatin analog octreotide, and the cephalosporin ceftriaxone are drugs which are associated with an increased risk of gallstones.

24. Give the mechanisms for each of these four **classes of drugs** which lead to their increasing the risk of cholelithiasis.

- Conjugated estrogens and contraceptive steroids
 - Cholesterol synthesis
 - Estrogens activate the hepatic estrogen receptor α
 - The activated hepatic estrogen receptor α stimulate SREBP-2-responsive genes
 - Activated SREBP-2-responsive genes leads to
 - ↑ cholesterol synthesis and secretion into bile
 - Supersaturation of bile with cholesterol
 - Lipoproteins
 - Estrogens cause ↑ expression of hepatic LDL receptor
 - ↑ hepatic LDL receptor leads to ↑ clearance of LDL
 - ↑ clearance of LDL causes
 - ↓ plasma LDL
 - ↑ plasma HDL
 - ↑ liver LDL



- ↑ uptake of LDL into the liver causes
 - ↑ cholesterol synthesis
 - ↑ secretion into bile
- Smooth muscle
 - Estrogens slow smooth muscle motility, leading to gallbladder stasis
- Clofibrate
 - Clofibrate cause ↓ activity of 7α-hydroxylase
 - ↓ 7α-hydroxylase leads to
 - ↓ synthesis and secretion of bile acids from cholesterol
 - ↓ cholesterol solubility in bile
- Octreotide
 - Octreotide cause
 - ↓ gallbladder emptying
 - ↓ small intestine transit
 - ↑ “dwell” time for cholic acid to be dehydroxylated into the 2 bile acid, deoxycholic acid
 - ↑ deoxycholic acid absorption in EHC and return to the liver
 - ↑ deoxycholic acid secretion into bile canaliculus
 - ↓ solubilisation of cholic and chenich acids
- Ceftriaxone

When the saturation of ceftriaxone in bile is exceeded, ceftriaxone

- Forms insoluble salts with calcium → biliary sludge

“Never never, NEVER give up on your dreams.”

Sir Winston Churchill



➤ Clinical

25. Give the natural history of asymptomatic stones biliary pain, and acute cholecystitis.

- Asymptomatic stones
 - Risk of symptoms developing, 1.5% per year
- Biliary pain
 - Recurrence pain after 1 episode, 6% per year (~70%)
 - Severe complications, 1% to 2% per year
- Acute cholelithiasis
 - Resolves, 50%
 - Duct stones, 15%
 - Gangrenous gallbladder, 7%
 - Empyema, 6%
 - Perforation, 3%
 - Empty edematous cholecystitis, 1%
- Recurrent choledocholithiasis after sphincterotomy, 12%

Tricks of the Art: Palpation of gallbladder

- Gallbladder (GB) may often be enlarged without a palpable liver; you can better feel the GB with the patient on her/his left side.
- Obstructive jaundice plus palpable GB-unlikely to be due to stones (unless stones in cystic duct or Hartmann's pouch).
 - 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 tumours rarely
 - Ovarian tumours may be palpated in the midline, including at the umbilicus
 - Distended bladder is symmetrical, unless a diverticulum is present



26. In the context of cholelithiasis, give the meaning of **Mirizzi syndrome**.

- Acute cholecystitis complicated by jaundice due to
 - Type I
 - Stones in cystic duct at neck of gallbladder compresses hepatic duct causing CD (cystic duct) / Hartmann pouch obstruction, or causes stricture in the extrahepatic bile duct
 - Type II
 - Stone erodes into the hepatic duct, forming a cholecystocholedochal fistula

SO YOU WANT TO BE A GASTROENTEROLOGIST!

- Give the **mechanism of the pain** experienced in acute cholecystitis.
 - Stones irritate the gallbladder (GB) mucosa
 - The irritated GB mucosa releases phospholipase A
 - Phospholipase A converts lecithin to lysolecithin
 - Lysolecithin stimulates prostaglandin synthetase
 - ↑ prostaglandin synthetase leads to the production of ↑ prostaglandin in the GB wall
 - ↑ prostaglandins cause pain from cholelithiasis

The selection criteria for the use of oral ursodeoxycholic acid (UDCA) dissolution of gallstones relate to the characteristics of the stones, biliary pain without complications, and a functioning gallbladder. Please see Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier 2010, Table 66.1, page 1122 for details.

"In order to succeed, your desire for success
should be greater than your fear of failure."

Bill Cosby



SO YOU WANT TO BE A GASTROENTEROLOGIST!

- Give 3 factors are associated with an ↑ risk of the patient with gallstones developing **gangrenous or emphysematous cholecystitis**.

Risk factors for the development complicated acute cholecystitis:

- Diabetic
- Cardiovascular disease
- Male gender
- WBC > 150,000 / mm³

27. Give the pathogenesis of 3 **complications** of gallstone disease.

- Emphysematous cholecystitis
 - Multiple air pockets in wall of gallbladder in patient with acute cholelithiasis
 - Air pockets formed from Cl. Welchii, E. Coli, anaerobic streptococci (gas-forming organisms)
 - May occur in diabetics or the elderly (atherosclerosis of cystic artery)
- Cholecystoenteric fistula
 - Gallstone erodes through the wall of the neck of gallbladder into the duodenum stones larger than 25 mm may obstruct
 - Terminal ileum (gallstone ileus)
 - Mortality rate, 20%
 - Gastric outlet (Bonvert syndrome)
 - Three signs on plain abdominal film which are pathognomic of gallstone ileus
 - Pneumobilia suggesting cholecystoenteric fistula (duodenum or jejunum, stomach or hepatic flexure)
 - Small bowel dilation
 - Gallstone in RLQ (right lower quadrant, site stone obstructing the terminal ileum)
- Mirizzi syndrome
- Porcelain gallbladder
 - Focal or diffusion
 - Intramural calcification of the pancreas
 - With focal calcification, risk of gallbladder adenocarcinoma is 20%

➤ Diagnostic imaging



Abdominal Ultrasound for stones	Sensitivity

In GB	95-98%

In CBD	50%

- It has been suggested that an abdominal ultrasound is the best test to exclude other intra-abdominal conditions which may give similar clinical findings of RUQ pain, fever, leucocytosis, hyperamylasemia (or elevated serum lipase concentration).
- However, this approach can be challenged based on the performance characteristics of abdominal ultrasound, CT scan, and hepatobiliary scanning.
- ERCP “gallstone pancreatitis” (GSP) – only 10% have stone in CBD
 - When to be suspected GSP
 - Jaundice
 - LE’s increasing

} ERCP + Stone removal

SO YOU WANT TO BE A GASTROENTEROLOGIST!

Cholescintigraphy (aka hepatobiliary scintigraphy) has a sensitivity of about 95% and a specificity of about 90% for acute cholecystitis, and a normal scan excludes acute cholecystitis.

- Give the names of the 2 of the chemicals used for hepatobiliary scintigraphy.
 - HIDA ○ 99 m Tc – labelled hydroxyl iminodiacetic acid
 - DISIDA (diisopropyl iminodiacetic acid)
- In the context of an abdominal ultrasound performed for cholelithiasis, give the meaning of the wall-echo shadow sign (aka “double-arc shadow”)
 - The wall-echo shadow sign is the presence of Echogenic stones and acoustic shadowing in a contracted gallbladder filled with stones

Please see Feldman M, et al. Sleisenger and Fordtran’s Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier 2010, Table 67.2, for details of the diagnostic criteria for acute acalculous cholecystitis.



Acute Cholangitis

➤ Diagnostic imaging

13. Give the pro's and con's of 4 imaging tests for the diagnosis of acute cholangitis.

Parameter	Abdominal ultrasonography	CT	MRCP	EUS	ERCP
○ Availability	Widely available	Helical CT is rare	Available	Limited	Available
○ Portability	Portable	No	No	Limited	Limited
○ Invasiveness	Non-invasive	Non-invasive	Non-invasive	Invasive	Invasive
○ Need for sedation	No	No	Some patients	Yes	Yes
○ Sensitivity for detection of stones	Low	High (best for helical CT)	High	As good as, if not better than ERCP	Gold standard in most studies
○ Sensitivity for detection of strictures	Low	Fair	Best non-invasive method	Good	Excellent
○ Sensitivity for detection of tumours	Low	Good	Good	Excellent	Fair
○ Advantages	Widely available and non invasive	Widely available and accurate	Accurate without radiation exposure	Excellent for small stones, can be done at same time as ERCP	Therapeutic capability
○ Disadvantage	Low sensitivity	Effects on renal function, poor detection of small stones, not portable	Not compatible in patients with implanted metal devices, poor detection of small stones, not portable	Invasive, poor imaging of intrahepatic ducts	Invasive, possible worsening of condition owing to contrast injection

Abbreviations: ERCP, endoscopic retrograde cholangiopancreatography; EUS, endoscopic ultrasonography; MRCP, magnetic resonance cholangiopancreatography

Printed with permission: John G. Lee. *Nature Reviews Gastroenterology and Hepatology* 2009;6:533-541, page 535.



Common Bile Duct Disease

➤ Diagnostic imaging

14. Give the advantages and limitations 7 imaging modalities for detecting stones in the common bile duct.

Imaging modality	Description	Advantages	Limitations
○ Transabdominal ultrasonography	– Non-invasive procedure whereby high-frequency sound waves are converted into images	▪ First-line imaging modality ▪ Noninvasive ▪ Widely available and inexpensive ▪ Sensitivity 22%–65%* ▪ Specificity 70%–98%*	Artifacts may be caused by pneumobilia, surgical clips, biliary stents, duodenal diverticula, and calcifying pancreatitis
○ Endoscopic ultrasonography	– Use of a duodenoscope with an ultrasound transducer at its tip; images are more accurate and detailed than ones obtained by traditional ultrasonography because of the proximity of the transducer to the organs of interest	▪ More cost-effective than ERCP as a diagnostic tool ▪ Sensitivity 85%–97%* ▪ Specificity 90%–95%*	Not widely available; operator dependent; artifacts may be caused by pneumobilia, surgical clips, biliary stents, duodenal diverticula and calcifying pancreatitis
○ Intraductal ultrasonography	– Imaging of the biliary tree with an ultrasound transducer mounted at the tip of a catheter inserted through duodenoscope	▪ Sensitivity 97%–100%*	Probes have limited durability; stones, sludge and air bubbles may be indistinguishable



Imaging modality	Description	Advantages	Limitations
○ Laparoscopic intraoperative ultrasonography	– Intraoperative use of a specialized laparoscopic probe with an ultrasound transducer at the tip that is positioned to visualize the biliary system	▪ Sensitivity 80%–83%* ▪ Specificity 99%–100%*	Technically difficult to perform, especially in obese individuals; operator dependent; suboptimal visualization of the intrapancreatic portion of the common bile duct; artifacts may be caused by pneumobilia; detects sludge and small stones that are of limited clinical significance
○ ERCP	– Injection of a contrast agent directly into the common bile duct and imaging at duodenoscopy; considered the “gold standard” against which other imaging modalities are compared	▪ Sensitivity 89%–90%* ▪ Specificity 98%–100%*	Operator dependent; overall complication rate 4%–6%; mortality associated with procedure 0.1%–0.5%
○ Intraoperative cholangiography	– Insertion of a catheter through the cystic duct at the time of surgery, followed by injection of a contrast agent into the common bile duct and fluoroscopic imaging	▪ Sensitivity 75%–100%* ▪ Specificity 97%–100%*	Prolongs the duration of the surgical procedure; fluoroscopy use in the operating room



Imaging modality	Description	Advantages	Limitations
○ Helical computed tomography cholangiography	– Computed tomography of the biliary system following intravenous administration of a contrast agent	▪ Sensitivity 71%–85%* ▪ Specificity 88%–97%*	Similar drawbacks to those with intravenous cholangiography
○ Intravenous cholangiography	– Injection of a contrast agent intravenously, followed by radiographic imaging of the biliary system	▪ Relatively non-invasive; provides information on the biliary ductal system ▪ Sensitivity 48%–50%* ▪ Specificity 95%–97%*	Risk of reaction to contrast agent (1%) or renal impairment Limited value in patients with elevated bilirubin level because of decreased excretion of dye into the biliary system
○ Magnetic resonance cholangiopancreatography	– Magnetic resonance imaging whereby the hepatobiliary and pancreatic system are visualized using a specialized sequence	▪ Can be used when endoscopic ultrasonography and ERCP is not possible (e.g., after Roux-en-Y gastric or biliary procedures); diagnostic accuracy decreased if stones < 5 mm or common bile duct >10 mm ▪ Sensitivity 85%–100%* ▪ Specificity 91%–97%*	Hard for patients with claustrophobia to tolerate May cause dysfunction of certain pacemakers or implantable cardiac defibrillators, or may dislodge of metallic prostheses

Abbreviation: ERCP, endoscopic retrograde cholangiopancreatography.

*Using different reference standards across multiple studies.

Printed with permission: Almadi MA, et al. Management of suspected stones in the common bile duct. CMAJ. 2012;184(8):884-92. Table 2.



➤ Diagnostic imaging

SO YOU WANT TO BE A GASTROENTEROLOGIST!

- Give the differential diagnosis for the situation where abdominal ultrasound shows:
 - Dilated intrahepatic duct
 - Normal extrahepatic duct
 - Small (contracted gallbladder) filled with stones
 - These three features on abdominal ultrasound suggest compression of the common hepatic duct, such as from
 - Tumor (Klatskin tumor at bifurcation of R. & L. intrahepatic ducts with the hepatic duct)
 - Stone in neck of gallbladder or cystic duct (Mirizzi syndrome, Type I)

28. Give the approximate values for the performance characteristics for diagnostic imaging studies of the biliary tree.

	Cholelithiasis (> 2 mm)		Acute cholelithiasis		Choledocholithiasis	
	Sens	Spec	Sens	Spec	Sens	Spec
○ Abdominal ultrasound with acoustic shadow	> 95%	> 95%	Murphy sign, PPV, > 90% (if cholelithiasis is present)		< 50% for stones ~ 75% for diameter > 6 mm (dilation)	
○ Oral cholecystography	> 90%	> 90%	-	-	-	-
○ Hepatobiliary scintigraphy	-	-	95%	90%	-	-
○ ERCP	80%	-	-	-	95%	95%
○ EUS	-	-	-	-	95%	97%
					PPV, 99%	
					NPV, 98%	
○ MRCP	-	-	-	-	93%	94%

Abbreviations: NPV, negative predictive value; PPV, positive predictive value; sens, sensitivity; spec, specificity



Clinical Gem: **Best Tests**

- For cholelithiasis – abdominal ultrasound
- For acute cholelithiasis – biliary scan
- For choledocholithiasis – MRCP or EUS – for low-to-moderate pretest probability

Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier 2010, Table 65.6, page 1108.

SO YOU WANT TO BE A GASTROENTEROLOGIST!

- In the context of suspected gallbladder disease, give the meaning of the **Couvoisier sign**.
 - Painless jaundice plus a palpable gallbladder suggests a cancer obstructing the bile duct.

SO YOU WANT TO BE A GASTROENTEROLOGIST!

- Give the anatomical reason why the gallbladder is at high risk for the development of **necrosis**.
 - The gallbladder is at high risk of developing necrosis because the blood supply to the gallbladder is the cystic artery, an end artery, thereby placing the gallbladder at risk of ischemic necrosis if the blood flow through the cystic artery becomes impaired.

SO YOU WANT TO BE A GASTROENTEROLOGIST!

- Time for a trick question! Is cholecystectomy associated with an increased risk of colorectal cancer?
 - “Yes, but.....”; the risk is statistically significant, but the relative risk is low, < 2.0.



➤ Prevention

- UDCA (ursodeoxycholic acid) to prevent stone formation
 - Gallstones and symptoms are frequent after bariatric surgery, when the patient is on a very low calorie diet.
 - As a result, there is
 - ↑ liver synthesis of cholesterol
 - ↑ gallbladder (GB) mucin
 - ↓ GB motility
 - Giving UDCA prophylactically reduces gallstones from 28% to 3%
- Criteria for use of UDCA
 - Functioning gallbladder on HiDA scan
 - Radiolucent stones
 - Patent cystic duct
 - 20% to 70% dissolution rates
 - Current indication
 - Prevention of development of cholelithiasis in high risk persons (e.g. bariatric surgery, short bowel syndrome)

SO YOU WANT TO BE A GASTROENTEROLOGIST!

- Give the success rate for UDCA for the dissolution of gallstones, when appropriately used.
 - ↓ risk of biliary pain and acute cholecystitis, even without dissolution of stones
 - Dissolution rates of stones
- | <u>Size, mm</u> | <u>Rates</u> |
|-----------------|--------------|
| < 5 | 70% |
| < 10 | 49% |
| >10 | 29% |
- Recurrence of stones when stopping UDCA after initial successful dissolution, 50% in 5 years



- ESWL – extracorporeal shock-wave lithotripsy
 - For large impacted stones, not amenable to endoscopic removal
 - Complications
 - Hemobilia (10%)
 - Biliary sepsis (4%)

SO YOU WANT TO BE A GASTROENTEROLOGIST!

Recommended selection criteria are available for **extracorporeal shock-wave lithotripsy** (ESWL) (Please see Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. *Saunders/Elsevier* 2010, Table 66.2, page 1123). These are identical for UDCA, except that diameter of the single or multiple stones is optimally < 6 mm (and 6-10 mm acceptably) for ESWL.

- Give the success rate for ESWL when appropriately used.

○ Free of stones	Months	Proportion
	6	47% to 77%
	12	68% to 84%

○ Recurrence (cumulative)	Years	Proportion
	3	27%
	5	41%
	10	54%

- Give 3 factors which predict poor response rates to ESWL.
 - Stones that are
 - Multiple
 - Large (> 16 mm diameter)
 - Dense (CT density > 84 Hounsfield unit)
- Give 3 factors which predict poor response rates to ESWL.
 - Failure of dissolution or recurrence
 - Biliary pain, 33%
 - Petechiae, 8%
 - Obstruction of cystic duct, 5%
 - Hematurin, 4%
 - Gallstone pancreatitis, 2%
 - Hepatic hematomas, < 1%



- Surgery
 - Open cholecystectomy
 - MR > 65 0.03%
 < 65 0.5%
 - Laparoscopic cholecystectomy
 - MR 0.15%
 - Intra-operative conversion to open procedure 2-8%
 - Bile duct injury (same as for open cholecystectomy 0.14-0.5%)
 - Nasocystic drain
 - Use a nasocystic drain of a “hot” gallbladder (cholecystitis) in high risk patients
 - For EUS, the probe must be < 1 cm from GI tract
 - Treatments with EUS
 - Make a fistula
 - Insert a stent
 - Drain. debride cavity

SO YOU WANT TO BE A GASTROENTEROLOGIST!

- Give the risks of laparoscopic cholecystectomy.
 - Major morbidity, 5%
 - Need to convert from lap “chole” to open cholecystectomy, 3%
 - Bile duct injury, 0.5% (depends on surgeon’s experience)
 - Mortality, 60/ 10⁵ (0.06%)

SO YOU WANT TO BE A GASTROENTEROLOGIST!

There are numerous causes of abdominal pain or other symptoms after cholecystectomy (please see Feldman M, et al. Sleisenger and Fordtran’s Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier 2010, Table 66.7, page 1137), and these may affect one post-cholecystectomy patient in four. These causes may relate to biliary causes, pancreatic causes, other GI conditions, and extraintestinal disorders.

- Give the commonest cause of post-cholecystectomy pain.
 - The commonest cause of post-cholecystectomy pain is due to choledocholithiasis. In some persons, microlithiasis can only be diagnosed by staining the stools.



29. Give 4 **post-cholecystectomy complications**.

- CHD, CBD leak
- Stricture
- Choledocholithias
- Persistent pain (post-cholecystectomy pain) – SOD, IBS

Abbreviations: CHD, common hepatic duct; CBD, common bile duct; SOD, sphincter of Oddi; IBS, irritable bowel syndrome.

Adapted from: Glasgow, Robert E. and Mulvihill, Sean J. Treatment of Gallstone Disease. *Sleisenger & Fordtran's Gastrointestinal and Liver Disease: Pathophysiology/Diagnosis/Management* 2006; pg. 1424--36.

Useful Quotes

"..... the natural history of gallstones in diabetic patients follows the same pattern observed in non-diabetic patients. Prophylactic cholecystectomy is generally not recommended in patients with insulin-resistant diabetes mellitus and asymptomatic gallstones".

* Note:

- When diabetic patients develop biliary pain, early cholecystectomy should be performed because these patients have an increased risk of developing gangrenous cholecystitis.

➤ High risk patient

- Percutaneous cholecystectomy, followed by lap'chole'
- Early surgery preferred for acute cholecystitis

Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. *Saunders/Elsevier* 2010, page 1105 and 1130.

Useful Quotes

"..... cholecystectomy may be undertaken during pregnancy with minimal fetal and maternal morbidity but only when necessary".

Feldman M, et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. *Saunders/Elsevier* 2010, page 1132.



SO YOU WANT TO BE A GASTROENTEROLOGIST!

- Give 6 indications for prophylactic cholecystectomy.

Prophylactic cholecystectomy should be considered in

- The stones
 - Porcelain gallbladder (especially focal intramural calcification)
 - Stone > 25 mm in diameter
- The patient
 - Children
 - First Nations Persons
 - ↑ risk of GS-related gallbladder (GB) cancer (Ca)
 -
 - Morbid obesity
 - Heart / lung transplantation
 - Chronic hemolytic anemias¹
 - Sickle cell disease
 - B-thalassemia
 - Laparotomy (for purposes other than for cholecystectomy)

¹ Do cholecystectomy at the same time as splenectomy

ASGE guidelines on competence in performing ERCP

- 200 cases performed by trainee with expert supervision
- 80-90% cannulation rate
- Continued completion of 50 sphincterotomies / year

Useful Trivia

“.... It is unlikely that the ampulla [of Vater] is obstructed [by impaction of a stone within the common channel of the ampulla of Vater] in the presence of a normal serum bilirubin [i.e., the absence of hyperbilirubinemia]....”

(Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier, Philadelphia, 2010, page 1035).



Acalculous Disease

➤ Risk factors

SO YOU WANT TO BE A GASTROENTEROLOGIST!

Complications such as gallbladder empyema, gangrene of the wall and perforation occur in at least a half of persons with acalculous cholecystitis.

- Give the three conditions most commonly associated with Acalculous cholecystitis (aka necrotizing cholecystitis).
 - Old men with cardiovascular disease
 - In patients with
 - Trauma
 - Burns
 - Major surgery
 - HAART treatment for HIV / AIDS
 - Recipients of bone marrow transplantation
 - Oncological therapy using cytotoxic drugs given through the hepatic artery
 - Note that: The mortality rate of acalculous cholecystitis is about 20%, compared to < 1% of cholecystitis associated with gallstones.

➤ Diagnostic imaging

30. Give the findings on abdominal ultrasound, CT scanning and hepatobiliary scanning which suggest the diagnosis of acalculous cholecystitis.

Acalculous cholecystitis is suggested by the following findings on diagnostic imaging

➤ Abdominal ultrasound (US)	➤ CT scan	➤ Hepatobiliary scan
○ Gallbladder (GB) wall > 4 mm*	○ GB wall > 4 mm	○ Lack of “hot spot”** (failure of filling of GB, with passage of radionucleotide into duodenum)
	○ Sloughed GB mucosa	
○ Positive US Murphy sign		
○ Collection of pericholecystic fluid	○ Pericholecystic fluid	
	○ Intramural air	

* in absence of ascites or hypoalbuminemia

** false negatives with fasting or ICU illness



31. Give the performance characteristics of 3 diagnostic imaging tests for acalculous cholecystitis.

Diagnostic Imaging test	Sensitivity	Specificity
➤ Abdominal ultrasound	67% to 92%	90%
➤ CT scan	> 95%	> 95%
➤ Hepatobiliary scan ¹	> 90%	90%

¹ The morphine-augmented cholescintigraphy increases specificity to about 95%

SO YOU WANT TO BE A GASTROENTEROLOGIST!

- In the context of acalculous biliary pain and in the setting of apparently an idiopathic post-cholecystectomy syndrome, give the meaning of the Meltzer-Lyon test.
 - The Meltzer-Lyon test is the collection and staining of the stool to establish the presence of microlithiasis as a possible cause of post-cholecystectomy syndrome.
- Give the microscopic appearance of the substance examined in the Meltzer-Lyon test.
 - The Meltzer-Lyon test involves collecting and examining the stools for microlithiasis in the setting of the post-cholecystectomy syndrome.
 - Microscopic examination may show Rhomboidal cholesterol crystals or granules of calcium bilirulonate.

➤ Treatment

Useful Quotes

“Cholecystectomy has not typically been recommended for patients with acalculous pain and a normal GBEF [gallbladder ejection fraction > 35% on hepatobiliary scanning after the slow IV infusion of CCK].”



SO YOU WANT TO BE A GASTROENTEROLOGIST!

- While cholecystectomy is not recommended for acalculous biliary pain in the presence of a GBEF (gallbladder emptying fraction) > 35%, what is the outcome of the patient with a GBEF < 35%.
 - In the patient with acalculous biliary pain and an abnormal GBEF (< 35%), long-term symptom relief will occur in 65% to 85% following cholecystectomy, and in 50% without cholecystectomy.

A Follow-up Useful Quote

“.....although the GBEF [gallbladder ejection fraction on hepatobiliary scanning] is used commonly to evaluate patients with acalculous biliary-type pain, it is not a reliable predictor of the response to cholecystectomy.”

“There is never a better measure of what a person is than what he does when he’s absolutely free to choose.”

William M Bulger



Congenital Abnormalities of the Biliary Tract

SO YOU WANT TO BE A GASTROENTEROLOGIST!

- Give the sensitivity of a bile duct > 6 mm as a sign for choledocholithiasis.
 - Only about 75%

Positive scintigraphy has a specificity of about 90%.

- Give the causes of a false-positive test.
 - Fasting, or when dealing with a critically ill patient may give a false-positive hepatobiliary scan (i.e., non-visualization).
- Give the method used to overcome the false-positive HIDA scan results in the ICU setting.
 - The patient is given IV morphine, causing ↑ SOD (sphincter of Oddi) pressure and gallbladder filling, unless the cystic duct is truly blocked. The morphine-augment cholescintigraphy reduces the likelihood of a false-positive test by only about 50%.

Biliary Atresia

- Definition: “biliary atresia is characterized by the complete obstruction of bile flow as a result of the destruction or absence of all or a portion of the extrahepatic bile ducts” (Feldman M., et al. *Sleisenger and Fordtran's Gastrointestinal and Liver Disease*. 9th Edition. *Saunders/Elsevier*, Philadelphia, 2010, page 1052).
- Pathology
 - Bile duct proliferation
 - Bile stasis in canaliculi and cells
 - Bile plugs in portal tracts
 - Edema
 - Fibrosis
- Surgical treatment
 - Kasai hepatoportoenterostomy
 - Liver transplantation (for failure of portoenterostomy)



Choledochal Cyst

- Definition: Choledochal cysts are congenital anomalies of the biliary tract that are manifested by cystic dilation of the extrahepatic and intrahepatic bile ducts” (Feldman M., et al. Sleisenger and Fordtran’s Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier, Philadelphia, 2010, page 1058).
- Types
 - CBD (common bile duct)
 - Diffuse, fusiform dilations I
 - Diverticula II
 - Dilation of intraduodenal portion of CBD III
(aka choledochal cyst)
 - Intra- and extrahepatic bile duct cysts IV
 - Intrahepatic cysts (Caroli disease) V
- Clinical
 - Abdominal pain
 - Jaundice
 - Palpable mass (cyst)
- Complications of choledochal cysts
 - Biliary tree
 - Cholangitis
 - Strictures
 - Cholangiocarcinoma (occurs in 30%, especially type I and II)
 - Pancreas
 - Recurrent pancreatitis

Caroli Disease

- Definition: Segmental, saccular, congenital dilation of intrahepatic ducts, without obstruction
- Cause / association
 - Intrahepatic duct stones
 - Bacterial cholangitis
 - Renal tubular ectasia
 - ARPKD (autosomal recessive polycystic kidney disease)



Caroli syndrome

- Definition: Same as caroli disease, plus
 - CHF (congestive heart failure)
 - Choledochal cysts

Trivia alert: Note subtle differences between Caroli disease and Caroli syndrome

➤ Alagille syndrome (Familial Intrahepatic Cholestasis)

- Definition: Alagille syndrome is autosomal dominant familial intrahepatic cholestasis due to a decrease in the number of interlobular portal bile ducts (ratio of interlobular portal bile ducts to portal bile ducts to portal tracts < 0.4) due to mutations in the jagged 1 (JAG₁) gene, leading to periportal fibrosis and cirrhosis.
 - 94% of Alagille syndrome patients have mutations in the JAG₁ gene, and the remainder have mutations in the gene coding for the NOTCH₂ receptor.
- Associated changes in
 - Face
 - Wide forehead
 - Deeply set and widely spaced eyes
 - Small chin
 - Triangular face
 - Ears
 - Big
 - Spine
 - Short
 - Butterfly vertebrae
 - Heart
 - Murmurs (commonly pulmonary stenosis)



Gallbladder Cancer

- Demography: 1/10⁵, with global incidence rates of GB-Ca parallel to incidence rates of cholelithiasis.

32. Give 7 conditions associated with ↑ risk of development of GB-Ca.

- Calcification of gallbladder
 - GB-Ca 80% have cholelithiasis (all types of stones, especially > 10 mm)
 - Porcelain gallbladder (selective mucosal calcification, type II / III)
- Polyps > 2 cm
 - Adenomyomatosis
 - Very small risk
 - Forget symptoms → laparoscopic cholecystectomy (LC), any size of polyp
 - No symptoms
 - ≥ 1 cm polyp → LC
 - < 1 cm plus stones → LC
 - < 1 cm, no stones → US q 6 to 12 months
 - Symptoms → LC, regardless
- Bile duct
 - Choledochal cysts
 - Caroli disease
 - Pancreatic duct draining into bile duct
 - Cholangiocarcinoma [cholelithiasis, 2% develop GB-Ca]
 - Au PBD (anomalous union of the pancreatic and bile ducts outside the duodenal wall in a long common channel)
 - Consider prophylactic cholecystectomy
- Primary sclerosing cholangitis (PSC)
 - 20% develop GB-Ca
 - 50% of masses in GB of PSC patient are cancer
- Biliary dysplasia
 - Toxins e.g. 2° bile acids, mustard oil
- Infection
 - Chronic Salmonella Typhi / paratyphi carrier state
 - E. Coli
 - H. pylori
- Family history, first degree relative



Cholesterolosis

- Definition: “Macrophages in the wall of the gallbladder” appearing foamy from accumulation of cholesterol esters plus triglyceride.
- Types
 - Diffuse collections of cholesterol in GB wall, ending at cystic duct
 - Focal collections of cholesterol
 - Polyps (2 to 10 mm)
 - Combined diffuse plus polypoid accumulations
- Microscopy
 - Foamy macrophages of variable distribution (please see above)
 - Hyperplasia of the mucosa
 - Hyperplasia may be villous in appearance

Adenomyomatosis

- Definition: “An acquired, hyperplastic lesion [of the gallbladder] characterized by excessive proliferation of surface epithelium with invaginations into the thickened muscularis (Rokitansky-Aschoff sinus) or even more deeply” to produce tiny diverticulae (Feldman M., et al. Sleisenger and Fordtran’s Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier, Philadelphia, 2010, page 1146).
 - In adenomyomatosis, the Rokitansky-Aschoff sinuses are
 - Deep
 - Branched
 - Hyperplasia of the muscle layer
- Type
 - Generalized
 - Fundic
 - Segmental (may produce a narrowing of the lumen of the gallbladder)
 - “segmental adenomyomatosis should be considered a potentially premalignant lesion” (Feldman M., et al. Sleisenger and Fordtran’s Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier,



Abbreviations

^{99m} Tc-MAA	Perfusion body scan with ^{99m} Technetium-labeled macroaggregated albumin
AaPO ₂	Alveolar-arterial pressure gradient for oxygen
AFLP	Acute fatty liver of pregnancy
AFP	Alpha- fetoprotein
AH	Autoimmune hepatitis
ALD	Alcoholic liver disease
ALF	Acute liver failure
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AMA	Antimitochondrial antibodies
ANA	Antinuclear antibodies
ARBs	Angiotensin receptor blockers
ASA	Anti-smooth muscle antibody
AST	Aspartate aminotransferase
ATN	Acute tubular necrosis
BID	Twice a day
BMI	Body mass index
BNP	Brain natriuretic peptide
BPM	Beats per minute
BUN	Blood urea nitrogen
CAD	Coronary artery disease
CAT	Computerized axial tomography
CBD	Common bile duct



CEE	Contrast enhanced echocardiography
CHD	Common hepatic duct
CLT	Cadaveric liver transplatation
CT	Computerized tomography
CTP	Child Turcotte Pugh
E	Hepatitis B e antigen
E/A ratio	Ratio of early to late (arterial) phases of ventricular filling
ECG	Electrocardiogram
EGD	Esophagogastroduodenoscopy
ELISA	Enzyme linked immunosorbent assay
ERCP	Endoscopic retrograde cholangiopancreatography
ESLD	End-stage liver disease
EUS	Endoscopic ultrasonography
EVBL	Endoscopic variceal band ligation
EVL	Endoscopic variceal ligation
EVR	Early virologic response
FH	Family history
FNH	Focal nodular hyperplasia
GAVE	Gastric antral vascular ectasia
GGT	Gamma-glutamyltransferase
GI	Gastrointestinal
H	Hemalysis
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus



HE	Hepatic encephalopathy
HH	Hereditary hemochromatosis
HOMA	Homeostatic model assessment
HRS	Hepatorenal syndrome
HRT	Hormone replacement therapy
HSC	Hepatic stellate cells
HVPG	Hepatic venous pressure gradient
IBS	Irritable bowel syndrome
ICP	Intracranial pressure
ICP	Intrahepatic cholestasis of pregnancy
INR	International normalized ratio
IV	intravenous
IVC	Inferior vena cava
IVDU	IV drug use
LCHAD	Long chain 3-hydroxyacyl-CoA-dehydrogenase
LDLT	Live donor liver transplantation
LP	Thrombocytopenia
MAP	Mean arterial pressure
MCV	Mean corpuscular volume
MDA	Malondialdehyde
MELD	Model for end stage liver disease
MPAOP	Mean pulmonary artery occlusion pressure
MRCP	Magnetic resonance cholangiopancreatography
MRI	Magnetic resonance imaging
MTOR	Mammalian target of rapamycin
NA	Not available



NAS	NASH activity score
NASH	Non alcoholic steatohepatitis
NNFL	Non-NASH fatty liver
NP	Not applicable
NRH	Nodular regenerative hyperplasia
NVR	No virologic response
OGIS	Oral glucose insulin sensitivity index
OLT	Orthotopic liver transplantation
OR	Odds ratio
PA	Pulmonary artery
PaO ₂	Partial pressure gradient for oxygen
PBC	Primary biliary cirrhosis
PCLD	Polycystic liver disease
PCR	Polymerase chain reaction
PEI	Percutaneous ethanol injection
PFT	Pulmonary function testing
PHG	Portal hypertensive gastropathy
PHT	Portal hypertension
PMN	Polymorphonuclear (neutrophil) cell count
PNH	Paroxysmal nocturnal hemoglobinuria
PO	Orally
PPH	Portopulmonary hypertension
PS	Performance status
PSC	Primary sclerosing cholangitis
PT	Prothrombin time
PV	Pulmonary vein



PVR	Pulmonary vascular resistance
QD	Once daily
QUICKI	Quantitative insulin-sensitivity check index
RBBB	Right bundle branch block
RBC	Red blood cell count
RFA	Radiofrequency ablation
RIBA	Recombinant immunoblot assay
RV	Right ventricular
RVR	Rapid viral response
SAAG	Serum ascites albumin gradient
SBP	Spontaneous bacterial peritonitis
SC	Subcutaneously
SMA	Smooth muscle antibodies
SMR	Standard mortality ratio
SOD	Sphincter of Oddi
SS	Simple steatosis
SVR	Sustained viral response
TACE	Transarterial chemoembolization
TAE	Transarterial embolization
TID	Thrice a day
TIPS	Transjugular intrahepatic portosystemic shunt
TMP-SMX	Trimethoprim sulfamethoxazole
UDCA	Ursodeoxycholic acid
ULN	Upper limit of normal
US	Ultrasound
VR	Viral response



PANCREAS



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Acute Pancreatitis

➤ Definitions

- Acute pancreatitis is “.....an event triggered by sudden pancreatic injury that is followed by sequential inflammatory responses” (Feldman M., et al. Sleisenger and Fordtran’s Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier, Philadelphia, 2010, page 901).
 - Alternate definitions:....an acute inflammatory process of the pancreas with variable involvement of other regional tissue or remote organ systems” (Feldman M., et al. Sleisenger and Fordtran’s Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier, Philadelphia, 2010, page 931).
 - “...best defined clinically by a patient with [or all of the following criteria: (1) symptoms such as epigastric pain, consistent with the disease; (2) a serum amylase or lipase greater than three times a year limit of normal; or (3) radiologic imaging consistent with the diagnosis, usually using computed tomography (CT) or magnetic resonance imaging (MRI) ((Feldman M., et al. Sleisenger and Fordtran’s Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier, Philadelphia, 2010, page 960).
- Acute pancreatitis is..... an event triggered by sudden pancreatic injury that is followed by sequential inflammatory responses (Feldman M., et al. Sleisenger and Fordtran’s Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier, Philadelphia, 2010, page 901).
- Chronic pancreatitis “.....is a process that usually begins with recurrent pancreatitis and ends with immune-related destruction of the pancreas and widespread glandular fibrosis” ((Feldman M., et al. Sleisenger and Fordtran’s Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier, Philadelphia, 2010, page 931).
- Hereditary pancreatitis is “.....recurrent acute or chronic pancreatitis in an individual from a family in which the pancreatitis phenotype appears to be inherited through a disease-causing gene mutation expressed in an autosomal dominant pattern.”
 - Caused by mutations in PRSS₁ (cationic trypsinogen) gene
 - Clinical phenotype: recurrent acute pancreatitis
 - Penetrance of genotype to phenotype 80%
- Familial pancreatitis is “....pancreatitis from any cause that occurs in a family with an incidence [of pancreatitis] that is greater than would be expected by chance alone, given the size of the family and



incidence of pancreatitis within a defined population” (familial may or may not be caused by a genetic defect).

- Usually caused by
 - SPINK1 mutations, or
 - CFTR – SPINK1 genotypes atypical (homozygous or atypical compound heterozygous).
 - Tropical pancreatitis is “.....a form of early age-onset, non-alcoholic chronic pancreatitis occurring in tropical regions what is often clustered among family members, and that has a complex genetic basis.”
 - SPINK1 N34S mutations are common
- Demography
- Wide variation in quoted incidence ~ 25/10⁵
 - Incidence depends on causes
 - Most common causes are alcohol excess and cholelithiasis
- Causes / associations
1. Give 20 **causes** of acute pancreatitis.
- Idiopathic
 - Pancreas divisum
 - Choledochoceles
 - Inherited
 - CFTR, SPINK 1 & 2, CT gene and other mutations
 - Infection
 - Viral (mumps, Coxsackie, CMV, HSV, HIV)
 - Bacterial (Mycoplasma, Legionella, Leptospira, Salmonella)
 - Fungal (Aspergillus)
 - Parasitic (toxoplasma, cryptosporidium, Ascaris)
 - Inflammation
 - Penetrating gastroduodenal ulcer
 - Crohn disease
 - Ischemic
 - Ischemia
 - Vascular bypass surgery
 - Vasculitis



- Immune – Idiopathic autoimmune pancreatitis
- Obstruction – Gallstones
 - Biliary sludge
 - ERCP
 - Juxta-ampullary diverticulum
 - Ampullary neoplasms
 - Pancreatic neoplasms
 - Ampullary stenosis
 - Sphincter of Oddi dysfunction (SOD)
- Trauma – Blunt trauma
 - Penetrating trauma
 - Post ERCP
- Metabolic – Hypertriglyceridemia
 - Hypercalcemia
- Medications/
toxin – Ethanol
 - Methanol
 - Scorpion venom
 - Drugs: immunosuppressant, pentamidine, DDI, furosemide, thiazides, sulfasalazine, 5-ASA, salicylates, L-asparaginase, azathioprine, valproate, estrogen, sulindac, and others (see next question please)

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- Give 4 systemic diseases associated with pancreatitis.
 - Endocrine – Diabetes (ketoacidosis)
 - Hypercalcemia
 - Hematology – HUS (hemolytic uremic syndrome)
 - MSK – SLE (systemic lupus erythematosus)
 - Transplantation – The surgery itself
 - Immune suppressant drugs

*Note: These conditions may of course be included in the answer to the previous question.

XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX

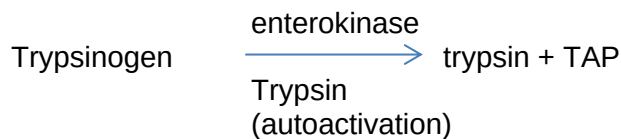


➤ Genetics

Acute pancreatitis may be caused by or associated with genetic defects which disrupt mechanisms which normally protects the process from trypsin associated injury, and therapy increases the susceptibility of the pancreas.

2. Give examples of four major **susceptibility genes** which cause or predispose to pancreatic disease.

- Cationic trypsinogen (PRSS₁) [protease serine 1]) gene mutations. There are 3 forms of trypsinogen
 - PRSS₁
 - Cationic trypsinogen (65%)
 - Protease serine 1 gene
 - PRSS₂
 - Anionic trypsinogen (30%)
 - PRSS₃
 - Mesotrypsin
- PST₁ (aka SPINK₁ [serine protease inhibitors Kazal type 1])
- Cystic fibrosis conductance regulator gene
- SBDS (Schwachman-Bodian-Diamond Syndrome) gene
- CASR (Calcium-sensing receptor) gene polymorphism
 - Trypsin
 - TAP (trypsinogen activation peptide) =



➤ Pathogenesis

- Inadvertent activation of trypsin in the pancreas is prevented by several protective mechanisms to prevent autodigestion



3. Give 6 major factors involved in the **pathogenesis** of acute pancreatitis.
- Failure of the normal mechanisms of protecting pancreas from autodigestion by trypsin and the pancreatic proenzymes activated by trypsin.
 - Activation of complement and Kinin systems
 - Associated genetic abnormalities
 - SPINK₁ (aka PSTI, pancreatic secretory trypsin inhibitor) mutations, resulting in loss of the normal effect of inactivating 20% of trypsin activity.
 - PRSS₁ (cationic trypsinogen gene)
 - Associated metabolic abnormalities e.g.
 - ↑ serum triglyceride
 - ↑ serum Ca²⁺
 - Acidosis
 - Disassociation
 - Between continued synthesis but blocked secretion of pancreatic enzymes
 - Enzymes accumulate in acini, causing damage
 - Possible colocalization of pancreatic enzymes in the lysosomes
 - Disruption of tight junctions
 - Pancreas: loss of paracellular barrier of acinar cells and intralobular pancreatic duct cells
 - GI tract: ↑ translocation of gut bacteria
 - Microcirculatory changes
 - Vasoconstriction
 - Release of VCAM-1 (an endothelial adhesion molecule)
 - PGs (prostaglandins)
 - PAF (platelet activating factor)
 - Leukotrienes
 - Ischemia
 - AV shunting in gut (plus ischemia → GI bleeding)
 - Possible reperfusion injury
 - Immune changes
 - Activation of complement and release of C5a
 - Recruitments of PMNs and macrophages
 - ↑ proinflammatory cytokines



- ↑ mediators of inflammation
 - Arachidonic acid metabolites
 - NO (nitric oxide)
 - Reactive oxygen metabolites
 - Failure of anti-autodigestion mechanisms
4. Give the four main mechanisms that have been suggested to **prevent autodigestion**.
- Separation of zymogen granules and lysosomes within the acinar cell
 - Trypsin inhibitors (SPINK) within the acinar cells and the pancreatic duct
 - The digestive enzymes secreted as precursors
 - Activation of trypsin actually occurs OUTSIDE the pancreas by duodenally secreted enterokinases (pepsinogen activated kinase)

Adapted from: Hirota M, et al. *J Gastroenterol* 2006;41(9):832-6.

5. Give the mechanisms by which the activity of trypsin is switched on and off.
- Activation of trypsin
 - TAP (trypsinogen activation peptide)
 - The trypsin plus TAP peptides form the inactive trypsinogen enzyme.
 - The TAP is cleared from trypsinogen to form the active trypsin.
 - The activation of the cleavage of TAP results from enterocyte brush border membrane enterokinase, or by other molecules of trypsin.
 - This activation of trypsin by trypsin is called “autoactivation”.
 - Trypsin is activated by ↑ Ca^{2+} (↑ Ca^{2+} blocks trypsin degradation), and is inactivated (degraded) in the acinar cell by ↓ Ca^{2+} (↓ Ca^{2+} blocks activation).
 - Degradation of trypsin also results from CTRC (chymotrypsin-C)
 - Dereactivation (autolysis) of trypsin
 - Trypsin may autolyse itself (“trypsin-mediated autolysis”) by acting at its own connecting chain.
 - CTRC (chymotrypsin C, aka enzyme Y) degrades the connecting chain calcium and
 - Calcium binding pockets (“switch” sites)
 - The local concentration of Ca^{2+} will either modify trypsin by



exposing or blocking the separate sites for exposing of the activation site ($\uparrow$ activation), or the autolysis ($\uparrow$ deactivation site).

- Calcium

- The local concentration of Ca^{2+} will activate or deactivate trypsin, either by exposing the activation site or the blocking site (autolysis).
- The intra-acinar (autoreaction) concentration of Ca^{2+} is detected ("sensed") by the G-protein coupled receptor CASR (calcium-sensing receptor).
- Low Ca^{2+} favours autolysis, and high Ca^{2+} favours autoreaction.
- Intra acinar cell Ca^{2+} concentrations may increase as a result of numerous factors:
 - $\uparrow$ extracellular Ca^{2+}
 - $\uparrow$ Ca^{2+} entry
 - Opening of Ca^{2+}
 - Channels
 - Tunnels
 - Bile reflux

➤ Types

6. Give the **types** of acute pancreatitis.

- Interstitial (edematous) pancreatitis
 - Mild disease on CT/MRI
 - No extrahepatic organ dysfunction
- Severe (necrotizing) pancreatitis
 - Atlanta criteria
 - Pseudocyst
 - Organ failure
 - $\text{SBP} < 90 \text{ mm Hg}$
 - $\text{Pa O}_2 \leq 60 \text{ mm Hg}$
 - Serum creatinine $> 2 \text{ mg/dL}$
 - $\text{GIB} > 500 \text{ mL/24 hr}$
 - Local complications (sterile or infected)
 - Abscess (not all guidelines use this term; infected pancreatic necrosis)
 - Peripancreatic necrosis



- Adverse early prognostic signs
 - Ranson's signs (3 or more criteria for non-gallstone pancreatitis)
 - APACHE – II (> 8 points)

Abbreviations: GIB, gastrointestinal bleeding; SBP, systolic blood pressure

➤ Clinical

7. Perform a focused **physical examination** for acute pancreatitis.

- Abdomen
 - Centre (periumbilical), Cullen sign
 - 1 or both flanks Grey, Turner sign
 - hepatomegaly
- Lung
 - Tachypnea
 - Shallow breathing signs of effusions, atelectasis
- CNS
 - Confusion
 - Agitation
 - Hallucinations
 - Coma
- Eyes
 - Jaundice
 - Band keratopathy
 - Lipemia retinalis
 - Purtscher retinopathy
- Salivary glands
 - Parotid glands large and tender
- Skin
 - Subcutaneous fat necrosis
 - Tender, red nodules
 - Distal extremities
 - Scalp, trunk, buttocks
 - Eruptive xanthomas
 - Thrombophlebitis
- MSK
 - Polyarteritis



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- In the context of Acute Pancreatitis, give the meaning of **Purtscher Retinopathy**.
 - In the patient with acute pancreatitis, there may be micro-embolization to the choroidal and retinal arteries.
 - This arterial embolization causes flame-shaped retinal hemorrhage, with cotton spots
 - These retinal lesions cause sudden blindness in the affected eye
 - Purtscher retinopathy is the development of sudden blindness in the persons with pancreatitis due to microembolization to the choroidal and retinal arteries, causing hemorrhages and cotton spots.

➤ Complications

8. Give 20 **complications** of acute 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)
 - CNS
 - Retinopathy
 - Psychosis
 - Heart
 - Shock (circulatory failure)
 - Death
 - Lung
 - Respiratory failure
 - GI
 - Bleeding
 - Pseudocyst
 - Abscess (infected pancreatic necrosis)
 - Endocrine
 - Hyperglycemia
 - Hypoglycemia
 - Hypocalcemia
 - Hypomagnesemia
 - Subcutaneous nodules due to fat necrosis
 - Nutrition
 - Malnutrition
 - Blood
 - Disseminated intravascular coagulation (DIC)
 - Kidney
 - Acute renal failure

Adapted from: Keller J, et al. *Best Practice & Research Clinical Gastroenterology* 2007; 21(3): pg. 524.



SO YOU WANT TO BE A GASTROENTEROLOGIST!

A patient with acute pancreatitis develops **upper GI bleeding** (UGIB).

- Give 5 causes of the UGIB which are related to the underlying acute pancreatitis.
 - Splenic artery - Rupture
 - Portal vein - Rupture
 - Splenic vein - Rupture
 - Gastric varices +/- esophageal varices
 - Pseudocysts - Pseudoaneurysms
 - Rupture of pseudoaneurysm (mortality rate, 40%)
 - Bleeding from wall of pseudocyst
 - Surgery, drainage - Necrotizing pancreatitis, WOPN, pseudocyst
 - Walled-off pancreatic necrosis (WOPN)
- Give the anatomical basis for the development of gastric varices arising from splenic vein thrombosis in a patient with chronic pancreatitis.
 - Obstruction of splenic vein → ↑ flow in short gastric veins → coronary vein → development of variceal channels in gastric cardia/fundus.

Risk stratification

There are numerous ways to predict the severity of pancreatitis, including clinical profile, scoring systems, organ failure, or anatomic complications.

Clinical factors relate to severity of pancreatitis

- Age
- BMI (body mass index)
- ↑ Hct (hematocrit) or BUN (blood urea nitrogen)
- Lung
 - Pleural effusions
 - Infiltrates



- SIRS ≥ 2 of the following
 - RR > 20 / min, or $p\text{CO}_2 < 32$ mm Hg
 - PR > 90 bpm
 - RT $36^\circ\text{C} > 38^\circ\text{C}$, or
 - WBC $< 4,000$ or $> 12,000$ / mm^2

Abbreviations: BMI, body mass index; BUN, blood urea nitrogen Hct, hematocrit; PR, pulse rate; RR, respiratory rate; RT, rectal temperature; SIRS, systemic inflammatory response syndrome

9. Give the **risk stratification** and management of the patient with acute pancreatitis.

- Clinical criteria-based scoring systems: Ranson, Glasgow, Apache (not accurate until 48 hours)
- Atlanta symposium criteria: Pancreatic necrosis (seen in 20% of acute pancreatitis)
- SIRS (systemic inflammatory response syndrome) leading to organ failure: cardiovascular, pulmonary, renal, GI bleeding
- Laboratory
 - Hematocrit
 - Urinary TAP (trypsinogen activation peptide; not surrogate markers of inflammation)
- Diagnostic imaging: CT, MR – sensitive for necrosis (note: the amount of necrosis does not correlate with the development of organ failure; necrosis may not develop for 24-48 hours, so CT may be negative for detectable necrosis)

10. Give 5 methods used to **estimate the severity** of acute pancreatitis.

➤ Clinical

- Apache II > 8
- Apache 0 > 10
- Ranson ≥ 3
- Glasgow score ≥ 3
- Evidence of systemic complications



➤ Laboratory

- Hematocrit $\geq 44\%$
- $\uparrow$ CRP

➤ CT scan

- CT $\geq 30\%$ pancreatic necrosis

Source: Vege Santhi Swaroop, and Baron Todd H. *Mayo Clinical Gastroenterology and Hepatology Board Review*: page 461.

Trivia

- Patients with acute pancreatitis and who are found within 24 hours of admission to have pleural effusion and/or infiltrate on chest X-ray are more likely to have a worse prognosis.
- These complications are more likely to develop if the necrotizing pancreatitis was treated with necrosectomy.

11. Give the performance characteristics of 4 **predictors of severity** of acute pancreatitis.

	Sensitivity	Specificity	PPV	NPV
○ Ranson (cut off, 3 signs)				
– At 48 hours	40% to 88%	43% to 90%	50%	90%
○ Apache-II				
– At admission	34% to 70%	76% to 98%		
– At 48 hours	< 50%	90% to 100%		
○ Hematocrit > 44%				
– At admission	72%			
– At 24 hours	94%			96%
○ C-reactive protein	60% to 100%	75% to 100%		
○ Fluid on peritoneal lavage	36% to 72%	80% to 100%		
○ Procalcitonin	86%	95%		

Abbreviations: NPV, negative predictive value; PPV, positive predictive value

Note: it is the NPV of Ranson criteria and hematocrit which are most helpful clinically, in terms of predicting who will not have severe acute pancreatitis.



MCQ Alert

- In a patient with acute pancreatitis, suspect severe pancreatitis (necrosis), if the stem provides
 - History / signs
 - Mention of cytokines / leukotrienes
 - Fever, hypotension, tachycardia, dyspnea, oliguria
 - Abdominal guarding, rebound tenderness, ileus
 - Hemorrhage
 - Persisting /non-responsive pain
 - Abnormal blood tests
 - Abnormal CT scan (e.g., hematocrit or WBC, but not the level of the elevation of an
 - Non-enhancing areas of large portions (> 50%) of pancreas
 - The patient has experienced repeated episodes of severe abdominal pain radiating to the back, in associating with high levels of alcohol ingestion. On the occasion she/ he had similar pain and alcohol abuse, and the serum amylase or lipase is normal. You are offered several plausible MCQ choices, as well as acute pancreatitis. Chronic pancreatitis is the answer
 - Caution: normal serum amylase or lipase do not R/O chronic pancreatitis.
 - In the patient with acute pancreatitis, suspect biliary tract gallstones if
 - Bilirubin > 4 mg/dL
 - ALT, AST > 1000 U/mL
 - If the patient with acute pancreatitis has also been drinking alcohol recently, the ALT, AST may be > 1000 U/mL, and the bilirubin may be increased (true, often > 15 mg/dL). But, alcoholics have an ↑
-
- Scoring systems for severity or complications of acute pancreatitis useful in
 - First 24 hours
 - Apache II
 - BISAP (bedside index for severity in acute pancreatitis)



- BUN (blood urea nitrogen), or Hct (hematocrit), especially when measured serially; also useful at 48 hours
- First 48 hours
 - Ranson score (most useful to exclude severe pancreatitis)
 - Glasgow score
 - Hct (hematocrit)

12. Give the specific predictions made from 4 **scoring systems** of acute pancreatitis.

○ Ranson score	– Pancreatic necrosis
	– Infected necrosis
	– Systemic complications
	– Death
○ Apache-II score	– Severity of pancreatitis
	– Death
○ Hematocrit	– Pancreatic necrosis
○ C-reactive protein	– Severity of pancreatitis
○ Peritoneal lavage	– Death
○ Procalcitonin	– Organ failure
○ BISAP	– Complications
	– Death
○ CT grading scores	– Local complications (pseudocyst, abscess)

Abbreviation: BISAP, bedside index for severity of acute pancreatitis

13. Give the **Ranson** prognostic criteria for acute pancreatitis.

➤ On admission

○ Age (years)	>55	>70
○ White blood cell count (cells/mm ³)	>16, 000	>18, 000
○ Blood glucose (mg/dL)	>200	>220
○ Lactate dehydrogenase (IU/L)	>350	>400
○ Aspartate aminotransferase (IU/L)	>250	>250



➤ During Initial 48 hours

○ Decrease in hematocrit (%)	>10	>10
○ Increase in blood urea nitrogen (mg/dL)	>5	>2
○ Calcium (mg/dL)	<8	<8
○ pO ₂ (mm Hg)	<60	NA
○ Base deficit (mEq/L)	>4	>5
○ Estimated fluid sequestration (L)	>6	>4

Source: Quoted from original paper in Steinberg, William M. *Sleisenger & Fordtran's Gastrointestinal and Liver Disease: Pathophysiology/ Diagnosis/Management* 2006: 1241-1270.

14. Give the components which comprise the **Marshall scoring system** for the diagnosis of **Multisystem Organ Failure (MOF)**.

- 2 or more falling on same day
- Mortality rate ~ 50%
- Heart
 - Myocardial infarction
 - Dysrhythmias
 - Pericardial effusions
- Lung
 - Pleural effusion
 - Pneumonia
 - Atelectasis
 - Elevated diaphragm
 - ARDS
- Kidney
 - Hypovolemia
 - Hypotension
 - Acute tubular necrosis
 - Shock
- CT Grading System (Balthazar) and CT Severity Index
 - Extent of fluid collection and necrosis



➤ Laboratory

- Pancreatitis-associated protein (PAP) and Pancreatic-specific protein (PSP) have the same accuracy as serum amylase for diagnosing acute pancreatitis.
- The most laboratory tests used to predict the severity of acute pancreatitis are surrogate markers of local inflammation.
- Urinary TAP (trypsinogen activation peptide) is a marker for
 - Pancreatic necrosis
 - Systemic inflammatory response (sepsis)
- The extent of elevation of serum amylase or lipase do not correlate with the severity of pancreatitis.
- Performance in acute pancreatitis
 - Elevated serum amylase or lipase concentrations are only ~85% sensitive, and their specificity, especially for values of $< 3\times$ ULN, is only ~50%.

15. Give 6 causes of an elevated serum amylase/lipase.

- Salivary glands
 - Salivary gland disease, e.g. mumps
- Stomach
 - Peptic ulcer disease with penetration
- Small bowel
 - Intestinal ischemia
 - Small bowel obstruction
 - Bowel perforation
 - Celiac disease
- Pancreas
 - Pancreatitis
 - Pancreatic cancer
- Colon, appendix
 - Appendicitis
- Biliary tree
 - Cholecystitis



- In a patient with acute pancreatitis, the best management steps are
 - Large volume IV infusion
 - Risk stratification for necrotizing pancreatitis
 - Evaluation for cause
 - Alcohol
 - Gallstones
 - Drugs
 - $\uparrow$ TG (> 1000 mg/dL)
 - $\uparrow$ Ca^{2+}
 - Post ERCP

16. Give the reason why **serial serum ionized Ca^{2+}** must be measured in the patient with acute pancreatitis.

- Hypocalcemia may occur in acute pancreatitis.
- Correct any associated hypomagnesemia
- Cautious use of IV calcium gluconate to prevent dysrhythmia (IV Ca^{2+} increases binding of Ca^{2+} to myocardial receptors; $\uparrow$ Ca^{2+} on myocardial receptors displaces K^+ from the myocardial receptors, leading to dysrhythmia)

Please see Feldman M, et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier 2010, Table 58.8, for Table of Complications of Acute Pancreatitis

17. Give 3 causes of **falsely negative serum amylase** in acute pancreatitis.

- Blood sampled too late after onset of symptoms ($T_{1/2}$, 10 hrs)
- Not correlated with severity of pancreatitis (may be normal with fatal disease, or with mild disease)
- Acute on chronic pancreatitis
- Hypertriglyceridemia-associated pancreatitis ($\uparrow$ triglyceride in serum may produce an inhibitor of amylase, resulting in falsely low serum amylase concentrations)



18. Give 6 causes of falsely **positive serum amylase**.

- Macroamylasemia (amylase binds to immunoglobulin in serum, and is not filtered / excreted by kidney)
- Disease of
 - Salivary glands
 - Fallopian tubes
 - Ovary
 - Cyst
 - Cystadenoma
- Kidney
 - Renal failure - ↓ clearance of amylase
 - Hemodialysis (> peritoneal dialysis)
- Psychiatric disorders
 - Munchausen syndrome

“Everyone wants to live on top of the mountain, but all the happiness and growth occurs while you're climbing it.”

Andy Rooney Og Mandino



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- In the context of an elevated serum amylase, give the rationale for measuring **UACR** (a urinary amylase-to-creatinine ratio), and **urinary salivary amylase**.
 - ↓ UACR
 - In macroamylasemia, where amylase is bound to immunoglobulin and persists in the blood because of lack of renal excretion, the UACR may be low
 - UACR may also be low with renal insufficiency
 - UACR may be high when contaminated with salivary amylase
 - ↑ urinary salivary amylase
 - Saliva contains amylase, and if the patient spits into the urine collection, the total amylase level will be increased, and the UACR will also rise.
 - Persons with Munchausen Syndrome may spit into urine sample, so that the urine total amylase and UACR are increased.
- Give the advantage of measuring serum lipase rather than amylase to diagnose acute pancreatitis.
 - Serum lipase concentrations are not elevated in disorders of salivary glands, fallopian tubes or ovary with Munchausen syndrome or macroamylasemia.
 - Measurement of the serum lipase concentration has greater sensitivity, and especially better specificity.

Recurrent attacks of acute pancreatitis may be caused by alcohol abuse or by gallstones. In the patient with both alcohol use and known gallstones, the finding of an ↑ ALT (> 3x ULN) is often used clinically as a reliable indicator of biliary pancreatitis.

➤ Diagnostic imaging

- Abdominal ultrasound may be hypoechoic in acute pancreatitis, but its usefulness may be limited by overlying bowel gas (in ~ 1/3), its poor sensitivity to detect CBD stones, and the challenge to differentiate hypoechoic areas from acute versus chronic pancreatitis, a malignancy.
- Sensitivity of detecting CBD stones EUS = ERCP = MRCP > US or CT
- In the patient with suspected necrotizing pancreatitis, EUS is superior to ERCP because of the lack of risk of introducing infection.



- Abdominal ultrasound not sensitive to detect cholelithiasis / choledocholithiasis in acute pancreatitis; use MRI or EUS
19. Give the way to distinguish on diagnostic imaging the possibilities of alcoholic pancreatitis versus biliary tract stones.
- Abdominal ultrasound
 - Not sensitive for bile duct (BD) stones
 - May show indirect evidence of
 - Stones
 - Dilated BD or cystic duct
 - Cholecystitis
 - Gallbladder wall > 4 mm
 - ↑ pericholecystic fluid

The **abdominal plain film** (APF) is useful to support the diagnosis of acute pancreatitis.

20. Give findings on the APF (abdominal plain film) which suggest acute pancreatitis, and distinguish between the “sentinel loop” and the “colon cut-off” signs.
- Stomach
 - Anterior displacement
 - Separation of the contours of the stomach and transverse colon
 - Duodenum
 - Descending portion displaced and stretched by head of enlarged pancreas
 - Jejunum / Ileum
 - “sentinel loop” (localized dilated segment of small bowel)
 - Ileus
 - Colon
 - “colon cut-off” sign
 - Spasm of colon with
 - Proximal dilation
 - Distal lack of gas
 - Irregular haustral pattern
 - Gallbladder
 - Calcified stones



- Pancreas
 - Stones
 - Calcification
 - Ascites
 - Retroperitoneal air (abscess)
 - Gas-forming organism
 - Microperforation of gut
 - Adjacent pseudocyst
- Treatment
 - Pain control
 - Risk stratification
 - IV fluids, approximately 250 cc/hr (3 cc/kg per hr) for 24 hr, then reassess for rate / volume depending upon clinical status.
 - NG/NJ tube feeding (no difference in outcome, NG = NJ feeding)
 - Antibiotics
 - Only if infected necrosis suspected (usually after day 10)
 - Do not give prophylactically since only 1/3 of patients with necrosis can develop infected necrosis
 - Early ERCP for
 - Gallstone pancreatitis (ALT 3XULN, PPV- 95%; ↑bilirubin on day
 - Sphincterotomy and stone extraction
 - CT-guided FNA for culture
 - Debridement
 - By surgery, endoscopy, radiology

Abbreviation: EUS, endoscopic ultrasound; FNA, fine needle aspiration; NG/NJ, nasogastric/ nasojejunal; ULN, upper limit of normal; US, ultrasound

Adapted from: Forsmark CE, and Baillie J. *Gastroenterology* 2007;132(5):2022-44.

- Complications
 - Pseudocyst “.....is a fluid collection that persists for 4 to weeks and becomes encapsulated by a wall of fibrous or granulation tissue (Feldman M., et al. *Sleisenger and Fordtran's Gastrointestinal and Liver Disease*. 9th Edition. Saunders/Elsevier, Philadelphia, 2010, page 941).



- Usually adjacent to the pancreas, but occasionally seen in pelvis or chest
- Conceptually, fluid filled sacs, sometimes with necrotic pancreatic debris
- Pseudocyst plus liquefied necrotic debris after 5 to 6 weeks may be termed WOPN (walled off pancreatic necrosis)
- When there is infection, may be called infected pseudocyst or infected necrosis, rather than an “abscess”
- Bleeding into a pseudocyst is usually from a pseudoaneurysm.
- Pancreatic abscess is “...a circumscribed intra-abdominal collection of pus occurring after an episode of acute pancreatitis or pancreatic trauma” (Feldman M., et al. Sleisenger and Fordtran’s Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier, Philadelphia, 2010, page 961).
 - Preferred terms:
 - Infected pseudocyst (always contains liquid)
 - Infected necrosis (liquid plus debris with the debris becoming liquefied after 5 to 6 weeks)

Suggested in-depth background reading Re Acute Pancreatitis

Feldman M., et al. Sleisenger and Fordtran’s Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier, Philadelphia, 2010:

Table 58.2 Ranson’s prognostic criteria, page 960

Table 58.3 Conditions that predispose to acute pancreatitis, page 963

Table 58.4 Drugs associated with acute pancreatitis, page 965

Table 58.5 Complications of acute pancreatitis, page 975

Table 58.7 Computed tomography (CT) severity index (CTSI), page 980

Alcoholic Pancreatitis

➤ Pathology

- “About 60% of persons who present with their first attack of acute alcoholic pancreatitis have already developed histologic chronic pancreatitis” (Feldman M., et al. Sleisenger and Fordtran’s Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier, Philadelphia, 2010, page 989).
- In persons with acute alcoholic pancreatitis who have not yet developed obvious chronic pancreatitis, stopping alcohol.
 - ↓ rate of progression to chronic pancreatic insufficiency
 - Does not alter the frequency of recurrent attacks of acute pancreatitis



➤ Pathophysiology

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- Give the pathophysiology of alcohol-associated damage to the pancreas.
 - Direct effect of alcohol and its “toxic” metabolites on pancreatic acinar cells.
 - ↑ lithogenicity of pancreatic fluid (alcohol-related ↑ secretion and viscosity of pancreatic juice → precipitation of protein (such as GP-2) → formation of pancreatic stones (crystals of calcium carbonate, polysaccharides, fibrillar proteins, and a gel-like matrix)
 - Acute and sometimes subclinical pancreatitis → scarring of preductular area → stasis of ductules → progression to fibrosis
 - Acute pancreatitis activates trypsin → ↑ inflammation → ↑ cytokines

21. Give the pathophysiology of chronic pancreatitis due to alcohol abuse.

- Direct injury by alcohol or a metabolite
 - Liver
 - Acetaldehyde
 - Pancreas
 - FAEs (fatty acid esters) → ↑ Ca_i^{2+}
- Oxidative stress
 - Production of free radicals
 - ↑ peroxidation of membrane lipids
- CCK
 - Alcohol-associated ↑ sensitivity of acinar cells to CCK
 - Redirection of CCK-mediation zymogen granule exocytosis from apical to basolateral membrane of acinar cell.
- Genes / enzymes
 - Alcohol-associated
 - Altered expression of genes responsive to physiologic stress
 - Over
 - ↑ expression / activity of necrosis / apoptosis



- Stellate cells
 - ↑ activity of pancreatic acinar cells associated stellate (myofibroblastic) cells
 - ↑ extracellular matrix → ↑ fibrosis → ischemia
 - ↑ proliferation
 - Phagocytosis
 - Alcohol / alcohol metabolites
 - Cytokines (from necrosis of cells)
 - Growth factors (PDGF, TGF-β1)
 - Transcription factors
 - Angiotensin II
 - Autocrine factors
- Protein precipitation (plugs)
 - Alcohol stimulates pancreatic secretion of fluid with ↑ protein, ↓ volume and HCO_3^-
- Gain of function gene mutation, leading to SAPE
 - CFTR (cystic fibrosis transmembrane conductance regulator gene)
 - PRSS1 (cationic trypsinogen gene)
 - SPINK1 (a trypsin inhibitor)
 - These genetic mutations are hypothesized to lead to repeated episodes of acute pancreatitis, which set in motion a process that leads to chronic pancreatitis (SAPE, sentinel acute pancreatitis event)

Abbreviations: Ca_i^{2+} , intracellular Ca^{2+} ; CCK, cholecystokinin; PDGF, platelet-derived growth factor; SAPE, sentinel acute pancreatic event; TGF, transforming growth factor

Influence of Obesity

- Associated with
 - Severe acute pancreatitis
 - Increased risk of developing multisystem organ failure



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In the context of acute pancreatitis, ↑ **BMI is a risk factor** for “severe” disease.

In obesity in acute pancreatitis, there are ↑ unsaturated fatty acids (UFAs) from the breakdown of visceral adipocyte triglycerides, which are proinflammatory.

- Give characteristics of acute pancreatitis which are more prominent in obesity (↑ BMI).
 - In the obese patient with acute pancreatitis, there are increased
 - ↑ local complications
 - Pancreatic necrosis
 - Infected
 - Sterile
 - Multisystem organ failure (MOF)
 - Respiratory failure
 - Renal failure
 - Sterile pancreatic necrosis
 - Death

ERCP-Associated Acute Pancreatitis

➤ Definition

- Pain + > 3x ↑ amylase within 24 hours requiring admission > 48 hrs
- Use prophylactic stents in high risk patients



22. Give 10 **risk factors** associated with the development of post-ERCP pancreatitis.

- Operator related
 - Lower ERCP volume
- Patient related
 - Younger age
 - Female sex (possibly)
 - Suspected sphincter of Oddi dysfunction (SOD)
 - Normal bilirubin
 - History of pancreatitis, recurrent of post-ERCP pancreatitis
 - Prior post-ERCP pancreatitis
- Procedure-related factors
 - Difficult or multiple cannulation attempts
 - Multiple pancreatic contrast injections
 - Pancreatic acinerization
 - Precut sphincterotomy
 - Endoscopic papillary balloon dilation
 - Sphincter of Oddi manometry
 - Distal common bile duct diameter ≤ 10 mm
 - Procedures not involving stone removal

Abbreviation: CCK, cholecystokinin; ERCP, endoscopic retrograde cholangiopancreatography

Printed with permission: Blero D, et al. Endoscopic complications--avoidance and management. Nat Rev Gastroenterol Hepatol. 2012;9(3):162-72. Box 1.

The placement of temporary prophylactic pancreatic duct stents is suggested for high risk patients following ERCP.



23. Give 3 features giving a high risk of post-ERCP pancreatitis and 3 features giving a low risk.

High	Low
○ Recent biliary sphincterotomy	○ Young
○ Ampullectomy	○ Female
○ Sphincter of Oddi dysfunction	○ Non-dilated bile ducts
○ Prior episode of post-ERCP pancreatitis	○ Trainee participation in procedure

Adapted from: Elta GH. *Gastrointest Endosc* 2008;67(2):262-64.; and Freeman ML, et al. *Gastrointest Endosc* 2001;54(4):425-434.

Indications for prophylactic pancreatic stent placement during ERCP

Necrotizing Pancreatitis and Abscess

➤ Pathological types

- Walled-off pancreatic necrosis (WOPN)
 - Several weeks after pancreatic necrosis and duct disruption, the cystic area contains liquid as well as solid material (non-enhancing pancreatic parenchyma on contrast-enhanced CT scan).
- Pancreatic abscess
 - “.....infected pseudocyst or infected liquefied collections without significant solid debris (pancreatic necrosis” (Feldman M., et al. Sleisenger and Fordtran’s Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier, Philadelphia, 2010, page 1038).
 - Strictly speaking, a pancreatic pseudocyst is not a cyst, because although there may be cystic spaces filled with pancreatic secretion fluid from a duct which has been disrupted by obstruction or inflammation, the cystic space does not have an epithelial lining, and so is actually not a true cyst.
 - Cytology of fluid in pseudocysts may show histiocytes.
 - ERCP / MRCP – shows communication with pancreatic duct



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- Give the pathophysiology of the failure of 3 organs in necrotizing pancreatitis.
 - Heart
 - SIRS (systemic inflammatory response syndrome)
 - Activation of
 - Trypsin
 - Phospholipase
 - Elastase
 - Release into portal circulation of TNF, PAS
 - Activation of hepatic Kupffer cells
 - ↑ CRP (C-reactive protein)
 - ↑ IL-6
 - Lung
 - ARDS (acute respiratory distress syndrome)
 - Breakdown of surface from
 - ↑ activity of phospholipase A
 - Kidney
 - ↓ SBP (hypotension) ↓ blood volume (hypovolemia)
 - GI tract
 - Microcirculatory changes e.g. vasoconstriction → ischemia, AV shunting in gut
- In the context of the patient with chronic pancreatitis and upper GI bleeding, what is “hemorrhage pancreaticus”.
 - Hemorrhage pancreaticus is bleeding from the wall of the pseudocyst into the pancreatic duct.

➤ Pancreatic necrosis

➤ Definition

- “Necrotizing pancreatitis is defined, in the absence of laparotomy or autopsy, by the presence of greater than 30% of non-enhancement of the pancreas on a contrast-enhanced CT scan”, or MRI (Feldman M., et al. Sleisenger and Fordtran’s Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier 2010, page 981).



➤ Pathology

- Necrosis of pancreatic tissue, often with associated peripancreatic fat necrosis, and accompanied by disruptions in pancreatic ducts.
- Necrotizing pancreatitis may be infected (1/3) or non-infected (2/3)

➤ Clinical course

- Persons with pancreatic necrosis resulting from an episode of acute pancreatitis may progress to developing chronic pancreatitis associated with exocrine (exo) or endocrine (endo) insufficiency.
 - Overtime, WOPN (walled-off pancreatic necrosis) develops, and if symptomatic may be safely drained with
 - Short stature
 - Surgery
 - Percutaneous drainage
 - Endoscopic drainage

➤ Investigation

- CT-FNA helps to establish if necrosis is infected

➤ Treatment

- Avoid using routine prophylactic antibiotics in necrotizing pancreatitis (i.e. to attempt to prevent non-infected necrosis from becoming infected).
- For infected necrosis or abscess
 - Use IV antibiotics which act against gram-negative aerobic or anaerobic species, and which penetrate the pancreas (e.g. imipenem, fluoroquinolones, metronidazole)
 - These antibiotics the mortality from infected pancreatic necrosis
- Avoid early debridement (necrosectomy)
 - Mortality rate 15% to 73%
 - Wait 4 weeks before considering surgical drainage

Development of insufficiency	No necrosectomy	Necrosectomy
Endocrine	26%	75%
Exocrine	13%	58%

- Up to two-thirds of patients having a surgical resection for pain from chronic pancreatitis develop steatorrhea.



Gallstone Pancreatitis

➤ Definition

- “..... an outcome following ERCP and sphincterotomy in gallstone pancreatitis [which] results from reduced biliary sepsis rather than impairment in pancreatitis”.

➤ Clinical

- Abdominal pain, ↑ serum lipase, ↑ ALT > 150 IU / L (2-3x > ULN): PPV (positive predictive value) 0.95 (95% likelihood of gallstone pancreatitis)

➤ Laboratory

- Serum lipase: amylase > 2.0 suggests alcoholic pancreatitis, not gallstone pancreatitis (sensitivity, 91%; specificity 76%).
- An almost normal AP and / or total bilirubin do occur with obstruction of the CBD (common bile duct).

24. Give a comment on the use of an elevated serum ALT as a test to support the **diagnosis of gallstone pancreatitis** by giving its performance characteristics.

- An elevated (> 3x ULN) is often serum ALT to differentiate biliary pancreatitis from alcoholic pancreatitis, has a specificity of 96%, but a sensitivity of only 48%, yielding a positive predictive value of 95%.
- Thus, a normal ALT does not exclude gallstone pancreatitis, but an ↑ ALT does suggest gallstone pancreatitis.

➤ Diagnostic imaging

- In this setting of ↑ suspicion of gallstone pancreatitis, don't be side-tracked if abdominal ultrasound is normal (pancreatitis → ileus → bowel air may obscure pancreas).

➤ Treatment

- It is these patients with acute cholangitis who are helped by ERCP plus sphincterotomy in mild-to-moderate gallstone pancreatitis.
- The ERCP and sphincterotomy must be done within 28 hours.

➤ Prevention

- “ERCP in patients with severe gallstone acute pancreatitis is best reserved for patients with suspected biliary obstruction.....” (Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier, Philadelphia, 2010, page 1035).



Drug-Associated Pancreatitis

Useful background: Classification of drugs associated with induction of acute pancreatitis

- Class I: implicated in > 20 reports, at least one documented case following re-exposure
 - Asparaginase
 - Azathioprine
 - Cytarabine
 - Didanosine
 - Estrogen preparations
 - Furosemide
 - Mercaptopurine
 - Mesalamine
 - Opiates
 - Pentamidine
 - Pentavalent antimonials
 - Steroids
 - Sulfasalazine
 - Sulindac
 - Tetracycline
 - Trimethoprim/sulfamethoxazole
 - Valproic acid

- Class II: implicated in > 10 reports
 - Acetaminophen
 - Carbamazepine
 - Cisplatin
 - Cyclopenthiiazide
 - Enalapril
 - Erythromycin
 - Hydrochlorothiazide
 - Interferon Alfa-2b
 - Lamivudine
 - Octreotide
 - Phenformin
 - Rifampicin

Printed with permission: Keller J, et al. *Best Pract Res Clin Gastroenterol* 2007;21(3):519-33.



Acute Recurrent Pancreatitis

➤ Less common causes

- Pancreas divisum
 - Symptoms may develop in those with acute recurrent pancreatitis arising from relative obstructions to the flow of pancreatic juice through the minor papilla.
 - The presence of pancreas divisum is associated with a high risk of post-ERCP pancreatitis
- Sphincter of Oddi dysfunction (SOD)
 - Postulated to be the cause of acute recurrent pancreatitis when the basal pressure in the pancreatic sphincter is > 40 mm Hg
- IBD and drugs
 - The ↑ rate of acute pancreatitis in persons with inflammatory bowel disease (IBD, risk is ↑ 4x in Crohn disease and 1.5x in Ulcerative Colitis) may be due to drugs used to treat the conditions, such as 5-ASA/ sulfasalazine or azathioprine / 6-mercaptopurine.
- Celiac disease
- Severe burns
- Smoking (possibly making the effects of alcohol worse)
- AIP (autoimmune pancreatitis)
 - ↑ IgG4
 - May be associated with
 - Acute pancreatitis
 - Chronic pancreatic insufficiency
 - Stricture of main pancreatic ducts
 - Diabetes

Chronic Pancreatitis

➤ Definition

- There are numerous definitions of chronic pancreatitis
 - Pancreatitis is a spectrum
 - Acute pancreatitis is an identifiable event, whereas
 - Chronic pancreatitis is an ongoing process of
- There may be typical symptoms and changes on diagnostic imaging, as well as the above changes in histology.



➤ Demography

- The incidence of chronic pancreatitis is approximately $8/10^5$ per year, and the prevalence is $27/10^5$.
- 10 year survival rate is 70%
- The standardized mortality ratio (SMR) is 3.6:1, with higher mortality rates associated with
 - Advanced age
 - Alcohol etiology
 - Continued alcohol use (↑ SMR by 60%)
 - Smoking (especially in alcoholics)

➤ Causes

25. Give 20 causes of chronic pancreatitis.

- Hereditary
 - CT (cationic trypsinogen) gene
 - Autosomal dominant
 - Hereditary pancreatitis (PRSS1 mutations)
 - Autosomal recessive or modifier genes
 - CFTR mutations
 - SPINK1 mutations
 - IgG4 associated
- Duct obstruction
 - Benign pancreatic duct obstruction
 - Traumatic stricture
 - Stricture after severe acute pancreatitis
 - Duodenal wall cyst
 - Pancreas divisum
 - Malignant pancreatic duct stricture
 - Ampullary or duodenal carcinoma
 - Pancreatic adenocarcinoma
 - Intraductal papillary mucinous neoplasm



- 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: pg. 1274.; and 2010: pg. 988; and Keller J, and Layer P. *Best Practice & Research Clinical Gastroenterology* 2008; 22(1): pg. 106.

Hereditary Pancreatitis and Gene Mutations

- PSTI (pancreatic secretory trypsin inhibitor) aka **SPINK₁** (serine protease inhibitor, Kazal type 1)
- SPINK₁ is colocalized in zymogen granules in the pancreatic acinar cells.
- SPINK₁ is secreted with trypsinogen.
- SPINK₁ presents the premature activation of trypsinogen in the pancreatic acinar cells.



- SPINK₁ mutations, or polygenic mutation of CFTR- SPINK₁ are associated with familial pancreatitis.

Useful additional material : Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier, Philadelphia, 2010, Table 57-4 (Clinical manifestation of cystic fibrosis) and Table 57-5 (Frequency of gastrointestinal manifestations in cystic fibrosis), page 941).

- SPINK₁ N34S is the most common SPINK₁ mutation
- SPINK₁ mutations lead to less trypsin inhibition.
- These loss-of-function polymorphisms are important
 - When acute pancreatitis occurs.
 - When there is recurrent premature activation of trypsin (e.g. CFTR or PRSS₁ mutation).
- An acute phase reactant
 - ↑ SPINK₁ with inflammation of pancreas
- “SPINK₁ acts as the first line defense against prematurely activated trypsinogen” (Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier, Philadelphia, 2010, page 937).
- SPINK₁ mutations such as with CFTR or PRSS₁ increase the risk of fibrosis.

Cationic Trypsinogen Gene (PRSS₁) Mutations

There are numerous gene mutations in PRSS₁.

26. Give the mutations which are Ca²⁺-dependent or Ca²⁺-independent mutations in PRSS₁.

- Ca²⁺ dependent
 - The main genetic mutations in PRSS₁ are R₁₂₂H and N₂₉I mutations.
 - PRSS₁ gene mutation is associated with hereditary pancreatitis.
 - The R₁₂₂H is a “conversion mutation” which alters the high fidelity regulatory mechanism of PRSS₁.
 - The R₁₂₂H and N₂₉I mutations of PRSS₁ result in
 - ↑ activation, or
 - ↓ inactivation



- The switch on/off represents a process to enhance trypsin activity (“gain-of-function”).
- Ca^{2+} -independent-mutation
 - Process related to maintenance of intracellular pH.

Schwachman-Bodian Diamond Syndrome (SBDS)

- SBS is caused by autosomal recessive mutation in SBDS (Schwachman-Bodian-Diamond syndrome) gene.
- The genetic defect in most cases of SDS is “....caused by gene conversion between the normal SBDS gene with a non-functional pseudogene designated SBD SP”.
- The differences between the SBDS gene and the SBDSP gene “.....are critical nucleotide deletions and nucleotide changes that render the SBDS gene product non-functional” (Feldman M., et al. Sleisenger and Fordtran’s Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier, Philadelphia, 2010, page 937).
- The non-functional SBDS gene products leads to
 - ↓ development of pancreatic acini
 - ↓ synthesis of zymogen granules in the pancreatic acinar cells
- The ↓ synthesis of zymogen granules → pancreatic hypoplasia and exocrine insufficiency
- Other common associations include
 - Bone marrow dysfunction
 - ↓ development of progenitor cells and bone marrow stroma
 - Neutropenia, leukopenia, anemia, thrombocytopenia, pancytopenia
 - MSK
 - Short stature
 - Long bone defects
 - Short ribs
 - Thoracic dystrophy
- Pathology
 - Acute inflammation
 - Lymphocytes
 - Plasma
 - Metaplasia
 - Chronic self-sustaining inflammation
 - Chronic self-sustaining inflammation



- Acute inflammation (lymphocytes, plasma cells, macrophages),
- Fibrosis within and between lobules
- Duct metaplasia
- Eosinophilic protein plugs in duct, as well as
- Destruction of acinar cells and islets of Langerhans.
- The similar histological changes of chronic pancreatitis may be seen in
 - Advanced ages
 - Diabetes
 - Chronic kidney disease

SO YOU WANT TO BE A GASTROENTEROLOGIST!

- Within the context of chronic pancreatitis, distinguish the histological features of ACP (autoimmune chronic pancreatitis) from IDCCP (idiopathic duct centric chronic pancreatitis)

	ACP	IDCCP
○ Cells	- ↑ lymphocytes - ↑ plasma cells - IgG4 positive	- Neutrophils, as well as lymphocytes and plasma cells
○ Veins	- Obstructive phlebitis	
○ Fibrosis	- “Wharled” (aka LPSP [lymphoplasmic sclerosing pancreatitis])	

SO YOU HAVE NOT GIVEN UP WANTING TO BE A GI JOE/JILL

- Give the pathology of obstructive chronic pancreatitis.
 - Obstructive chronic pancreatitis is
 - A distinct disease entity
 - Caused by a single dominant narrowing or stricture of the pancreatic duct
 - Caused by diffuse interlobular and intralobular fibrosis”
 - This fibrosis is “.....usually equally and symmetrically distributed in the affected area.”

(Feldman M., et al. Sleisenger and Fordtran’s Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier, Philadelphia, 2010, page 993).



➤ Clinical

Abdominal pain is common in persons with pancreatitis. It is now questioned whether the pain is due to increased pressure in the duct or parenchyma of the pancreas, resulting in tissue ischemia.

27. Give evidence for 3 alternate theories relating to neuroimmune interaction, for the **pain** of chronic pancreatitis.

- Nerves
 - ↑ number and diameter of nerves in the pancreas
 - ↑ inflammation around these nerves and ganglia
 - Axons release pain mediators, such as
 - Substance P
 - CERP
 - Glutamate
- GAP-43 (growth-associated protein 43)
 - ↑ NGF (nerve growth factor) and TrkA (NGF receptor)
 - ↑ endogenous proteases
- CCK
 - ↑ sensitivity of pancreas to stimulation by CCK
 - ↑ duct pressure
 - Redirecting pancreas enzymes to basolateral rather than apical portion of acinar cells

➤ Complications

28. Give the factors responsible for the development of **diabetes mellitus** in chronic pancreatitis.

- Loss of Islet cells
 - From chronic pancreatitis disease-associated destructive process
 - From resection of pancreas
 - ↑ amylase → ↑ insulin resistance
- Hepatic insulin receptors
 - ↓ number
 - ↓ function



29. Give the median times for the development of complications of chronic pancreatitis.

Complication	Etiology of pancreatic disease	Approximate median time (years) to onset of complication
○ Pancreatic insufficiency	○ Alcohol	13
	○ Idiopathic	
	– Early onset	26
	– Late onset	17
○ Diabetes	○ Alcohol	20
	○ Idiopathic	
	– Early onset	26
	– Late onset	12

➤ Laboratory

Diagnostic tests of chronic pancreatitis

- There is no “gold standard” for diagnostic form (structure) and function.
- The tests are for altered pancreatic form (structure) and function.
- The performance characteristics improve as the disease becomes more severe; why is this?

Because “..... 30% to 50% damage to the [pancreatic] gland is necessary before direct pancreatic function tests yield reliable results (Feldman M., et al. Sleisenger and Fordtran’s Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier, Philadelphia, 2010, page 999).

- It is in the persons with mild-to-moderate disease that you wish to be able to make an early diagnosis.



30. Give the effect of disease severity on the performance characteristics of the combined **secretin-CCK test** for chronic pancreatitis.

	Sensitivity	Specificity
Overall	67%	90%
Moderate-severe	79%	

- Pancreatic function testing may be abnormal even in the absence of structural changes.
- However, persons with abnormal pancreatic structure as shown on ERCP may have hormonal stimulation test results.

31. Give 6 tests of exocrine pancreatic functions.

- Direct invasive intubation tests
 - CCK/secretin stimulation
 - Lundh meal
 - ERCP and pancreatic aspiration
- Indirect non-invasive tests
 - Stool fats and nitrogen
 - Stool trypsin and chymotrypsin
 - Breath tests
 - Oral function tests (bentiromide test and pancreolauryl test)
- Blood determinations
 - Trypsinogen
 - Lipase
 - Pancreatic amylase

Adapted from: Pandolfi SJ. *Sleisenger & Fordtran's Gastrointestinal and Liver Disease: Pathophysiology/Diagnosis/Management* 2006: pg. 1197-1199; and 2010: pg. 928.

➤ Diagnostic imaging

- Accuracy of detection on abdominal ultrasound: gallstones, > 90%; dilated CBD, 55-91%; CBD stones, 20-75%
- Contrast enhanced CT useful to grade pancreatitis, and to detect necrosis as well as neoplasm; equivalent to gadolinium-enhanced dynamic MRCP (but contrast-enhanced MRCP is superior to contrast



enhanced CT to detect CBD stones) (Arvanitakis M, et al. *Gastroenterology* 2005:715-23.

- Microlithiasis occurs in 37-89% of persons with idiopathic acute pancreatitis, and some experts recommend cholecystectomy for associated symptoms
- Definitions
 - Microlithiasis, stones < 3 mm
 - Biliary sludge, a suspension of crystals, mucin, glycoproteins, cellular debris, and protein across material
 - Biliary crystals, crystals of calcium bilirubinate, calcium carbonate, or cholesterol monohydrate; the use of duodenal drainage to assess the presence of biliary crystals has a sensitivity of 65%, and a specificity of 94-100%
 - The risk of pancreatitis following ERCP is high in persons with IAP (ideopathic acute pancreatitis), sphincter of Oddi dysfunction (SOD), or a post history of pancreatitis (12.5% risk)

Abbreviations: IAP, ideopathic acute pancreatitis; SOD, Sphincter of Oddi dysfunction

In situations where the results of pancreatic structure vary from the functional tests, it is suggested that “.....hormonal stimulation testing appears to be somewhat more sensitive and specific than ERCP” (Feldman M., et al. *Sleisenger and Fordtran’s Gastrointestinal and Liver Disease*. 9th Edition. *Saunders/Elsevier*, Philadelphia, 2010, page 999).

32. Give the performance characteristics for 3 **diagnostic imaging** tests chronic pancreatitis:

Diagnostic imaging test	Sensitivity	Specificity
○ Abdominal ultrasound	50% to 80%	80% to 90%
○ CT	75% to 90%	> 85%
○ Multidetector CT	> 80%	~100%
○ ERCP	70% to 90%	80% to 100%
○ EUS		
> 3 diagnostic criteria	83%	57%
Advanced disease	73%	81%
> 4 criteria	90%	86%



- MRCP agrees with ERCP in about 90% of patients, with lower values for changes that are
 - Subtle
 - In pancreatic tail
 - Side branches of pancreatic duct

A caution about EUS:

- Certain patient- and disease-related factors can mimic the EUS changes of pancreatitis, and lead to a false diagnosis:

Chronic

Patient-related	Disease-related
○ Age	○ Diabetes mellitus
○ Tobacco	○ Chronic renal disease
○ Alcohol	

33. For 6 laboratory and/or diagnostic imaging tests for chronic pancreatitis, give the use for detecting big versus small duct disease.

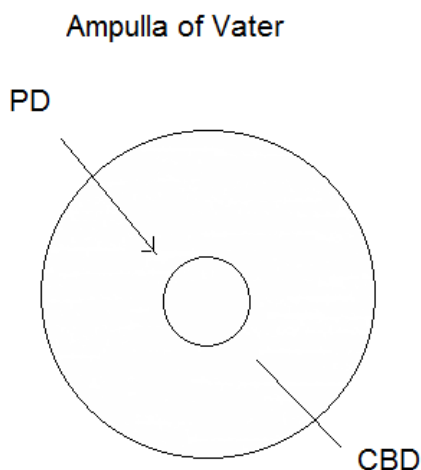
Diagnostic test	Possible findings in 'big duct' disease	Findings in 'small duct' disease
○ Fecal elastase	– Usually low (<100/g of stool)	– Usually normal
○ Serum trypsin	– Usually low (< 20 ng/mL)	– Usually normal
○ Abdominal ultrasonography	– Pancreatic atrophy – Pancreatic duct dilation – Pancreatic calcifications – Pseudocyst	– Usually normal
○ Computerized tomography	– Pancreatic atrophy – Pancreatic duct dilation – Pancreatic calcifications – Pseudocyst	– Usually normal or equivocal
Diagnostic test	Possible findings in 'big duct'	Findings in 'small'



	disease	duct' disease
○ MRCP	- Pancreatic atrophy - Pancreatic duct dilation - Irregularity or stricture - Pancreatic calcifications - Pseudocyst	- Usually normal or equivocal
○ Endoscopic ultrasonography	- Abnormal (> 4 features of chronic pancreatitis)	- May be abnormal
○ ERCP	- Abnormal	- Normal or minimally abnormal
○ Direct hormonal stimulations test (e.g. secretin test)	- Abnormal	- Usually abnormal

Abbreviations: MRI, magnetic resonance imaging, MRCP, magnetic resonance cholangiopancreatography.

Source: Lieb JG II, and Forsmark CE. Aliment Pharmacol Ther. Review: Pain and Chronic Pancreatitis. *Journal Compilation* 2009;29:713.



CBD, common bile duct; PD, pancreatic duct
Scope 11 mm: CBD size –compare to scope



- Diameter of CBD
 - Age
 - < 50 6 mm
 - > 50 ↑ mm / 10 yrs
 - After cholecystectomy – 11 mm

- Treatment

- 34. Give 20 current approaches to the **management of pain** in the patient with chronic pancreatitis.
 - General measures
 - Manage associated/causative factors
 - Cessation of alcohol intake, smoking
 - Analgesics
 - Gabapentin
 - SSRIs, TCAs
 - Neural interruption
 - Percutaneous or endoscopic (EUS) nerve blocks
 - Surgical (thoroscopic) 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)
 - Endoscopy
 - Pancreatic sphincterotomy, stent placement and stone extraction may be useful therapy for “big-duct” chronic pancreatitis (dilation of main pancreatic duct seen on diagnostic imaging, in contrast to small duct disease (aka minimal [structural] change chronic pancreatitis).



- Surgical drainage, if pancreatic duct dilated (Puestow)
- Organ resection
 - Partial, complete, with/without pancreatic islet cell transplant
- Surgery
 - Complete or partial relief of pain from chronic pancreatitis is superior with surgical than with endoscopic therapy (e.g. 75% vs 32%).
 - The 80% immediate reduction of pancreatic pain using pancreatics jejunostomy or the modified Pueston operation falls with the duration of follow-up.

Adapted from: Forsmark CE. *Sleisenger & Fordtran's gastrointestinal and liver disease: Pathophysiology/Diagnosis/Management* 2006: pg 1288-1294.

- Pancreatic pain relief after thoracoscopic splanchnicectomy “average about 50% to 75% at one year and drops to 25% to 50% with longer follow-up” (Feldman M., et al. *Sleisenger and Fordtran's Gastrointestinal and Liver Disease*. 9th Edition. *Saunders/Elsevier*, Philadelphia, 2010, page 1009).
- ESWL (extracorporeal shock-wave lithotripsy) provides 2-year pain improvement in ~62%.

35. Give 5 causes for **failure to achieve pain relief** after biliary sphincterotomy for pancreatic pain.

- Nonpancreaticobiliary pain, especially functional gastrointestinal disease
- Subtle chronic pancreatitis with a normal pancreatogram
- Inadequate initial sphincterotomy
- Ductal edema post sphincterotomy
- Restenosis
- Residual pancreatic sphincter hypertension (SOD)
- Failure in SOD types II, or III



Pancreatic Enzyme Replacement

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- Give the rational for the use of non-enteric rather than enteric coated pancreatic enzyme replacement products to reduce the pain of pancreatitis.
 - Normally
 - When fat and protein enter the duodenum and proximal jejunum, CCK is released from I cells, and stimulates the release of pancreatic digestive enzymes (proteases, but not fluid or HCO_3^-).
 - Pancreatic serine proteases secreted into the duodenum destroy an intestinal CCK-releasing factor.
 - With ↓ CCK-releasing factor, there is ↓ CCK release and ↓ continued secretion of pancreatic enzymes.
 - Pancreatic enzymes and feedback control of secretion of pancreatic enzymes
 - Taking replacement pancreatic enzymes by mouth destroys the intestinal CCK-releasing factor.
 - With ↓ intestinal CCF-releasing factor, there is ↓ CCK, ↓ secretion of pancreatic enzymes, and less pancreatic pain.
 - Why non-enteric rather than enteric coated pancreatic replacement enzymes.
 - Non-enteric coated pancreatic replacement enzymes are delivered to the feedback-sensitive duodenum and proximal jejunum, from which CCK-releasing factor is released and destroyed.
 - Enteric coated enzymes will partially bypass the duodenum and proximal jejunum, so that there is less destruction of CCK-releasing factor, and this results in more CCK being released.

Please see Harrison's Internal Medicine, 17th Edition, 2008, Table 307-8, page 2016, for the protease and the lipase activities of commonly prescribed pancreatic enzyme supplements.

36. Give **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

Printed with permission: Mihaljevic AL, et al. *Best Practice & Research Clinical Gastroenterology* 2008; 22(1): 170.

37. Give 6 post-operative complications from **pancreatic resection**.

- Pancreas
 - Pancreatitis
 - Fistula
- Bile duct
 - Leak
 - Cholangitis
- Stomach
 - Gastroparesis
- Surgical site
 - Skin wounded infection
 - Intra-abdominal abscess
- Pancreatic pseudocyst
 - Prevalence in chronic pancreatitis, 25%
 - Communication with pancreatic duct, 70%
 - Complications of pseudocysts, 20% to 40%
 - Diagnostic ERCP-associated risk of infection, 15%
 - Surgical decompression of cyst
 - Long-term success rate, 90%
 - Recurrence of
 - Pseudocyst, 10%
 - Pain, 5%
 - Operative mortality, 3%

Autoimmune Pancreatitis (AIP)

➤ Definition:

- Autoimmune pancreatitis (AIP) is a distinct process of chronic periductal inflammation, whirling interstitial, fibrosis, sclerosis, and obliterative phlebitis and atrophy of acinar cells of the pancreas, associated with IgG4-associated systemic disease (ISD) affecting pancreas, bile ducts, salivary glands, kidneys, retroperitoneum, and lymph nodes



- 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 arterioles), and IgG4 positive immunostaining of $\geq$ IgG4 positive cells per HPF
 - Type I, lymphoplasmacytic sclerosing pancreatitis, and type II idiopathic duct centric pancreatitis
- Demography
- More frequently males (80%), over 50 years (80%)
- Pathology
- Two forms
 - Lymphoplasmacytic sclerosing pancreatitis (LPSP)
 - Idiopathic duct centric chronic pancreatitis (IDCP)
 - Less common than LPSP
 - Dense infiltration of pancreas with T lymphocytes and plasma cells which express IgG4 on their surface, possibly directed towards UBR₂ (ubiquitin-protein ligase E3 component N-recognin).
- Clinical
- Pain is not a prominent feature

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- In the context of **autoimmune pancreatitis (AIP)**, what is **Mikulicz syndrome**?
 - Mikulicz syndrome is a variant of Sjogren disease characterized by a massive IgG4 – positive mononuclear infiltration of the salivary and lacrimal glands, in which autoimmune pancreatitis may be one manifestation.

➤ Diagnosis

38. Give the **Mayo Clinic HISOR diagnostic criteria** for the diagnosis of autoimmune pancreatitis (AIP), and the features characteristic for the diagnostic groups.

- Histology
 - At least one of the following:
 - Periductal lymphoplasmacytic infiltrate with obliterative phlebitis and storiform fibrosis



- Lymphoplasmacytic infiltrate with storiform fibrosis with abundant IgG4 cells (>10 IgG4 cells/HPF)
- Imaging
 - Typical: diffusely enlarged gland with delayed 'rim' enhancement, diffusely irregular, attenuated main pancreatic duct
 - Other: focal pancreatic mass/enlargement, focal pancreatic ductal stricture, pancreatic atrophy, calcification, pancreatitis
- Serology
 - Elevated serum IgG4 level (normal 8-140 mg/dl)
- Other organ involvement
 - 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

Abbreviations: HPF, high power field; IgG4, immunoglobulin G4

➤ **Japan Pancreas Society** criteria for the diagnosis of AIP

Diagnostic criteria: for diagnosis, criterion I must be present together with criterion II and/or III

- I. Imaging criterion: diffuse narrowing of the main pancreatic duct with irregular wall (more than one third the length of the entire pancreas) and enlargement of the pancreas
- II. Laboratory criterion: abnormally elevated levels of serum gammaglobulin and/or IgG, or the presence of autoantibodies
- III. Histopathologic criterion: marked lymphoplasmacytic infiltrate and dense fibrosis

Abbreviations: AIP, autoimmune pancreatitis; IgG, immunoglobulin G

Printed with permission: Gardner, et al. *AM J Gastroenterol* 2009; 104: 1620-1623.

➤ Diagnostic groups of AIP

- Group A: diagnostic pancreatic histology
 - Presence of one or more of the following criteria:
 - Specimen demonstrating the full spectrum of LPSP
 - >10 IgG4 cells/HPF on immunostatin of pancreatic lymphoplasmacytic infiltrate



- Group B: typical imaging and serology
 - Presence of all the following criteria:
 - CT or MRI scan showing diffusely enlarged pancreas with delayed and 'rim' enhancement
 - Pancreatogram showing diffusely irregular pancreatic duct
 - Elevated serum IgG4 levels
- Group C: response to corticosteroids
 - Presence of all the following criteria:
 - Unexplained pancreatic disease after negative workup for other etiologies
 - Elevated serum IgG4 and/or other organ involvement confirmed by presence of abundant IgG4 positive cells
 - Resolution or marked improvement of pancreatic and/or extrapancreatic manifestations with corticosteroid therapy

Abbreviations: AIP, autoimmune pancreatitis; CT, computed tomography; HPF, high power field; IgG, immunoglobulin G; LPSP, lymphoplasmacytic sclerosing pancreatitis; MRI, magnetic resonance imaging

Printed with permission: Gardner, et. *AM J Gastroenterol* 2009; 104: 1620-1623.

➤ Laboratory

- ↑ IgG4 antibody
- The IgG4 antibody also reacts to the PBP (plasminogen-binding protein) of *H. pylori*.
- Other organs may have similar inflammatory infiltration
- Elevated serum IgG4 is 75% sensitive and 93% specific for AIP; IgG4 > 2XULN are highly specific, but ↑ IgG4 may also be seen in 1.5% of pancreatic cancers

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- Give the diagnostic performance characteristics of ↑ IgG4 for AP.
 - The sensitivity in North America for IgG4 > 140 mg/dL is 76%, with a specificity of 93%.
 - Beware that ~ 10% of persons with pancreatic adenocarcinoma will have ↑ IgG4.
 - Note that a normal IgG4 does not exclude the diagnosis of AP.



➤ Diagnostic imaging

- CT/MRI shows “sausage-shaped” enlargement of pancreas, peripheral (RIM) enhancement, and delayed enhancement; ERCP shows characteristic diffusely irregular and narrowed pancreatic duct

39. Give 8 diagnostic imaging manifestations of autoimmune pancreatitis.

- Abdominal ultrasound, EUS
 - Pancreas
 - Hypoechoic
 - Diffusely enlarged
- CT
 - Pancreas
 - Enlarged
 - “Sausage-shaped”
 - IV contract
 - Delayed
 - Prolonged
 - Rim around the pancreas (delayed images)
 - Mass effect from focal swelling
 - Pancreatic duct
 - Diffuse or segmental narrowing (strictures)
 - Atypical imaging features:
 - Pancreatitis
 - Focal pancreatic mass
 - Focal pancreatic duct stricture
 - Pancreatic atrophy
 - Persistent distal biliary stricture
- MRI, MRCP
 - Pancreas
 - Diffusely enlarged ($\downarrow T_1$ – and $\uparrow T_2$ – weighted intensity)
 - Atrophy
 - Calcifications
 - Pancreatic duct
 - Attenuated main duct
 - Biliary strictures
- ERCP
 - Pancreatic duct
 - Diffuse or segmental narrowing from strictures

See Feldman M., et al. Sleisenger and Fordtran’s Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier, Philadelphia, 2010, Table 59.2, page 993 for Diagnostic Criteria for Autoimmune Pancreatitis.



40. Compare and contrast the diagnostic imaging of autoimmune chronic pancreatitis (AIP) versus alcoholic chronic pancreatitis (ACP).

Site	ACP	AIP
○ Duct	Duct dilation	Duct narrowing
○ Pseudocyst	Common	Rare
○ Calcification or stone	Common	Rare
○ Pancreatic parenchyma	Atrophy	Enlargement

Printed with permission: Dite P, et al. *Best Practice & Research Clinical Gastroenterology* 2008; 22(1): pg. 136.

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- Within the context of chronic pancreatitis, distinguish the histological features of Autoimmune chronic pancreatitis (ACP) from Idiopathic duct centric chronic pancreatitis (IDCCP)

	ACP	IDCCP
○ Cells	- ↑ lymphocytes - ↑ plasma cells - IgG4 positive	▪ Neutrophils, as well as lymphocytes and plasma cells
○ Veins	- Obstructive phlebitis	
○ Fibrosis	- “Wharled” (aka LPSP [lymphoplasmic sclerosing pancreatitis])	

➤ Treatment

- Consistent response to 30-40 mg prednisone, tapering with improvement in serum IgG4 and imaging

“The price of greatness is responsibility.”

Winston Churchill



41. Give the expected response to steroid therapy in AIP.

Category	Criteria
○ Pathological features	– ↓ periductal lymphoplasmacytic infiltrate with obliterative phlebitis (LPSP) – IgG4 positive cells – ↓ lymphoplasmacytic infiltrate with fibrosis
○ Serology	– ↓ elevated serum IgG4 level
○ Other organ involvement	– ↓ parotid/lacrimal gland involvement – ↓ mediastinal lymphadenopathy – ↓ retroperitoneal fibrosis
○ Steroid therapy	– Resolution of pancreatic/extrapancreatic manifestations with steroid therapy

Abbreviation: LPSP, lymphoplasmacytic sclerosing pancreatitis

Printed with permission: Dite, Petr., et al. *Best Practice & Research Clinical Gastroenterology* 2008; 22(1): pg. 138.

Cysts and Tumours

➤ Pathology

There are four **main types** of pancreatic cysts

- Pre-malignant
 - MCN (mucinous cystic neoplasm)
 - IPMN (intraductal mucinous neoplasm)
 - Main duct (MD – IPMN)
 - Branch duct (BD – IPMN)
 - Malignant potential MD >> BD – IPMN
- Not pre-malignant
 - Serous cystadenoma
 - Pseudocysts



42. Classify and give 20 types of 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
 - Hydati cyst
- Angiomatous cysts
- Cystic neoplasms
 - *Mucinous tumours*
 - Mucinous cystadenoma (macrocytic adenoma) and cystadenocarcinoma
 - Intraductal mucin hypersecreting neoplasm; “Mucinous ductal ectasia”
 - *Non-mucinous tumours*
 - Serous cystadenoma (microcystic adenoma)
 - Papillary cystic tumour
 - Cystic cavitation of pancreatic adenocarcinoma or lymphoma
- Acquired cysts
 - Central cavitory necrosis
 - Pseudocyst
 - Parasitic cyst
- Misdiagnosed nonpancreatic lesions
 - Splenic artery aneurysm
 - Choledochal cyst
 - Mesenteric cyst
 - Duodenal duplication cyst or diverticulum
 - Lesser sac biloma
 - Lymphangioma
 - Hypoechoic solid tumour



- Metastases, with cystic component

Printed with permission: Degen L, et al. *Best Practice & Research Clinical Gastroenterology* 2008; 22(1): 92.

➤ Diagnosis

43. Give the **diagnostic features** of 3 types of pancreatic cysts.

Cyst type	EUS features	Fluid appearance	Cytology	CEA	Amylase
○ SCA	- Microcystic, honeycombed, 20% macrocystic	● Thin, clear, some-times bloody	▪ Cuboidal cells clear glycogen-positive cytoplasm	Low	Low
○ MCN	- Macrocystic	● Viscous, clear	▪ Mucin-rich fluid, columnar mucin-positive cells, with variable atypia	High	Low
○ PMN	- Cystic branch duct dilation	● Viscous, clear	▪ Mucin-rich fluid, columnar mucin-positive cells, with variable atypia	High	High
○ Cystic PET	- Variable	● Variable, typically non-mucinous	▪ Small cells, scant cytoplasm, monomorphic nuclei	Un-known	Low
○ SPT	- Mixed solid and cystic	● Bloody	▪ Papillary structures, macrophages, myxoid stroma, monomorphic neoplastic cells	Low	Low
○ LEC	- Solid, heterogeneous - Subtle posterior enhancement	● Thick and milky, gray or frothy	▪ Anucleated squamous cells, lymphocytes	Variable	Low



Cyst type	EUS features	Fluid appearance	Cytology	CEA	Amylase
○ PP	-Macrocytic, thick wall -Unilocular, internal debris	●Thin, dark, non-mucinous	▪Inflammatory cells without evidence of mucin or epithelial cells	Variable	High

Abbreviations: EUS: Endoscopic ultrasound; IPMN, intraductal papillary mucinous neoplasm; LEC, lymphoepithelial cysts; MCN, mucinous cystic neoplasms; PD: Pancreatic duct; PET, pancreatic endocrine tumour; PP, pancreatic pseudocysts; SCA, serous cystadenoma; SPT, solid pseudopapillary tumours

Printed with permission: Fasanella KE, and McGrath K. *Best Practise and Research Clinical Gastroenterology* 2009; 23:35-48; Brugge WR. *2009 ACG Annual Postgraduate Course*:231-234.

➤ Treatment

44. Give the traditional therapeutic approach to the management of cystic lesions.

	Pseudocyst	Serous	Mucinous	Malignant
➤ Head	○ Drain	-Monitor	●Monitor	▪Resect
➤ Body	○ Drain	-Monitor	●Resect	▪Resect
➤ Tail	○ Resect	-Resect*	●Resect*	▪Resect
➤ Cyst fluid CGA < 3.1 mg/ml suggests serous cystadenomas, whereas CEA > 480 mg/ml suggest mucinous fluid				

*Approach varies with risk of surgery

"With the new day comes new strength and new thoughts."

Eleanor Roosevelt



45. Compare and contrast the viscosity, amylase, concentration, CEA and CA2-4 levels, and cytological findings in pancreatic serous cystadenoma, benign and malignant mucinous cystic neoplasm (MCN), intraductal papillary mucinous tumour and pseudocyst.

Parameter analyzed	Serous cystadenoma	MCN-Benign	MCN-Malignant	IPMT	Pseudocyst
○ Viscosity	↓	↑	↑	↑	↓
○ Amylase	↓	↓	↓	↑	↑
○ CEA	↓	↑	↑	↑	↑
○ CA 2-4	↓	↓/↑	↑	?	↓
○ Cytologic findings	Usually negative, rarely cuboidal cells	Occasionally mucinous epithelial cells	Benign – occasional mucinous epithelial cells	Papillary cluster of mucinous cells	Histiocytes

Adapted from: Castillo, Carlos Fernandez-del., and Jimenez, Ramon E. *Sleisenger & Fordtran's gastrointestinal and liver disease: Pathophysiology/Diagnosis/Management* 2006:1322.

• Pseudocysts

➤ Definitions

- Non-epithelized fluid collection > 4 wk old, as a consequence of AP, CP, trauma from disruption of pancreatic duct (PD), acute pancreatitis (AP), chronic pancreatitis (CP)
- Localized necrosis of pancreatic tissue, or pancreatic as well as peripancreatic fat necrosis, cause a leak in the pancreatic duct and the cystic space filled with amylase-rich fluid.
- The acute pseudocyst may become chronic “..... as a sequelae of chronic pancreatitis and downstream pancreatic ductal obstruction with fibrotic strictures or stones” (Feldman M., et al. *Sleisenger and Fordtran's Gastrointestinal and Liver Disease*. 9th Edition. *Saunders/Elsevier*, Philadelphia, 2010, page 1039).
- WOPN (walled-off pancreatic necrosis)
 - Internal debris in OPN, rather than fluid in pseudocyst, is predictor of inferior outcome
 - Nasocystic or PEG-cystic cavity drain
 - Necrosectomy, 90% success rate within 4.1 month



- Diagnosis
 - CEA, CA19-9, amylase
 - Suggestive of pseudocyst vs neoplasm
 - Size itself not an indicator of need to drain pseudocyst for symptoms

46. Give 8 clinical, diagnostic imaging and laboratory features that distinguish pseudocysts from cystic neoplasms of the pancreas.

Feature	Pseudocyst	Cystic neoplasm
➤ Clinical		
○ Gender	- More commonly male	▪ Usually female
○ Age	- 30-40 years	▪ 60-70 years
○ Alcohol abuse	- Common	▪ Uncommon
○ History of acute or chronic pancreatitis	- Common	▪ Uncommon
○ Diagnostic imaging (ultrasonography [US], endoscopic US [EUS], or computed tomography [CT])	- Unilocular - No solid component - Associated gland calcification	▪ Unilocular or multilocular ▪ Solid component ▪ Rim calcification of cyst ▪ Mural nodules of wall
○ Communication between cyst and pancreatic duct on ERCP	- 70%	▪ Rare (except for IPMN)
➤ Cyst fluid		
○ Amylase	- High	▪ Low
○ Carcinoembryonic antigen	- Low	▪ High
○ Cytology	- Inflammatory cells	▪ Glycogen ▪ Mucin-containing cells ▪ Malignant cells

Adapted from: Forsmark, Chris E. *Sleisenger & Fordtran's gastrointestinal and liver disease: Pathophysiology/Diagnosis/Management* 2006:1297.



➤ Diagnostic imaging

47. Give the diagnostic imaging changes on CT or MRI that suggest that a lesion in the pancreas is a true rather than a “false” (pseudo) cyst.

True cysts, in contrast to a pseudocyst, have

- Septae
- Loculations
- Solid material
- Calcification of the wall

➤ Treatment

48. List 8 **indications for treatment** of a person with a pancreatic pseudocyst.

- Pseudoaneurysm formation
- Fistula formation into adjacent viscera
- Expansion of the pseudocyst producing abdominal pain
- Expansion of the pseudocyst producing duodenal or biliary obstruction
- Abscess formation.
- Pancreatic ascites (tracking of pancreatic juice into the peritoneal cavity or pleural space)
- Pleural effusion
- Rupture
- >6 cm, 6 weeks after episode of pancreatitis
- Concern for malignant cystic lesion

Adapted from: Kim HC, et al. *Acta Radiol.* 2008;49(7):727-34; and Christensen NM, et al. *Am J Surg.* 1975;130(2):199-205.

➤ Surgical drainage vs EUS drainage

- EUS drainage better if necrotic cyst not infected (abscess)
- PCD (percutaneous drainage) of pancreatic pseudocyst may have prolonged drainage if connection with pancreatic duct
- Do a dynamic high resolution CT after drainage to R/O pseudoaneurysm



- **Serous Cystadenoma**
 - Body or tail of pancreas
 - Many tiny cysts
 - Fibrous septa
 - Honeycomb appearance
 - Scar with stellate appearance
 - Stellate scar may be calcified
 - Cyst filled with clear, watery fluid (no mucin)
 - Central. "sunburst" calcification (on CT scan)
 - Cytology of fluid may show cuboidal cells with glycogen-rich cytoplasm.
 - Rarely malignant (3%)
 - No communication with pancreatic duct

- **Mucinous Cystic Neoplasm (MCN)**
 - May be benign, but in individual patient assume to be malignant
 - Body or tail of pancreas
 - Thick wall
 - Occasional septa
 - Thick mucus material (or blood)
 - Stroma (ovarium-like)
 - Fluid in cyst
 - ↑ CEA
 - In benign MCN
 - Cytology shows
 - Adenocarcinoma cells
 - Columnar
 - Mucinous epithelial cells with atypia
 - No communication with pancreatic duct on ERCP / MRCP larger cysts with nodules in wall are more likely to be malignant than benign MCN.
 - Lesions are never multifocal, so once the single lesion is removed, surveillance is not necessary.
 - 5-year survival rate after resection of tumor, 30% to 63%



49. Give a comparison of pancreatic serous versus mucinous cystadenoma.

	Serous cystadenoma (SCA)	Mucinous cystadenoma (MCA)
○ 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)

50. Give a comparison of IPMT versus pancreatis pseudocyst.

	IPMT	Pseudocyst (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: pg. 586.



- **Intraductal Papillary Mucinous Neoplasms (IPMN)**

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In the context of a pancreatic tumor and

- Patient – no pain or weight loss
- Tumor – large, but no obstruction of biliary tree
- Blood test – ↑ LDH (lactate dehydrogenase)
- Give the most likely pathological diagnosis.
 - Only 1% of pancreatic tumors are lymphomas or extranodal non-Hodgkin lymphomas, and the typical patient-, tumor- and its characteristics are given above.

➤ Definition

- “.... Papillary neoplasms within the main pancreatic duct showing mucin hypersecretion that often leads to duct dilation and chronic obstructive pancreatitis.
- Thick (viscous) mucous with ↑ CEA, ↑ amylase

➤ Demography

- Male: female ratio: 1-2.4
- Mean age of diagnosis: 65 years

➤ Genetics

- As compared with pancreatic adenocarcinoma, in IPMN there are more frequent molecular changes in SKT 11/LKB1 inactivation and PIK3CA mutation, and less frequent mutations in K-Ras and P53 tumour suppressor genes, P16 and DPC4
- In IPMN, overexpression of fascin (an actin-bundling protein), methylated PPENK, and human telomerase reverse transcriptase

➤ Types

- Three types of IPMN, including main, branched or main plus branched (mixed) pancreatic ducts

➤ Pathology

- Cytology
 - Columnar mucinous epithelial cells with variable atypia

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- Grape-like cluster of cysts, localized or diffuse dilation of main pancreatic duct, patulous ampulla of Vater
 - Lesions of main or branchial pancreatic ducts, with proliferation of the mucinous epithelium leading to ductal and cystic dilation
 - 20-30% of IPMNs are multifocal, arising from a field defect in the entire pancreas that can cause multiple primary neoplasms.
 - Range histologically from benign, low grade (LGD), or high grade dysplasia to invasive cancer, with various grades of histology, probably being present with the same specimen
 - Main duct IPMNs are more likely to become malignant and to grow faster: 63% develop HGD/cancer in 5 years, vs 15% for branched chain IPMNs
- Clinical
- Symptoms arise from mucin distending involved pancreatic duct; (may see mucus extruding from ampulla on ERCP)
 - 5-year survival rate after resection, > 75%
 - Main duct IPMN or branching chain IPMN > 3 cm are more likely to be malignant.
- Laboratory
- Increased serum bilirubin predicts the presence of malignancy
 - ↑ CEA in 80-95% of IPMNs
51. Give the significance of ↑ amylase concentration in the fluid aspirated from a pancreatic cyst.
- Amylase in a gut aspirate only signifies that the cyst which contained the fluid was in communication with a pancreatic branch duct or main duct.
- Diagnostic imaging
- MRI
 - CT
 - CT using pancreatic protocol (detects IPMN in 97% of cases)
 - MRCP
 - Breath-hold MRCP
 - MRCP with secretin (S-MRCP),
 - MRCP is superior to CT to demonstrate communication between ducts, and cyst morphology



- EUS
- ERCP
- PET scanning sensitivity, 57-90%; specificity, 85-97%
- Exclude pancreas divisum (MRCP, 100% accurate; CT, sensitivity 90%, specificity, 97%)

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- Give 2 “pathognomonic” findings which help to differentiate between the types of pancreatic cyst.
 - ERCP-mucus dripping from ampulla of Vater → IPMN
 - CT-central, sunburst calcification → serous cystadenoma

➤ Treatment

- Chemotherapy
- Cyst ablation with ethanol or paclitaxel (a chemotherapeutic agent which inhibits the disassembly of microtubules and induces apoptosis with complete resolution of cysts in 79%, may be reasonable for IPMNs with low risk of malignancy:
 - No symptoms
 - < 3 cm size
 - Main duct < 6 mm
 - No mural nodules, thickness or septations
- Endoscopy
 - NG (nasogastric) drain
 - Stent
 - After surgical resection, invasive > 40%, non-invasive > 70%; resections recur in a median of 20 months, and 58% of these recurrences involve distal sites.
- Surgery
 - Sendai guidelines for resection



52. Give the **Sendai Guidelines** for resection of IPMNs.

- Symptomatic - All IPMN (MD- and BD – IPMN) with symptoms
- Asymptomatic - All MD-IPMNs
 - BP-IPMNs > 3 cm
- EUS - All IPMN with
 - Nodules
 - Thickening
- CEA - > 192
- Surveillance EUS, ERCP, MRCP (CT scan) - Enlargement on surveillance every 6-12 months

An ↑ CEA > 192 in IPMN predicts future or present malignant degeneration.

53. Give the pros and cons of nasogastric drains versus pancreatic stents.

Nasogastric drain	Stent
➤ Pros	
○ Flushing and fluoroscopy at any time	-Easy, quick, dislocation rare - Not disabling, patients stay mobile, feel better
➤ Cons	
○ Discomfort; easily dislocated; leads to immobilization of patients, nose-pain; flushing often futile and tedious, no direct control during flushing	-No flushing -Control needs endoscopic session

Printed with permission: Giovanni M. *Best Practice & Research Clinical Gastroenterology* 2004; 18(1): pg.192.



Pancreatic Duct Adenomatous Cancer

➤ Demography

- Incidence 10/10⁵
- Prevalence because the mortality rate is so high, prevalence figures are meaningless.
- 10% are metastatic
 - Pancreas supplied by splanchnic artery
 - Renal cell , especially late
- 1% endocrine
- 90% acinar / 10% ductal
- Site

A curiosity!

Persons with annular pancreas have an increased risk of developing hepatopancreatic adenocarcinoma.

➤ Pathology

- Most pancreatic carcinomas are from duct cells (PDCA), and may secrete mucin.
- Site
 - Pancreas
 - 70% HOP (head of pancreas)
 - 150% BO (body)
 - 15% TOP (tail)
 - Wall of duodenum
 - Ampullary of Vater
 - Distal bile duct (aka common bile duct)

➤ Predisposing factors



54. Give 10 genetic and 10 non-genetic diseases/associations of pancreatic cancer.

- Familial

First degree relatives affected	↑ relative risk
1	2.3x
2	6 x
3	32 x

- Hereditary pancreatitis

- Hereditary pancreatitis
 - Autosomal dominance if abnormal trypsin gene
 - 40x ↑ risk of pancreatic cancer by age 70
- Cationic trypsinogen (CT)
- CFTR
- SPINK

- 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 tumour induction by exogenous carcinogens
- DPC₄ (aka SMAD₄)
- EGF (epidermal growth factor) receptors
- SONIC hedgehog product
- Inactive tumour suppression gene (p59, p16 [DKN2A])
- Familial pancreatic cancer
- Familial ovarian and breast cancer

- Polyp syndromes

- FAP
- HNPCC-Lynch mismatch MLH1, MSH2, BRCH2
- HNPCC
- Peutz-Jeghers syndrome
- Cowden syndrome



- Life style
 - Smoking
 - ↑ risk 1.5 x
 - Interacts to further increase risk in
 - Alcoholism
 - GSTT₁
 - Alcohol
 - High-saturated fat (red meat) low vegetable/low vitamin diet
- Diet
 - Low intake of
 - Fresh fruits
 - Vegetables
 - Selenium
- 7-fold increased risk after exposition to dichlorodiphenyltrichloroethane or deviates (e.g. ethylene)
- Metabolic
 - Chronic pancreatitis
 - Diabetes
 - Partial gastrectomy
 - The risk of pancreatic cancer is increased in chronic pancreatitis, especially when the pancreatitis is due to
 - Alcohol
 - Cystic fibrosis
 - Other forms of hereditary pancreatitis
 - Tropical pancreatitis
- Miscellaneous
 - Diabetes mellitus
 - Cystic fibrosis
 - Fanconi anemia
 - Familial adenomatous polyposis
 - Ataxia telangiectasia
 - Neuroendocrine tumours

Adapted from: Keller J, et al. *Best Practice & Research Clinical Gastroenterology* 2007; 21(3): pg. 522.



55. Give 5 **precursor lesions** for PDCa.

- PIN – Pancreatic intraepithelial neoplasia
- MCN – Mucinous cystic neoplasms
- IPMN – Intraductal papillary mucinous neoplasms
- SPT – Solid pseudopapillary tumor
 - 20% risk of solid-pseudopapillary carcinoma
 - Abnormal expression of β -catenin and p120
 - ↓ expression of E-cadherin protein, or E-cadherin protein localized to cell nucleus
- Cystic islet cell tumor
- Serous cystadenomas may rarely (3%) be malignant (serous cystadenocarcinoma)

Note: Early events include K-Ras mutation and p16 loss, whereas late events include TP53 and APC₄/SMAD₄ loss.

Because the mortality rate for pancreatic ductal cancer (PDCa) is so high, it is important to recognize precursor lesions.

➤ Laboratory

- ↑ CA19-9 (tumor marker) occurs in
 - 70% to 80% of persons with pancreatic adenocarcinoma
 - Some persons with biliary obstruction and cholangitis
- The tumor marker CA 19-9 has a sensitivity of 86% and a specificity of 87% to diagnose pancreatic ductal cancer (PDCa).
- CA19-9 may be falsely positive in the presence of jaundice or cholangitis (-a-b).
- Because CA 19-9 is not suitable for screening, the diagnosis of PDCa is usually made by diagnostic imaging of the abdomen.
- Diagnostic imaging: “EUS is superior to Ct for detection of co-existent [pancreatic] malignancy [in a pseudocyst] particularly when the lesion is small” *Saunders/Elsevier*,
- EUS also has the substantial advantage of FNA.

Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. Philadelphia, 2010, page 1014.



56. Give the names of **immunohistochemical markers** which may be used to confirm that a tumor in the pancreas is mucus secreting, and is not derived from acinar or neuroendocrine cells of the pancreas.

- Markers for mucin
 - MUC₁, MUC₂, MUC₄
 - CEA (carcinoembryonic antigen)
 - CA 19-9, Ca 125
 - DuPan₂
- Markers for cytokeratins
 - 7, 8, 18, 19 (cytokeratin 7 is usually absent from pancreatic tumors arising from acinar or neuroendocrine cells).
- Diagnostic imaging
 - Cystic neoplasms may mimic a pseudocyst, especially when there are nodules or internal septations.

57. Give 7 diagnostic imaging tests of PDCA.

- Endoscopic
 - ERCP (endoscopic retrograde cholangiopancreatography)
 - Evaluation of recurrent pancreatitis (Avoid in chronic pain syndromes)
 - Pancreatic duct disruptions or leaks
 - Symptomatic pancreatic pseudocysts
 - Drainage of pancreatic necrosis
 - Palliative stenting
- EUS (endoscopic ultrasound)
 - Diagnostic procedure in acute and chronic pancreatitis
 - Consider before transmural drainage of pancreatic fluid collection/necrosis/pseudocyst



- Pancreatic mass < 2 cm
 - Sensitivity
 - EUS 98%
 - CT 91%
- Usually used to complement CT for staging
- More sensitivity than CT to determine if there is vascular invasion
- Suitable to obtain biopsy (FNA, fine needle aspiration), as also is CT
- Useful for celiac plexus block
- Types of EUS
 - Radial (Olympus) 360° perspective
 - Linear (for sampling or injection) (Pentax)
- Non-endoscopic
 - AbUS (abdominal ultrasound)
 - Helical CT pancreatic protocol
 - Dual-phase scanning after Po/Iv contrast, with pancreatic arterial phase at 40 sec and portal venous phase at 70 sec after IV contrast agent is given.
- Pancreas protocol for h (helical) CT
 - Oral contrast, to distinguish between pancreas and duodenum
 - Hypoattenuating –adenocarcinoma
 - Hyperattenuating – neuroendocrine tumor
 - 10% are isoattenuating, so use indirect signs
 - Indirect signs
 - Dilated PD, CBD, double duct (PD+CBD)
 - Mass effects
 - Pancreatic atrophy
 - Abnormal pancreatic contour
 - 97% correct diagnosis of PDCA
 - 100% accurate in predicting unresectable disease
 - 85% of persons predicted to have resectable disease by CT turn out to actually have unresectable disease



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- Give the CT criteria for unresectable PDca.

The CT criteria for unresectable PDca are

- Distant metastases (does not include lymph nodes)
- Encasement of celiac axis e.g. SMA or aorta
- Occlusion of PV, SMV or VC

Abbreviations: PV, portal vein; SMA, superior mesenteric artery; SMV, superior mesenteric vein; VC, vena cava

- MRI, MRA, MRV, MRCP
 - Magnetic resonance imaging
 - Gadolinium contrast used for MRA, MRV, MRCP
 - Image weighting
 - T₁ – MRI (solid)
 - T₂ – MRCP (fluid)
 - Use MRI to directly biopsy pancreatic mass
- Staging sensitivity for PCa
 - MRI 84%
 - CT 91%
- PET (positron emission tomography using radioactive fluorodeoxyglucose [FDG] F18)
 - Shows focal area of ↑ uptake of FDG in pancreas, and “hot spots” (↑ FDG uptake) of metastases in liver.
 - Does not show details of anatomy of pancreas, s do CT or MRI.
 - Performance characteristics: sensitivity of 95% to detect malignant pancreatic tumors.

See Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier, Philadelphia, 2010, Table 60.8, page 1027; Epidemiologic and Biological Characteristics of Pancreatic Cystic Neoplasms)



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There are numerous good tests to diagnose and to stage PDCA. It is important to establish whether the patient is a surgical candidate for pancreatic resection, or if they are **non-resectable**.

- Give a non-endoscopic and non-diagnostic imaging test for non-resectability of PDCA.
 - Staging laparoscopy with peritoneal lavage and cytology yields data rendering a patient to be declared non-resectable, despite lack of this evidence on CT/MRI.
 - Staging laparoscopy, 25%
 - Peritoneal cytology, 10%
- A patient with a predicted resectable PDCA has a Whipple pancreaticoduodenectomy. The patient is hopeful for a 5-year mortality rate of 11% to 25%, and a median survival of 11 to 20 months. The patient asks, based on her/his case, what are the factors which predict that he/she will have a better outcome.
- Predictors of outcome in patients with resectable PDCA:
 - Size, < 3 cm
 - Margins, negative
 - Metastases (to lymph nodes), none
 - Blood loss during surgery, < 750 mL

➤ Treatment

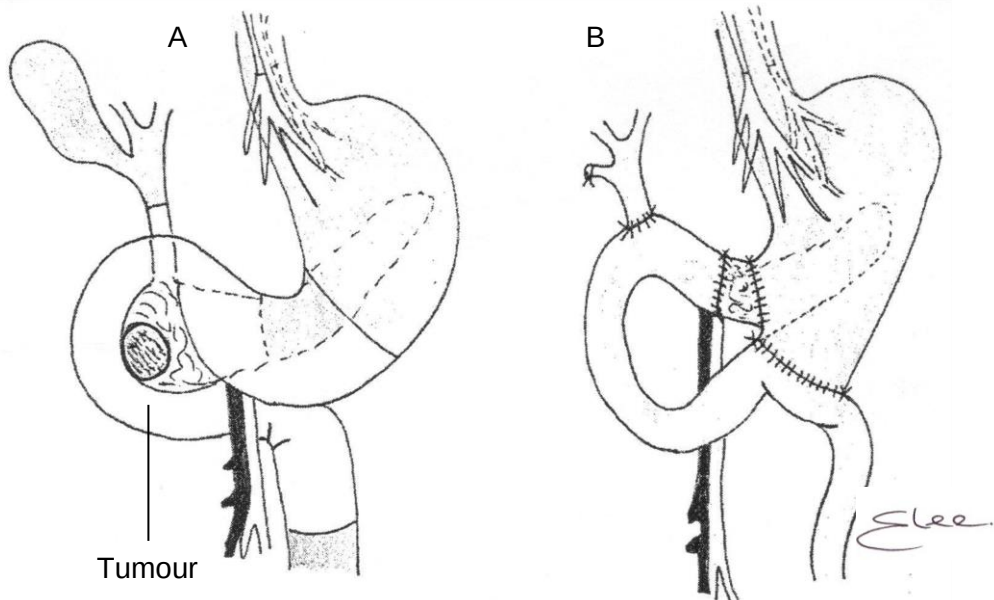
Surgical resection

58. Give three factors which usually preclude surgery for pancreatic cancer (i.e. not a surgical candidate).

- Metastases
- Ascites
- Mental caking
- Large celiac axis node
- Vascular, involvement (especially hepatic artery)
- Surgery for resectable lesion



59. Give a description and draw a picture of the **Whipple Procedure**.



- 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 performed.
- 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. ; Printed with permission: *Sleisenger & Fordtran's Gastrointestinal and Liver Disease: Pathophysiology/Diagnosis/Management* F82-8: page 106.

- Non-resectable
 - Endoscopic stenting
 - Laparoscopy
 - Laparotomy
 - Chemo'/radiation
 - Pain control

Note:

- Arterial (SAM, CA) involvement – not a surgical candidate
- Degree of involvement of circumference of vessel reflects likelihood of vessel invasion



Chemoradiation Therapy

- Chemotherapy agents
 - Gemcitabine / 5-FU
 - 2 months longer survival
 - Palliation for fit patients (pain control)
 - Taxol
 - Inject directly into PCa mass
- Radiation
 - Palliation
 - Focal radiation
- Contrast-enhanced harmonic EUS (CH-EUS) technology visualizes pancreatic parenchymal perfusion and the microvasculature.
- CH-EUS-determined hypo-enhancement pattern diagnosed ductal carcinoma with high sensitivity and specificity.
- CH-EUS is superior to multi-detector-row computed tomography (MDCT) in distinguishing small ductal carcinomas from other tumors.
- Combining CH-EUS with EUS-FNA improves the sensitivity with which EUS-FNA identifies ductal carcinomas.

Source: Kitano M et al. Am J Gastroenterol 2012; 107: 303-310.

➤ Pain control

- Celiac plexus neurolysis (CPN) (CP block)
 - EUS or CT directed
 - Local anesthesia given before CPN
 - 50 mcg/hr – fentanyl patch post CPN for 2 weeks
60. Give 3 complications of CPN/CPB (celiac plexus neurolysis (CPN) / celiac plexus block (CPB))
- Postural hypotension
 - 2 wk worsening of pain, before pain / quality of life improve
 - Diarrhea (2%) 48 hours post CPN (celiac plexus neurolysis)/ CPB (celiac plexus block)



Non-adenomatous Cancers of the Pancreas

61. Give 4 types of non-adenomatous acinar or ductal tumors of the pancreas.

- Lymphoma
 - High index of suspicion
 - Flow cytometry needed
 - Round
 - Discrete
 - More hypoattenuating
- NET (neuroendocrine tumor)
 - Functioning
 - Non-functioning
 - Gastrinoma
 - Insulinoma
 - Glucagonoma
 - VIPomas
 - Somatostatinoma
- AIP (autoimmune pancreatitis)
- TB (tuberculosis)

Pancreatic Neuroendocrine Tumours (NET)

- Non-functioning
 - > 50% are malignant
 - Usually in pancreatic head
 - Often large
 - Have worse survival compared to functioning pancreatic neuroendocrine tumours
 - Resect all sporadic tumours, or if > 2 cm in MEN I
- Functioning
 - **Gastrinoma**
 - 1 per year/10⁶ population
 - Malignant ~ 66%



- 20% associated with MEN I
- > 50% of sporadic and > 70% of hereditary gastrinomas are in the duodenum
- Resection of all sporadic gastrinomas and in MEN I if > 2.5 cm

➤ **Insulinoma**

- 1 per year/10⁶ population
- Benign in ~90%
- Solitary in 95%
- <2 cm in 85-90%
- 4% are MEN I
- In MEN I patients insulinomas are multiple in 90%
- Enucleation if solitary; pancreatic
- tomy if multiple
- Clinical features
 - Neuroglycopenia (90%)
 - Amnesia or coma (47%)
 - Confusion (80%)
 - Visual changes (59%)
 - Convulsions (17%)
 - Altered consciousness (38%)
 - Sympathetic overdrive (60-70%)
 - Weakness (56%)
 - Sweating (69%)
 - Tremors (24%)
 - Palpitations (12%)
 - Hyperphagia (14%)
 - Obesity (<50%)

➤ **Glucagonoma**

- Occur in 10-15% of patients
- Frequently multiple (>30%)
- Tumours >3 cm are aggressive (metastases)
- Resect lesion if > 3 cm in the body/tail and if > 2 cm in the pancreas head
- Tumours < 1 cm require yearly follow-up by CT or MRI from an early age

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➤ Clinical

62. Give the clinical and laboratory features of the glucagonoma syndrome

- Migratory necrolytic erythema (70-90%)
- Weight loss (80%)
- Glucose intolerance (40%-90%)
- Normochromic, normocytic anemia (35%-90%)
- Hypoaminoacidemia (80%)
- Diarrhea (25%)
- Thromboembolism (15%-25%)
- Glossitis, cheilitis (15%-40%)
- Psychiatric symptoms (0%-17%)

Adapted from: Metz, D.C., and Jensen, R.T. *Gastroenterology* 2008; 135: 1469-1492.

➤ **VIPoma**

- Neuroendocrine tumor, usually (> 80%) of the pancreatic tail, secreting ↑ PNM-27 (vasoactive intestinal peptide)

➤ Clinical

- ↑ VIP → WDHH syndrome
Watery diarrhea
Hypokalemia → renal and heart failure
Achlorhydra

➤ Pathology

- Single tumor
- Large
- ~ 75% in tail of pancreas
- High rate of metastases



➤ Pathophysiology

- ↑ PHM-27 in VIPoma NET tumor
- PHM-27 shares a common precursor with VIP2
- When ↑ PHM-27 → VIP-like actions → ↑ activity of adenylate cyclase
→ ↑ cAMP
 - ↑ Cl⁻ secretion (diarrhea)
 - Secondary hyperaldosteronism

SO YOU WANT TO BE A GASTROENTEROLOGIST!

- Give the pathophysiology of the flushing, bones disease and hyperglycemia which occur in VIPoma.
 - Flushing - Vasodilation
 - Bone disease - ↑ osteolysis of bone
 - Hyperglycemia - Glycogenolytic effect of VIP

➤ Treatment

- Octreotide (benefit does not always reflect changes in blood levels of VIP)
- Surgical resection
- Caution alert: do not use in pregnancy (risk of uterine ischemia)

Serum VIP levels are increased with VIPoma, especially when the patient is having diarrhea (levels may fluctuate).

63. Give 3 other causes of chronic diarrhea which may also be associated with ↑ VIP, but without an associated secreting pancreatic endocrine tumor.

- Laxative abuse
- Short bowel syndrome (surgical resection of a portion of the small bowel)
- Radiation enteritis



➤ Somatostatinoma

The clinical and laboratory findings in patients with Pancreatic (Pan) and intestinal (Int) somatostatinomas.(the approximate frequency of symptoms is shown).

	Somatostatinoma	
	<i>Pancreatic</i>	<i>Intestinal</i>
○ Diabetes mellitus	95	20
○ Gallbladder disease	94	40
○ Steatorrhea	85	10
○ Hypochlorhydria	85	15
○ Diarrhea	75	25
○ Weight loss	50	35

➤ Local treatment – liver metastases

- Liver resection
- Chemoembolization
- Radiofrequency ablation

➤ Systemic therapy

- Somatostatin analogues
- Somatostatin receptor radionuclide therapy
- MIBG radionuclide therapy
- Chemotherapy, especially for poorly differentiated tumours

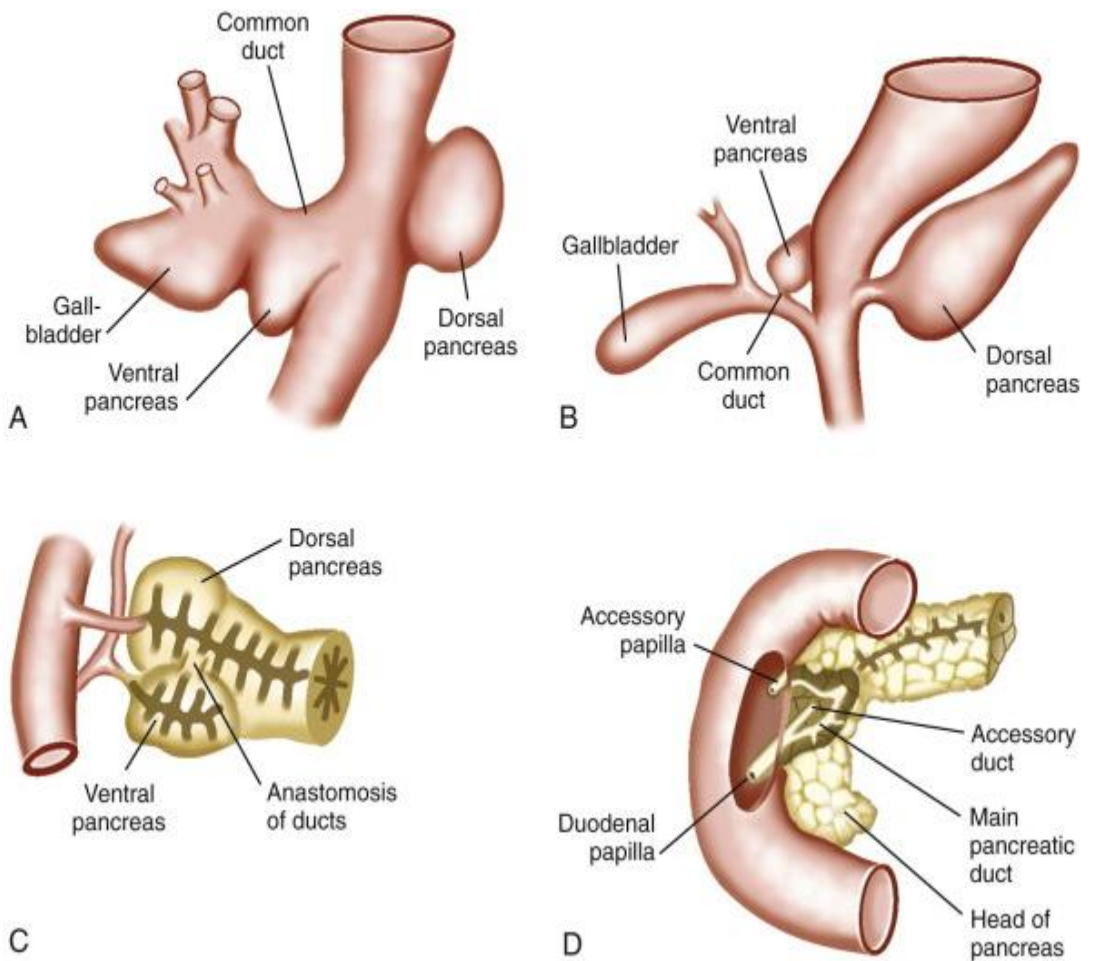
Printed with permission: Alexakis N, and Neoptolemos JP. *Best Practice & Research Clinical Gastroenterology* 2008; 22(1): 199.



Congenital abnormalities

Annular Pancreas

- Incidence
 - Annular pancreas (AP) – $100/10^5$
- Embryology



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- Give the stages in the **embryonic development** of the pancreas.
 - At about 4 weeks of gestation (A), dorsal and ventral buds are formed from the duodenum.
 - At 6 weeks (B), the ventral pancreas extends toward the larger dorsal pancreas.
 - By about 7 weeks (C), fusion of dorsal and ventral pancreas has occurred and ductular anastomosis is beginning.
 - At birth (D), the pancreas is a single organ, and ductular anastomosis is complete.

Printed with permission: Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier, Philadelphia, 2010, Figure 55-10, page 915

➤ Clinical (in adults)

- Pancreatitis
- Biliary obstruction

➤ Diagnostic imaging

- Abdominal film
 - “double bubble” sign (from foregut obstruction)
- CT
 - Enlarged head of pancreas
 - No focal mass
- MRCP
- ERCP
 - “ring like” pancreatic duct surrounding the duodenum plus normal pancreatic duct (failure of the normal left ventral bud of the pancreas of fully rotate during normal embryological development)
- Laparotomy

Source: Spiegel BM. Acing the GI board exam. Slack Incorporated 2009, page 79.

➤ Treatment

- Surgical duodenostomy



Cystic Fibrosis (CF) Involving the Pancreas

➤ Genetics

Useful background: Characteristics of CFTR (Cystic Fibrosis Transmembrane Conductance Regulator)

- CFTR is a peptide which functions as an anion channel.
- Cl^- and HCO_3^- pass through this channel, causing alkaline pancreatic fluid secretion.
- In the pancreas, CFTR is in the apical membrane of the pancreatic duct cell.
- CFTR is regulated.
- The regulation of CFTR is by way of three regulatory domains
 - NBD (nucleoside binding domain) 1 and 2.
 - R (regulatory) domain
 - R domain binds to cytoplasmic glutamine to stimulate Cl^- secretion.
 - $\text{NBD}_{1/2}$ binds to cytoplasmic ATP to stimulate HCO_3^- secretion.
 - The conformation of the CFTR protein changes depending upon whether it is bound to $\text{NBD}_{1/2}$.
- The second messenger system regulates NBD_1 , NBD_2 and the R domain of CFTR.
- For CFTR, second messenger system includes
 - ATP
 - PKA
 - Ca^{2+}
 - Glutamate intra-acinar cell)
- The second messenger system in turn is stimulated by secretin and VIP as well as Ach.
 - Secretin/VIP → receptors → $\uparrow$ cAMP → $\uparrow$ PKA (protein kinase A)-mediated phosphorylation of R domains of CFTR.
 - Ach → $\uparrow$ Ca_i^{2+} (intracellular Ca^{2+})
- Numerous genetic mutations of CFTR have been described.
- The commonest genetic mutation in CFTR is ΔF508 , a three-base pair deletion of the phenylalanine-coding codon 508.
- When there are major mutations in CFTR alleles, the function of CFTR is lost.
- When CFTR no longer functions normally as a regulated anion channel in the apical membrane of the pancreatic duct cell, mucus is not hydrated, ducts are blocked and tissue atrophies.



- There may be modifier genes, or environmental factors which influence the clinical features of CF (gastric fibrosis).
- Many organs are affected in CF, and vary with the nature of the genetic changes e.g. alter the impact and environmental factor on causing pancreatitis, such as alcohol damage leading to pancreatitis.
- The clinical impact of CFR, a susceptibility gene, may also be affected by an unidentified modifier gene.
- A modifier gene interacts with a susceptibility gene to “increase the risk of developing a pathological outcome” (Feldman M., et al. Sleisenger and Fordtran’s Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier, Philadelphia, 2010, page 937).

➤ Pathology

- The usual **phenotype change** in CFTR in the pancreas cause
 - Thick, inspissated macromolecules such as mucus.
 - This blockage causes
 - Fibrosis
 - Dilated ducts
 - Pseudocysts
 - Chronic inflammation
 - Atrophy

SO YOU WANT TO BE A GASTROENTEROLOGIST!

- Give 7 **pathological features** of the pancreas in cystic fibrosis.
 - Inspissated secretions in ducts
 - Blockage extends to acinar cells
 - Epithelial flattening and atrophy
 - Dilation of acini with calcium-rich eosinophilic concretions
 - Pseudocysts
 - Hyperplasia and necrosis of ductular and acinar cells
 - Inflammation (mild)
 - Fibrosis
 - Calcification
 - Late loss of islet of Langerhans (glucose intolerance is common, but CFRD [cystic fibrosis-related disease] is uncommon).



➤ Clinical

64. Give 20 **GI/hepatobiliary manifestations** of cystic fibrosis.

- Esophagus
 - Gastroesophageal reflux
- Stomach
 - Peptic ulcer disease
- Small bowel
 - Fat malabsorption
 - Meconium ileus
 - Ileal atresia
 - Intussusception
- Colon
 - Volvulus
 - Distal intestinal obstruction syndrome (meconium equivalent)
 - Fecal masses
 - Constipation
 - Impaction
 - Rectal prolapse
 - Hemorrhoids
- Peritoneum
 - Peritonitis
- Pancreas
 - Nutritional failure caused by pancreatic insufficiency
 - Diabetes
 - Calcification
 - Maldigestion
 - Fat soluble vitamin deficiencies
 - Steatorrhea and azotorrhea



- Gallbladder
 - Gallstones
 - Atrophic gallbladder
- Liver
 - Focal biliary cirrhosis (FBC)
 - Cirrhosis
 - Portal hypertension
 - Non-alcoholic fatty liver disease (NAFLD)
 - Hepatomegaly
 - Premature death

Adapted from: Whitcomb, David C. *Sleisenger & Fordtran's gastrointestinal and liver disease: Pathophysiology/ Diagnosis/Management* 2006: pg. 1214,; and Castillo, Carlos Fernandez-del., and Jimenez, Ramon E. *Sleisenger & Fordtran's gastrointestinal and liver disease: Pathophysiology/ Diagnosis/Management* 2006: pg.1322.

65. Give 10 **non-GI/Hepatobiliary manifestations** of cystic fibrosis in the adult.

- Eye
 - Venous engorgement
 - Retinal hemorrhage
- Lung
 - Sinusitis
 - Nasal polyposis (secondary to mucous membrane hypertrophy)
 - Lower respiratory infections
 - Bronchiectasis
 - Chronic infection with *Pseudomonas aeruginosa*
- Endocrine
 - Glucose intolerance
 - Diabetes mellitus
- GU
 - Male infertility (sterility; congenital bilateral absence of vas deferens [CBAVD]), epididymis, and seminal vessels)
 - Female infertility (increased viscosity of vaginal mucous)



- Nutrition
 - Clubbing
 - Short stature
- Skeletal
 - Retardation of bone age
 - Demineralization
 - Hypertrophic pulmonary osteoarthropathy
- Other
 - Salt depletion through excessive loss of salt via the skin
 - Heat stroke
 - Hypertrophy of apocrine glands
- Premature death

Adapted from: Whitcomb DC. *Sleisenger & Fordtran's gastrointestinal and liver disease: Pathophysiology/Diagnosis/Management* 2006: pg. 1214.

- Laboratory
 - CF - diagnosis
 - Sweat chloride testing
 - Nasal bioelectrical response
 - Rectal potential difference
 - Genetic testing
 - CF – complications (steatorrhea)
 - ↓fat soluble vitamins

“Belief in oneself is one of the most important
bricks in building any successful venture.”

Lydia M. Child



➤ Diagnostic imaging

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- Give 10 radiological features of **meconium ileus** / DIOS (distal intestinal obstruction syndrome).
 - Proximal ileum
 - Hypertrophy of wall
 - Distal ileum
 - Dilation, or
 - Narrowing from inspissated meconium
 - Bead-like appearance from pellets of meconium
 - Air/gas
 - Little air or air-fluid levels
 - Bubbles of gas in meconium
 - Colon
 - Empty
 - Microcolon
 - Associated
 - Volvulus
 - Atresia
 - Ascites
 - Calcification
 - Intussusception
 - Rectal prolapse
 - Cancer
 - Stomach
 - Small intestines
 - Pancreas
 - Biliary tree



➤ Treatment

- Pancreatic enzyme supplements
 - Enteric-coated minimicrospheres with / without gastric acid inhibition (H2RAs, PPIs)
- Nutritional support begins with 2 tablets with meal and adjust dose to maintain normal growth and to correct symptoms such as steatorrhea.
 - Calories
 - Protein
 - FSV (fat soluble vitamins) A, D, E, K
- Anti-oxidants e.g. vitamin E
- Manage complications
- Genetic consultation re family testing

66. Give the **adverse effects** of long-term use of high dose pancreatic enzyme supplements.

- Mouth, Anus
 - Irritation
- Kidney
 - ↑ uric acid (high purine content of supplements) → hyperuricemia
- Colon
 - Strictures (fibrosing colopathy)

"Optimism is the faith that leads to achievement.
Nothing can be done without hope and
confidence."

Helen Keller



Pancreas Divisum (PD)

- Definition: A congenital abnormality caused by: “failure of the dorsal and ventral pancreatic ducts to fuse”.
 - Most of the pancreatic secretions then drain “.....through the relatively small dorsal duct of Santorini and minor [accessory] papilla rather than the ventral duct of Wirsung and the major papilla” (Feldman M., et al. Sleisenger and Fordtran’s Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier, Philadelphia, 2010, page 918).
- Genetics
 - CFTR gene (and at a lower level, SPINK1 and PRSS1) mutations and pancreas divisum might be cofactors associated with the occurrence of acute recurrent or chronic pancreatitis.
 - In patients with CFTR gene mutations, pancreas divisum is found in 47%
 - The frequency of pancreas divisum is the same in patients with idiopathic pancreatitis, chronic alcoholic pancreatitis, and in controls without any pancreatic diseases (5-7%).
- Treatment
 - Sphincterotomy of minor papilla or placement of stent in minor (accessory) papilla may be helpful for symptoms of pancreatitis (acute or chronic), especially with pain characteristic of acute recurrent pancreatitis.
 - Pancreas divisum should no longer be considered as a cause of pancreatitis (controversy).

Source: Bertin C, et al. Am J Gastroenterol 2012; 107: 311-317.

“Setting goals is the first step in turning the invisible into the visible.”

Tony Robbins



Abbreviations

AIP	Autoimmune pancreatitis
CCK	Cholecystokinin
CT	Computed tomography
CT	Cationic trypsinogen
EUS	Endoscopic ultrasound
FNA	Fine needle aspiration
HGD	High grade dysplasia
HPF	High power field
IAP	Ideopathic acute pancreatitis
IgG	Immunoglobulin G
IgG4	Immunoglobulin G4
IPMN	Intraductal pancreatic mucinous neoplasia
ISD	IgG4-associated systemic disease
LEC	Lymphoepithelial cysts
LGD	Low grade dysplasia
LPSP	Lymphoplasmacytic sclerosing pancreatitis
MCN	Mucinous cystic neoplasms
MDCT	Multidetactable CT
MRCP	Magnetic resonance cholangiopancreatography
MRI	Magnetic resonance imaging
NG/NJ	Nasogastric/ nasojejunal
PD	Pancreatic duct
PET	Pancreatic endocrine tumour
PP	Pseudopapillary tumours
S-MRCP	MRCP with secretin
SOD	Sphincter of Oddi dysfunction
ULN	Upper limit of normal
US	Ultrasonography





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Appetite and Food Intake

Satiety Signals (Anorectic Peptides)

1. Give the 5 satiety signals arising from the GI tract.

- Stomach, adipocytes
 - Leptin
 - Ghrelin
 - GRP (gastrin-releasing peptide)
- Pancreas
 - NPY (neuropeptide Y)
 - Pancreatic polypeptide)
 - Insulin
- Small intestine
 - CCK (cholecystokinin)
 - PYY (peptide YY)
 - GLP-1 (glucagon-like peptide 1)
 - Oxyntomodulin
 - APO A-IV

SO YOU WANT TO BE A GASTROENTEROLOGIST!

- Give an explanation of the mechanism of the effect of **Apo- A IV** on producing satiety.

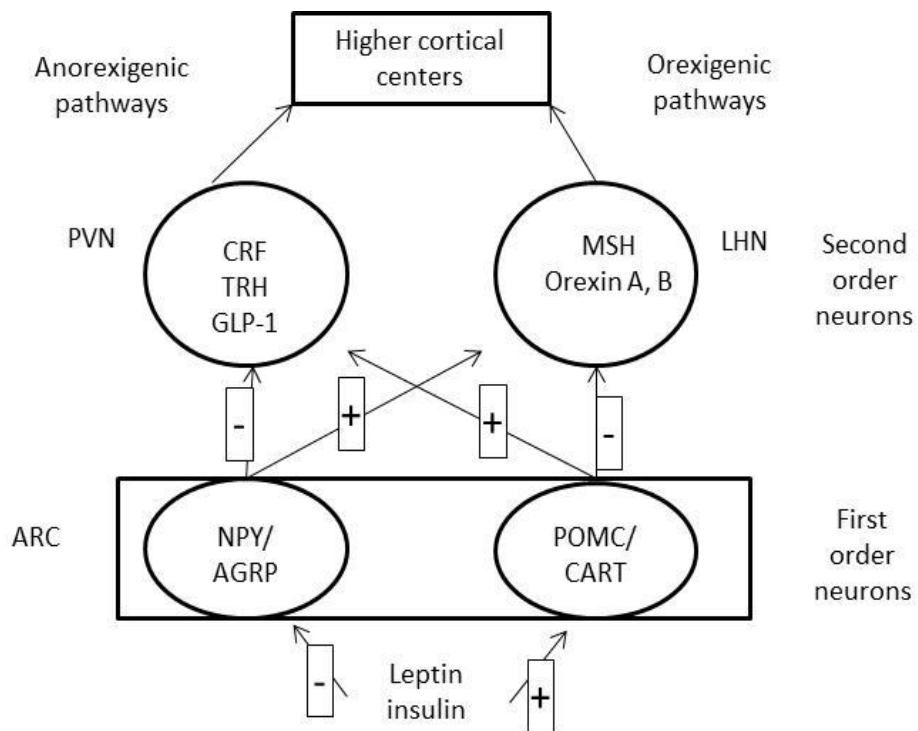
Apo – A IV

- Produced in
 - Enterocytes, in response to dietary fat release PYY, and NPY (neuropeptide Y) PP → ↑ enterocyte production of Apo – A IV
 - Arcuate nucleus of hypothalamus
- Anorectic effect of Apo – A IV acts centrally
- Give 3 GI signals which increase appetite.

Trick question! There is only one GI peptide which stimulates appetite, ghrelin (leplin, lowers appetite; ghrelin, gain in appetite).



2. Give 8 central (CNS) and peripheral (non-CNS/GI) **signals which influence food intake.**
 - Cortex – Orexigenic and anorexigenic pathways
3. Give the **CNS networks** implicated in the control of food intake
 - First order neurons
 - Arcuate nucleus – NPY, AGRP, POMC, CART
 - Paraventricular nucleus (PVN) – CRF, TRH, GLP-1
 - Lateral hypothalamic nucleus (LVN) – MSH, Orexin A, B



Abbreviations: AGRP, agouti-related protein; ARC, arcuate nucleus; CART, cocaine and amphetamine regulated transcript; CCK, cholecystokinin; CRF, corticotrophin releasing factor; GLP-1, glucagon-like peptide; LHN, lateral hypothalamic nucleus; MSH, melanocyte-stimulating hormone; NPY, neuropeptide Y; NS, nervous system; NTS, solitary nucleus; POMC, proopiomelanocortin; PVN, paraventricular nucleus; PYY, peptide YY3-36; TRH, thyrotrophin-releasing hormone.

Printed with permission: Foxx-Orenstein AE. 2008 ACG Annual Postgraduate Course Book: pg. 148.



Eating Disorders

4. Give the diagnostic criteria for **anorexia nervosa**.

- Refusal to maintain minimal normal body weight
- Intense fear of weight gain
- Body-image disturbance (e.g. feeling fat when emaciated)
- Absence of three consecutive menstrual cycles
- Specific type
 - Restricting type: Person does not regularly engage in binge eating or purging behaviour (e.g. self-induced vomiting, use of laxatives)
 - Binge-eating/purging type: Person regularly engages in eating or purging behaviour (e.g. self-induced vomiting, use of laxatives)

Note: this table was adapted from the DSM-IV diagnostic criteria for anorexia nervosa

Printed with permission: Williamson DA, et al. *Best Practice & Research Clinical Gastroenterology* 2004; 18(6): pg 1074.

5. Give the diagnostic criteria for **bulimia nervosa**.

- Episodes of compulsive binge eating
- Lack of control over eating binges
- Use of extreme methods for controlling weight (self-induced vomiting, laxative abuse, diuretic abuse, restrictive dieting, or excessive exercise)
- At least two binge eating episodes per week for at least 3 months
- Obsessive overconcern with body shape, body weight, and body size
- Specific type
 - Purging type: Person regularly engages in purging behaviour (e.g. self-induced vomiting, use of laxatives, use of diuretics, or enemas)
 - Non-purging type: Person does not engage in purging behaviour (e.g. self-induced vomiting, use of laxatives, use of diuretics, or enemas)

Note: this table was adapted from the DSM-IV diagnostic criteria for bulimia nervosa

Printed with permission: Williamson DA., et al. *Best Practice & Research Clinical Gastroenterology* 2004; 18(6): pg 1080.



6. The psychiatric eating disorder bulimia nervosa may be associated with the misuse of laxatives.

● Give three clinical features that could confirm your suspicions of laxative abuse.

- Vital sign
 - Hypothermia
 - Bradycardia
 - Arrhythmia
- Hair
 - Hair loss
- Teeth
 - Loss of dental enamel
- Parotids
 - Large parotid glands
- Skin
 - Dry skin
 - Languor
 - Scars or calluses on the dorsum of hand
- Ankle
 - Pedal edema

7. Give 10 guidelines for the use of **enteral tube feeding** (ETF) in the adult patient.

- Conditions where tube feeding should be a part of routine care
 - Protein-energy malnutrition (greater than 10% weight loss) with little or no oral intake for 5 days
 - Less than 50% of the required oral nutrient intake for previous 7-10 days
 - Severe dysphagia or swallowing-related difficulties, e.g. head injury, strokes, motor neuron disease
 - Major, full-thickness burns
 - Massive small bowel resection (in patients with 50-90% small bowel resection, ETF is given to hasten gut regeneration and return to oral intake, often in combination with parenteral nutrition)
 - Low-output enterocutaneous fistulae* (<500 ml/day)



- Conditions where tube feeding would normally be helpful
 - Major trauma
 - Radiation therapy
 - Mild chemotherapy

- Conditions where tube feeding is of limited or undetermined value
 - Immediate postoperative period or post-stress period if an adequate oral intake will be resumed within 5-7 days
 - Acute enteritis
 - Less than 10% of the small intestine remaining (parenteral nutrition is usually indicated)

- Conditions/situations in which tube feeding should not be used
 - Complete mechanical intestinal obstruction
 - Ileus or intestinal hypomotility
 - Severe uncontrollable diarrhea
 - High-output fistulae
 - Severe acute pancreatitis
 - Shock
 - Aggressive nutritional support not desired by the patient or legal guardian, in accordance with hospital policy and existing law
 - Prognosis not warranting aggressive nutritional support

*If the fistula is proximal, the feeding should be distal. If the fistula is distal, sufficient proximal length must be present to allow sufficient absorption. Fistulae due to malignancy, radiation and distal obstruction are unlikely to close spontaneously

Printed with permission: Stratton RJ, and Smith TR. *Best Practice & Research Clinical Gastroenterology* 2006; 20(3): pg. 457.

"A journey of a thousand miles begins with a single step."

Lao Tzu



8. Give 10 **complications** of enteral tube feeding (ETF).

- Mechanical
 - Tube blockage by feed or tube kinking
 - Tube malposition (e.g. into trachea)
 - Insertion trauma
 - *Nasogastric* damage to nasal septum, esophagus, stomach, perforation (rare)
 - *Gastrostomy/enterostomy* damage to stomach, small bowel, bleeding, peritonitis, leakage, irritation and infection around site
 - Loss of tube into GI tract
- Feed/flow related
 - Diarrhea or constipation, bloating, cramps
 - Aspiration pneumonia/regurgitation
- Metabolic
 - Fluid and electrolyte disturbances
 - Hypo- and hyper-natremia, kalemia, phosphatemia, glycemia
- Infections
 - Infection around ostomy site
 - Infection of feed or administration set (very rare if commercial feed and set used according to guidelines)
- Organ dysfunction
 - Aspiration pneumonia may precipitate respiratory distress
- Psychological
 - Effects on self-image
 - Anxiety and depression
 - Social isolation (if unable to eat, if confined to bed/home)

Printed with permission: Stratton RJ, and Smith TR. *Best Practice & Research Clinical Gastroenterology* 2006; 20(3): pg. 459.



Malnutrition

- Normal values

Basal energy expenditure approximately 0.8 kcal/min, or 1150 kcal / day

Recommended daily energy intake, ~ 22 to 25 kcal / kg.

9. Give 5 methods of nutritional assessment.

➤ Subjective global assessment

- History
 - Changes in weight (< 90% IBW [ideal body weight])
 - Changes in dietary intake
 - Gastrointestinal symptoms
 - Functional capacity
 - Stress of disease
- Physical examination
 - Loss of subcutaneous fat
 - Muscle wasting: deltoids, quadriceps, biceps, supra/subscapular muscles
 - Edema: ankles, sacrum, ascites
 - Skin rashes
 - Eye changes
 - Neurological changes
 - Indirect calorimetry
- Classification
 - Well nourished: no history or physical findings of malnutrition
 - Moderately malnourished: weight loss 5-10% of usual body weight (UBW), mild Signs of malnutrition
 - Severely malnourished: weight loss 10% of UBW, severe signs of malnutrition

➤ 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
- Muscle function
- 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 (total body K⁺)

Abbreviations: BMI, body mass index (kg/ m²); IBW, ideal body weight; UBW, usual body weight

Adapted from: De Legge MH. *Sleisenger & Fordtran's Gastrointestinal and Liver Disease: Pathophysiology/Diagnosis/Management* 2006: pg. 357-359.

“Go as far as you can see; when you
get there, you’ll be able to see farther.”

J. P. Morgan



10. Give a **classification** of the causes of malnutrition, and indicate how these could be suspected from a **directed history**.

Etiologies	History
○ Decreased diet intake and decreased assimilation	- Unintentional weight loss >10% body wt - Decreased food intake ▪ Socioeconomic ▪ Anorexia ▪ Self-restricted diets e.g. alcoholism
○ Increased metabolism - Critical acute illness - Chronic inflammation	▪ Critical illness ▪ Gastrointestinal symptoms - Dysphagia - Nausea/vomiting - Chronic diarrhea - Abdominal pain (sitophobia [fear of eating])
○ Increased losses	- Chronic diarrhea, vomiting
○ Mixed metabolic abnormality	- HIV/ AIDS - Cancer - Chronic liver disease - Heart failure - COPD - Chronic infection(e.g. TB)

Printed with permission: Alberda C, et al. *Best Practice & Research Clinical Gastroenterology* 2006; 20(3): pg.427.



Increased Body Mass Index / Obesity

➤ Definition

11. Give a definition of adult obesity, and state the effect on the risk of comorbidities.

Classification	BMI (kg/m ²)	Risk of comorbidities
○ Normal range	18.5-24.9	Average
○ Overweight	≥ 25.0	
○ Preobesity	25.0-29.9	Increased
○ Obesity class I	30.00-34.9	Moderate
○ Obesity class II	35.00-39.9	Severe
○ Obesity class III	≥ 40.0	Very severe

Printed with permission: Formiguera X, and Canton A. *Best Practice & Research Clinical Gastroenterology* 2004; 18(6): pg 1126.

- Optimal waist circumference
 - Women < 35 inches / 88 cm
 - Men < 40 inches / 102 cm
- BMI (wt (kg) / height (m²))

Definition	BMI, kg / m ²
Normal	< 25
Overweight	25 – 29.9
Obese	≥ 30
Severe obesity	≥ 40 (or > 35 plus comorbidities)



➤ Demography

- Increased body mass index (BMI) above 25 kg/m² is seen in about two thirds of Americans, and of these half (one third of all Americans have a BMI > 30 kg/m². Obesity is associated with many morbidities such as diabetes mellitus, systemic hypertension, musculoskeletal problems, and fatty liver disease (simple steatosis, non-alcoholic steatohepatitis).

➤ Diagnosis

12. Give the diagnostic criteria for the “**Metabolic Syndrome**”.

Risk factor		Abnormal level
○ Waist circumference	– Men	>102 cm
	– Women	>88 cm
○ Fasting blood glucose		≥100 mg/dl
○ Serum triglyceride		≥ 150 mg/dl, or under treatment with fibrates
○ Serum HDL cholesterol	- Men	<40 mg/dl
	- Women	<50 mg/dl
○ Arterial blood pressure		≥ 130/ ≥85 mm Hg, or under pharmacologic treatment

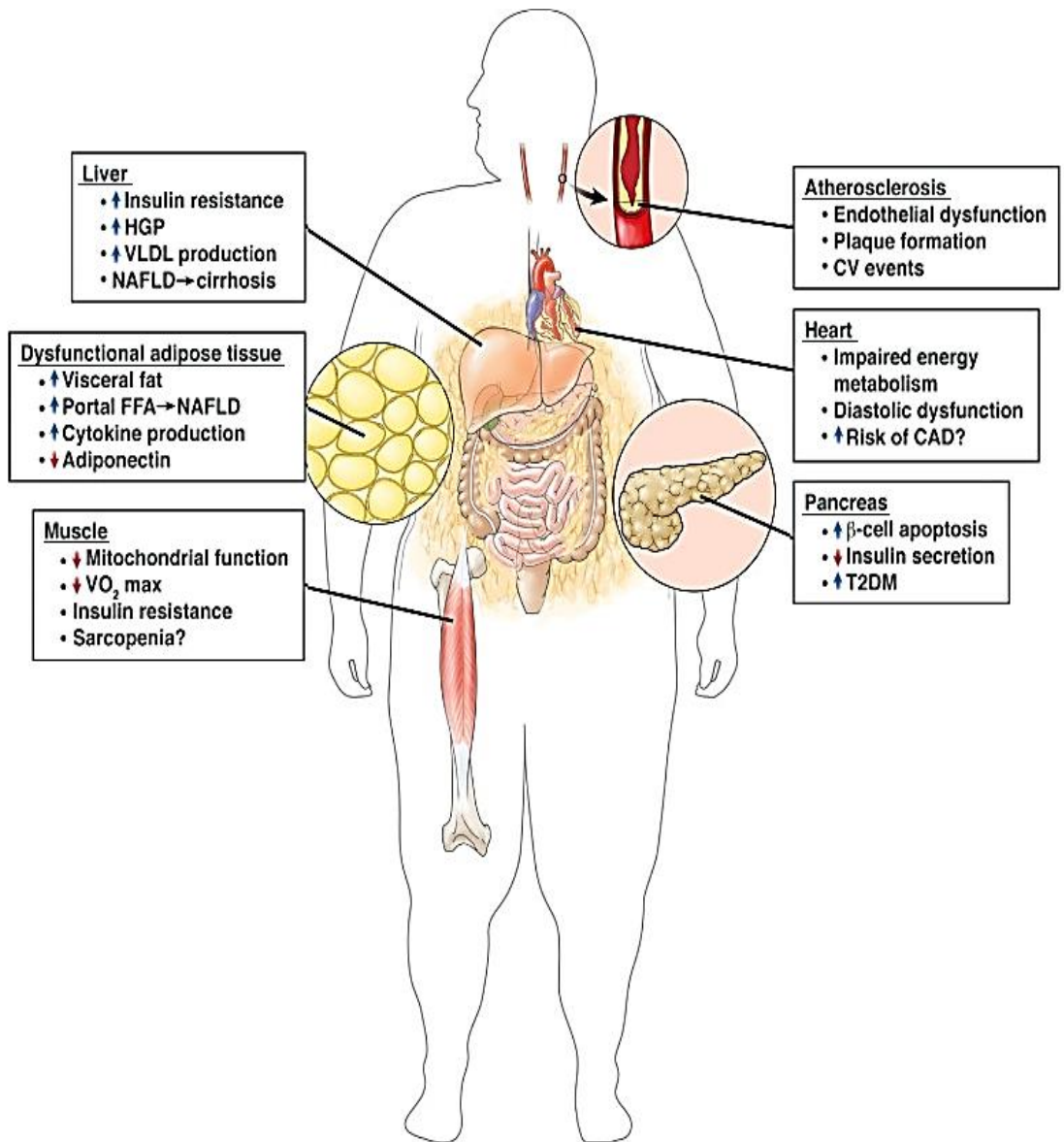
Printed with permission: Cortez-Pinto H, and Camilo ME. *Best Practice & Research Clinical Gastroenterology* 2004;18(6): pg 1092.

"Optimism is the faith that leads to achievement.
Nothing can be done without hope and
confidence."

Helen Keller



13. Give 15 **complications** of obesity.



- Morbidity ($\text{BMI} > 40 \text{ kg/m}^2$) reduces life expectancy.

Obesity and triglyceride-derived toxic lipid metabolites accumulate in ectopic tissues and lead to multiorgan dysfunction, T2DM and CVD.

Printed with permission: Cusi K. Gastroenterology. 2012;142(4):711-725.



14. Give 10 GI/liver complications of obesity.

- Esophagus - GERD, Barrett's epithelium, adenocarcinoma
- Stomach – retention, adenoma carcinoma, gastric cardia cancer
- Colon – Hemorrhoids, diverticulosis, colorectal cancer (CRC), non-specific abdominal pain
- Liver (NAFLD, SS/NASH), cirrhosis, hepatocellular cancer (HCC)
- Pancreas - Pancreatitis, cancer
- Gallbladder – Stones, cancer

Abbreviations: NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; SS, simple steatosis

Printed with permission: Freeman HJ. *Best Practice & Research Clinical Gastroenterology* 2004; 18(6): 1169.

➤ Treatment

- The only effective treatment is long-term reduced calorie intake, in conjunction, in selected patients, with bariatric surgery
- Drug used to reduce appetite or to produce a mild malabsorption lead to very modest and often non-maintained weight loss.
- Bariatric surgery remains the only effective and enduring treatment for morbid obesity.
- Because physicians will increasingly be caring for patients who experience complications from their bariatric surgery, this topic is important to consider.
- Many different approaches are used to lose weight, and these vary widely in their success in helping the patient to achieve their ideal body weight.

Maintaining achieved purposeful weight loss is usually difficult.

15. Give two processes which make the **maintenance of weight loss** so challenging.

- Recidivism
- Reduction in basal energy expenditure (BEE) as a result of weight loss, requiring an even further ↓energy intake even though the ideal body weight has been achieved with the initial short-term dieting.



16. Classify 6 classes of **drugs to treat obesity** in addition to behavior modification (diet, exercise) for weight reduction.

- Sympathomimetic
 - Noradrenergic sympathomimetic drugs, phentermine and diethylpropion
 - Only approach for short-term use (no more than 3 months)
 - ↑ satiety
 - ↓ food intake by acting on nerve terminals
 - ↑ release of norepinephrine
 - ↓ uptake of norepinephrine
- Serotonergic (sibutramine) blocks orexigenic and stimulates anorexigenic systems
- Serotonin agonist, lorcaserin
 - Selective agonist of serotonin 2C receptor → ↓ food intake
 - 10 mg o bid provided
 - % of persons losing ≥ 5% of baseline weight in 1 year:
 - Lor 47.5
 - PL 20.3%
 - TG 20.2%
 - % of persons maintaining weight loss in second year:
 - Lor 67.9%
 - PL 50.3%
 - TG 17.6%
 - TG in terms of weight loss ~ 3 kg to 4 kg / year
 - ↓ SBP / DBP, HR, total / LDL cholesterol, CRP, fibrinogen, fasting glucose and insulin concentrations in blood
 - Because lorcaserin is a selective agonist of the serotonin 2 C receptor, rather than the 2B serotonin receptor, there should be no lorcaserin-associated cardiac valvular disease (such as was seen with fenfluramine).
- Pancreatic lipase inhibition: orlistat (Xenical®)

Abbreviations: CRP, C-reactive protein; DB, diastolic blood pressure; Lor, lorcaserin; PL, placebo; SBP, systolic blood pressure; TG, therapeutic gain



- Orlistat
 - Inhibits activity of pancreatic lipase
 - 120 mg po tid, continued loss of weight at one year, as % of initial body weight
 - “placebo” (lifestyle changes) 5.5 to 6.6
 - Orlistat plus lifestyle changes 8.5 to 10.2
 - Therapeutic gain 1.9 to 4.7

AEs (adverse effects)

- GI
 - Nausea
 - Fatty/oily stools/spotting 12-48 hours after a high fat meal
 - Increased defecation frequency
 - Liquid stools
 - Fecal urgency
 - Flatulence
 - Flatus with fecal discharge
 - Fecal incontinence
- Nutrition
 - ↓ absorption of fat soluble vitamins A, D, E
 - ↓ weight
- Liver
 - Uncertain association of liver injury
 - 3 / 10⁵ orlistat users
- Kidney
 - Oxalate-induced acute renal injury

17. Give the mechanisms of the development of acute **oxalate-induced renal injury** in persons taking orlistat.

- Orlistat → ↓ digestion of TG → ↑ TG in stool → ↑ binding of Ca²⁺ - less Ca²⁺ -oxalate and ↑ luminal oxalate - ↑ absorption of oxalate → ↑ oxalate excretion by kidney, with ↑ deposition of oxalate in renal parenchyma
- Note: Ca²⁺ - oxalate in the lumen of the intestine requires the fatty acids (Fas) removed from dietary TG (triglyceride), in order for the luminal Ca²⁺ to become bound to FAs (Ca²⁺ - FA), then for the oxalate to be absorbed by the intestine, and excreted into the urine.



- The above description of the pathophysiology of oxalate damage to the kidney suffers from the problem that orlistat blocks pancreatic lipase, so fewer rather than more Fas are present in the intestinal lumen to bind to the Ca^{2+} in Ca^{2+} - oxalate.
- Endocannabinoids: CB-1 antagonists
 - Clinically meaningful weight loss is off-set by psychiatric AEs
 - Not approved for use
- Anti-depressants
 - Bupropion
 - SR 300-400 mg / day
 - Especially useful for prevention of weight gain when smokers stop smoking
 - Alters the metabolism of norepinephrine
 - Fluoxetine
 - 60 mg po per day
 - SSRI (selective serotonin reuptake inhibitor)
- Antiepileptics: Insufficient evidence to recommend use at this time for weight loss
- Diabetes – Treating drugs
 - Metformin
 - ↓ hepatic glucose production
 - ↑ insulin sensitization in peripheral tissue
 - ↑ anorexic effect
 - Metformin very modest weight loss when used or prevention of diabetes (~2.5% of initial body weight)
 - Other oral diabetic drugs give only minimum weight loss
- GLP-1 mimetic
 - ↑ glucose-dependent insulin secretion
 - ↓ appetite
 - Slows gastric emptying



- NPY antagonists
- Anti-ghrelin agents
- GH (growth hormone) fragment
- Dietary supplements
 - Non-evidence-based use

Adapted from: Palamara KL, et al. *Cardiol Rev* 2006;14(5):238-58.

18. Give the neurological signs which suggests **vitamin E deficiency**.

- Ataxia
- Gait abnormalities
- Hyporeflexia
- Peripheral neuropathy

Clinical caution:

- Vitamin E deficiency is common in patients with cirrhosis (cholestasis → ↓ absorption of fat soluble vitamins → vitamin E deficiency)
- The neurological signs of vitamin E deficiency are similar to those of HE (hepatic encephalopathy).
- Don't confuse the two; when in doubt, give vitamin E (tocopherol 1000 IU per day) to the patient with HE.

19. Give the ocular and dermatological signs of **vitamin A** (retinol) deficiency.

- Eyes
 - Night blindness
 - Dry eyes (xerophthalmia)
 - Corneal xerosis
 - Conjunctival xerosis



Micronutrients

20. Outline the principle causes of **micronutrient deficiencies**.

- Reduced intake
 - Sitophobia
 - Complicated meals
 - Underlying disease (tumour)
- Impaired absorption
 - Rapid emptying
 - Poor mixing of food and duodenal juice
 - Pancreaticocibal asynchrony
 - Bacterial overgrowth
 - Rapid transit
- Disturbed distribution/metabolism
 - Enterohepatic circulation ↓
 - Enteropancreatic circulation ↓
 - Micronutrient interactions
- Increased loss
 - Occult bleeding
 - Disturbed protein binding
 - Increased renal elimination

Printed with permission: Schölmerich J. *Best Practice & Research Clinical Gastroenterology* 2004; 18(5): pg.917-933.

Clinical Pearl / Gem:

- In patients with diarrhea and skin rash (vesicular pustular plaques, red, scaling) on face and leg, think of Zn (zinc) deficiency.

“Success isn’t something that just happens –
success is learned, success is practiced and then
it is shared.”

Sparky Anderson



21. Give 5 **gastrointestinal hormones**, and their behavioural brain effects on food intake.

Gastrointestinal hormone	Behavioural brain effects on Intake
➤ Foregut	
○ Leptin	↓
○ Ghrelin	↑
○ Obestatin	?
○ Pancreatic polypeptide (PP)	↓
➤ Hindgut	
○ Cholecystokinin (CCK)	?
○ Gastric inhibitory polypeptide (GIP)	↓
○ Glucagon-like peptide-1 (GLP-1)	↓
○ Peptide YY (PYY)	↓

Printed with permission: Vincent, et al. *Nature Clinical Practice Gastroenterology & Hepatology* 2008; 5(5): pg 270.

Food Intolerances

22. Give 8 examples of **immunological reactions to foods** (food allergy, eg. immune-mediated mechanisms).
- Skin
 - Immediate gastrointestinal hypersensitivity
 - Oral allergy syndrome
 - Acute urticarial
 - Atopic dermatitis
 - Acute angioedema



- Lung
 - Acute bronchospasm
 - Asthma
- Gut
 - Esophagus
 - Eosinophilic esophagitis
 - Small bowel
 - Celiac disease
 - Dermatitis herpetiformis (DH)
 - Cow's milk enteropathy
 - Food protein-induced enterocolitis
 - Food protein-induced proctocolitis or proctitis
 - Eosinophilic gastroenteritis

Adapted from: Klein S. *Sleisenger & Fordtran's Gastrointestinal and Liver Disease: Pathophysiology/Diagnosis/Management* 2006:pg 467-483.

23. Give 8 examples of **adverse reactions to food or food additives** (not including immunological reactions to food).

- Allergic eosinophilic gastroenteritis
- Eosinophilic esophagitis
- Food intolerance (non-immune mechanisms)
- Food protein-induced enterocolitis syndromes
- Food toxicity or food poisoning
- Idiosyncratic reactions
- Metabolic reactions
- Pharmacological reactions
- Physiological reactions
- Psychological reactions

Adapted from: Klein S. *Sleisenger & Fordtran's Gastrointestinal and Liver Disease: Pathophysiology/Diagnosis/Management* 2006: pg 467-483.



24. Outline a **management approach** to the patient with suspected food allergies as a cause of GI symptoms.
- Establish foods and food additives that reproducibly cause symptoms
 - Careful history, including diet history
 - Elimination diet
 - Skin testing and/or RAST
 - Consider IgG testing
 - Food antigen challenge
 - Exclude and manage other disorders that may mimic GI food allergy
 - Initiate treatment for food allergies
 - Elimination diet
 - Avoidance of specific foods
 - Medications for after accidental exposure (antihistamines, epinephrine, corticosteroids)
 - Preventive measures (oral cromoglycate, avoid co-precipitating factors, e.g., medications)
 - Education about hidden sources of antigens and cross-reacting foods

Adapted from: Ferreira CT, and Seidman E. *J Pediatr* (Rio J) 2007;83(1):7-20.

“Attitude is a little thing that makes a big difference.”

Winston Churchill



SO YOU WANT TO BE A NUTRITIONIST!

- Give the steps in the gut-brain-liver axis which helps to maintain even levels of **blood glucose** concentration during fasting.
 - Fasting
 - ↑ TG breakdown
 - ↑ FFA
 - ↑ FFA
 - ↓ insulin sensitivity
 - ↑ insulin resistance
 - ↓ uptake of glucose by muscle
 - ↑ PPAR α
 - induced ER proteins
 - FIT
 - $\frac{1}{2}$ (fat inducing transcripts)
 - $\frac{1}{2}$ lead to formation of hepatic lipid droplets
 - ↑ oxidation of FFA
 - ↑ acetyl CoA
 - ↑ ketone bodies
 - ↑ glycerol
 - ↑ synthesis of glucose
 - Feeding lipids
 - ↑ acyl-CoA synthase mediated production of long-chain fatty acyl-coenzyme A
 - ↑ long-chain fatty acyl-coenzyme A – signals vagal afferents to the nucleus of the solitary tract.
 - Stimulation of the nucleus of the solitary tract increases glutamatergic neurotransmission through vagal efferents to the liver.
 - Feeding carbohydrates
 - Rapid absorption of glucose
 - Increased glutamatergic neurotransmission from the nucleus of the solitary tract decreases hepatic glucose production, even before the ingested carbohydrate is digested and glucose absorbed from the intestine.



Abbreviations

AGRP	Agouti-related protein
ARC	Arcuate nucleus
BMI	Body mass index
CART	Cocaine and amphetamine regulated transcript
CCK	Cholecystokinin
CNS	Central nervous system
COPD	Chronic obstructive pulmonary disease
CRF	Corticotrophin releasing factor
GLP-1	Glucagon-like peptide
IBW	Ideal bodyweight
LHA	Lateral hypothalamic area
LHN	Lateral hypothalamic nucleus
MSH	Melanocyte-stimulating hormone
NPY	Neuropeptide Y
NAFLD	Non-alcoholic fatty liver disease
NASH	Non-alcoholic steatohepatitis
NPY	Neuropeptide Y
NS	Nervous system
NTS	Solitary nucleus
POMC	Proopiomelanocortin
PVN	Paraventricular nucleus
PYY	Peptide YY3-36
SS	Simple steatosis
TRH	Thyrotrophin-releasing hormone
UBW	Usual body weight





MISCELLANEOUS



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GI therapy and Pregnancy

1. For the following GI conditions for a woman list the medications **to avoid** during attempts to become pregnant.
 - Nausea/vomiting
 - Cisapride
 - Dyspepsia, GERD
 - Sodium bicarbonate
 - Omeprazole
 - Bismuth subsalicylate (for *H. pylori* eradication)
 - Misoprostol (PGE₂)
 - EGD/colonoscopy
 - Avoid EGD in first trimester (T1) (because you can't monitor the fetus)
 - Full colonoscopy rarely indicated
 - Avoid diazepam, propofol in T1 (for sedation)
 - Liver disease
 - Interferon
 - Ribavirin
 - B blockers
 - Penicillamine
 - Liver transplant
 - Mycophenolate
 - Sirolimus
 - Constipation
 - Castor oil
 - Mineral oil
 - Tegaserod



- Diarrhea
 - Kaopectate
 - Alosetron
- IBD
 - Methotrexate
 - Ciprofloxacin
- IBS
 - Amitriptyline
 - Nortriptyline
 - Imipramine
 - SSRIs
 - Bismuth

Adapted from: Kane S. *AGA Institute 2007 Spring Post Graduate Course Syllabus* pg. 511-513.

“The things you do for yourself are gone when you
are gone, but the things you do for others remain as
your legacy.”

Kalu Ndukwe Kalu



Microbiology

2. Give the advantages and disadvantages of 4 common **microbiological techniques**.

Technique	Method	Advantage	Disadvantage
➤ Culture	○ Bacteria grown on selective mediums	- Cheap, widely available, and easy to use	- Grossly underestimates fecal populations
➤ PCR-T/DGGE denaturing/temperature gradient gel electrophoresis	○ Using either temperature or a denaturing agent to separate DNA strands, which are then run on a gel	- Very useful in detecting difference in bacterial populations	- Does not identify bacteria unless bands on the gel are cut and sequenced
➤ FISH (fluorescent <i>in situ</i> hybridization)	○ Oligonucleotide probes designed to hybridize with specific species	- Allows spatial organization of microbiota to be studied	- Slow, will only detect the bacteria probed for
➤ Quantitative PCR	○ Specific primers detect either individual species or genus	- Can detect small number of bacteria and quantify them	- Laborious
➤ 16S rDNA sequencing	○ Bacterial DNA isolated and ribosomal DNA cloned and then sequenced	- Enormous quantities of data at individual species level	- Very costly, available in only a few specialist centers

Printed with permission: Parkes GC, et al. AJG 2008;103: pg. 1561.



HIV / AIDs

- Pathophysiology: Mechanisms of HIV transmission into the gastrointestinal tract.
 - Once released from the basal surface of the epithelial cell, HIV-1 infects CCR5+ lymphocytes in the lamina propria. The virus efficiently replicates in activated CD4+ T cells of the lamina propria. The distribution of HIV coreceptors within the mucosa may also permit infection of cells central to antigen presentation such as macrophages and dendritic cells. Dendritic cells of the lamina propria express C type lectin that traps the virus and assists in the dissemination of HIV-1 from the gastrointestinal tract to secondary lymphoid organs. After 2 weeks of infection T cell death occur by cell lysis apoptosis and by cytotoxic lymphocytes, resulting in rapid depletion of lamina propria CD4+ T cells.

Abbreviation: CCR, CC-chemokine receptors

Source: Siew C. Ng & Brian Gazzard. *Nat Rev Gastroenterol. Hepato* 2009;6:592-607, page 594.

➤ Clinical

3. List 7 liver diseases/conditions/presentations in HIV-infected persons even in the **post-HAART** era.
 - HCV (coinfection in 25%) - faster development of fibrosis, poorer response to HCV treatment
 - HBV, HBV-associated ↑ mortality
 - Alcohol liver disease (associated life style)
 - NAFLD (fat redistribution from HAART [lipodystrophy])
 - Cholangiopathy (intra- and extra-hepatic)
 - Asymptomatic ↑ in transaminases, alkaline phosphatase
 - Kaposi's sarcoma
 - Opportunistic infection:
 - Cholangiopathy: mycobacterium
 - Fungal: cryptological, histological, coccidiomycosis, extra pulmonary pneumocystitis carcinoma
 - Nodular regenerative hyperplasia (vasculopathy)

Adapted from: Wilcox, C. Mel. Gastrointestinal Consequences of Infection with Human Immunodeficiency Viurs. *Sleisenger & Fordtran's Gastrointestinal and Liver Disease: Pathophysiology/ Diagnosis/Management* 2006; pg.676-79.



4. Give 10 gastrointestinal manifestations of HIV infection

- Upper gastrointestinal tract
 - Esophagitis
 - Esophageal ulcers (eg caused by cytomegalovirus or candida spp.)
- Small intestine and colon
 - HIV associated enteropathy
 - HIV associated diarrhea
- Anorectal
 - Non-specific proctitis
 - Anal fistula and/or abscess and/or fissure
 - Rectal ulcers
 - Weight loss and wasting

Printed with permission: Siew C. Ng & Brian Gazzard. *Nat Rev Gastroenterol Hepato* 2009;6:592-607: page 595

5. Give 20 causes of **abdominal pain** in patients with HIV/AIDS, not including non-AIDS specific conditions.

Organ	Causes
○ Stomach	
– Gastritis	▪ CMV
	▪ Cryptosporidia
– Focal ulcer	▪ Proteinuria
	▪ CMV
	▪ PUD
– Outlet obstruction	▪ Cryptosporidia
	▪ CMV
	▪ Lymphoma
	▪ PUD
– Mass	▪ Lymphoma
	▪ KS
	▪ CMV



Organ	Causes
○ Small bowel	
– Enteritis	▪ Proteinuria ▪ Cryptosporidia ▪ CMV ▪ MAC
– Obstruction	▪ Lymphoma ▪ KS
– Perforation	▪ CMV ▪ Lymphoma
○ Colon	
– Colitis	▪ Proteinuria ▪ CMV ▪ Enteric bacteria ▪ HSV
– Obstruction	▪ Proteinuria ▪ Lymphoma ▪ KS ▪ Intussusception
– Perforation	▪ CMV ▪ Lymphoma ▪ HSV
– Appendicitis	▪ KS ▪ Cryptosporidia ▪ CMV
○ Liver, spleen	
– Infiltration	▪ Proteinuria ▪ Lymphoma ▪ CMV ▪ MAC
○ Biliary tract	
– Cholecystitis	▪ Proteinuria ▪ CMV ▪ Cryptosporidia ▪ Microsporidia



Organ	Causes
- Papillary stenosis	▪ CMV ▪ Cryptosporidia ▪ KS
- Cholangitis	▪ CMV
○ Pancreas	
- Pancreatitis	▪ CMV ▪ KS ▪ Pentamidine ▪ ddl
- Tumour	▪ Lymphoma ▪ KS
○ Mesentery, peritoneum	
- Infiltration	▪ MAC ▪ Cryptococcus spp. ▪ isoplasmosis ▪ Tuberculosis ▪ Coccidioidomycosis ▪ Toxoplasmosis ▪ KS ▪ Lymphoma

Abbreviations: AIDS, acquired immunodeficiency syndrome; CMV, cytomegalovirus; ddl, didanosine; HSV, herpes simplex virus; KS, Kaposi's sarcoma; MAC, Mycobacterium avium complex; PUD, peptic ulcer disease

"To give pleasure to a single heart by a single act is better than a thousand heads bowing in prayer."

Mahatma Gandhi



Abdominal Pain

Unusual causes of abdominal pain

- Epiploic appendagitis
 - Inflamed fat tags on anti-mesenteric border of colon
 - CT scan changes
 - Focal, oval of fat on anti-mesenteric side of colon (often on left side)
 - Inflammatory stranding
 - Penetrating vein → thrombosed → linear central attenuating line
- FMF (familial Mediterranean fever)
 - Defect in FMF gene on chromosome 16 → abnormal pyrin → ↑ IL-1β → inflammation
 - Inflammation of
 - Peritoneum
 - Pleura
 - Arthritis
 - Skin (cellulitis-mimicking)
 - Family history
 - May be triggered by exercise

6. Give the feature which raise suspicion for **familial Mediteranean fever (FMF)**.

- “Mediterranean origin” (Italy, Greece, Turkey, Middle East)
- Family history
 - Acute abdomen
 - Pleurisy
 - Arthritis
 - Skin rash
 - Amyloidosis
- Laboratory
 - ↑ ESR
- Treatment
 - Colchicine prophylaxis
 - Avoid surgery



7. Give five causes of **RUQ pain**.

- Peptic ulcer disease (gastric or duodenal ulcer)
- Pancreatitis
- Hepatitis
- Cholecystitis
- Renal colic
- Pneumonia/pleurisy
- Empyema/pericarditis
- Coronary artery disease

8. Give four '**red flag**' situations that indicate that surgery is necessary in the patient with an **acute abdomen**.

- Progressive abdominal distension
- Tender abdominal mass with fever and hypotension (abscess)
- Septicemia plus abdominal findings
- Suspected bowel ischemia (acidosis, fever, tachycardia)
- Deterioration of patient while on conservative treatment

Gum Hypertrophy

9. Give 5 causes of gum hypertrophy.

- Gingivitis (e.g. 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 NJ and O'Connor S. 4th ed. Oxford. *Blackwell Science* 2001 .



Halitosis

10. Give 6 non-dental causes of halitosis.

➤ Infection

- Poor oral hygiene
- Putrid (due to anaerobic chest infections with large amounts of sputum)

➤ Metabolic

- Fetor 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 NJ and O'Connor S. 4th ed. Oxford. *Blackwell Science* 2001.

Systemic Amyloidosis

11. Give 6 conditions which can, often rarely, but nonetheless **affect every organ system**, including the GI tract.

➤ Infection

- Tuberculosis
- Whipple disease
- Syphilis
- AIDs / HIV
- Coccidiomycosis

➤ MSK

- Amyloidosis
- Sarcoidosis
- Lupus



When to suspect amyloidosis of GI tract / liver

- Primary AL amyloid
- Secondary (reactive, such as GI / liver) AA amyloid fibrils
 - CVS
 - Restrictive cardiomyopathy
 - CHF (congestive heart failure)
 - CNS / PNS
 - Peripheral neuropathy
 - Kidney
 - Proteinuria
 - Nephrotic syndrome
 - GI
 - Gastric stasis
 - Diarrhea
 - Bleeding (vascular friability → mucosal erosions)
 - Liver (diffuse process)
 - Hepatomegaly
 - Ascites
 - AP >> ALP

Exam Alert: Congo red deposits in submucosal blood vessels

- Think reactive (AA) amyloidosis

Useful background: Conditions that are associated with systemic AA amyloidosis

- Inflammatory arthritis
 - Adult Still disease
 - Ankylosing spondylitis
 - Juvenile idiopathic arthritis
 - Psoriatic arthropathy
 - Rheumatoid arthritis



- Chronic infections
 - Bronchiectasis
 - Osteomyelitis
 - Tuberculosis
 - Skin abscesses (usually from injected drug abuse)
- Immunodeficiency states
 - Common variable immunodeficiency
 - HIV or AIDS
- Hereditary periodic fevers
 - Familial Mediterranean fever (FNF)
 - Hyperimmunoglobulin D syndrome
 - Muckle Wells syndrome
 - TNF receptor associated periodic syndrome
- IBD
 - Crohn disease
 - Ulcerative colitis
- Neoplasia
 - Castleman disease
 - Renal cell carcinoma
 - Adenocarcinoma of the lung, gut, and urogenital tract
- Systemic vasculitis
 - Behcet disease
 - Systemic lupus erythematosus

Printed with permission: Prayman T. et al. *Nature Reviews, Gastroenterology and Hepatology* 2009;6:608-617, Box 1:page 611.



➤ Treatment

Disease	Aim of treatment	Example of treatment
○ AA amyloidosis	- ↓ acute phase response - ↓ production of serum amyloid A protein	● Anti-inflammatory and immunosuppressive therapy in patients with rheumatoid arthritis and Crohn disease (e.g. anti TNF antibodies) - Colchicine for patients with Familial Mediterranean fever ● Surgery for patients with osteomyelitis and rare cytokine producing tumours
○ AL amyloidosis	- Suppress production of monoclonal immunoglobulin light chains	● Chemotherapy directed at plasma cell dyscrasia
○ Hereditary amyloidosis	- Eliminate source of genetically variant protein	● Orthotopic liver transplantation for patients with familial amyloid polyneuropathy
○ B2 microglobulin amyloidosis	- Reduce plasma concentration of B2 microglobulin	● Renal transplantation

Printed with permission: Macmillan Publishers Ltd: Prayman T. et al. *Nature Reviews, Gastroenterology and Hepatology* 2009;6:608-617, Table 2: page 614

“Courage is what it takes to stand up and speak;
courage is also what it takes to sit down and
listen.”

Winston Churchill



Nails and Skin

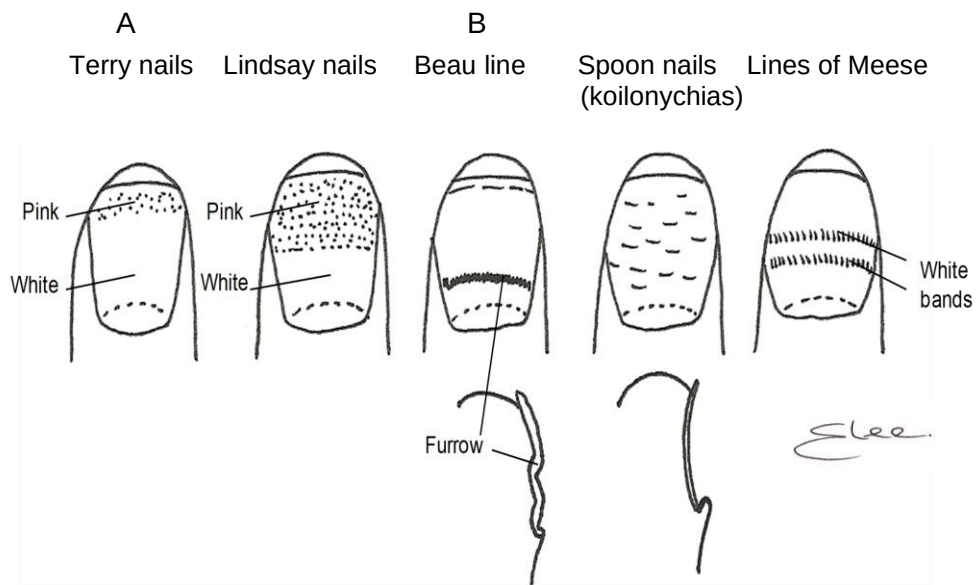
➤ Nails

12. Give 5 conditions of causing alteration in the normal appearance of the nails of the hands.
- Terry's nails (from the British physician who first described them in 1954)
 - Whitening of the proximal 80% of the nail, leaving a small rim of peripheral reddening.
 - Seen in
 - Older people
 - Heart failure
 - Cirrhosis
 - Non-insulin dependant diabetes.
 - Red half moons in nail beds (variety of Terry's nails, also described by Terry)
 - Lunula that is red and also called the nails of cardiac failure
 - Azure half moons in nail beds
 - The nails of Wilson disease
 - The lunulae are light blue.
 - Muehrcke's lines (from the American nephrologist who first described them in 1956)
 - 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 ($< 2 \text{ gm}/100 \text{ ml}$), and disappear with its resolution.
 - Beau lines
 - Transverse grooves on the fingernails of patients recovering from a serious illness
 - First described by the French physician Joseph H.S Beau (1806-1865).



- Mee's lines (also called Reynolds or Aldrich lines)
 - Transverse white lines distal to the cuticle.
 - Seen in
 - Arsenical or thallium poisoning
 - Cancer chemotherapy
 - Hodgkin's lymphoma
 - Other systemic disorders (such as severe cardiac or renal disease).
 - First described by the Dutch physician R.A Mees.
- Nail pitting
 - Early but non-specific sign of psoriasis
- Yellow nail syndrome
 - A yellowish colour of the nail plates due to abnormal lymphatic circulation.
- Brittle nails
 - Seen in various dysmetabolic states such as
 - Hyperthyroidism
 - Malnutrition
 - Iron or calcium deficiency
 - They are characterized by
 - Irregular, frayed, and torn nail borders
- Splinter hemorrhages
 - Linear red hemorrhages
 - Extending from the free margin of the nail bed toward the proximal margin.
 - Seen with
 - Subacute bacterial endocarditis
 - Trichinosis
 - Trauma.
- Leukonychia-white nails, beginning at the lunula-may be normal; seen in cirrhosis, leprosy, arsenic poisoning, vasomotor disturbance of fingers





Adapted from: Mangione S. Physical Diagnosis Secrets. *Hanley & Belfus*, Philadelphia, 2000, page 412.

➤ Skin

- Acanthosis nigrans
 - Black velvety rash, typically in / on
 - Axillar
 - Nape of neck
 - Hands
 - Associated with
 - Cancer (paraneoplastic syndrome)
 - Stomach
 - HCC
 - Lung
 - Metabolic syndrome



- Acrodermatitis enteropathica (zinc deficiency)
 - Associations
 - Alcoholism
 - TPN
 - Chronic diarrhea
 - Crohn disease
 - Celiac disease
 - Caution: the patient suspected to having refractory celiac disease, and have red scaling, vesiculopustular plaque and legs, think of zinc deficiency, the correction of which may allow the gluten enteropathy to respond to a gluten-free diet.
- Seborrheic keratosis
 - Usually small areas, of no common morbid association
 - Sudden, extensive outbreaks of Seborrheic keratosis (aka Leser-Trelat) is a paraneoplastic syndrome associated with cancer
 - Lung
 - GI
 - Stomach
 - Colon
 - Liver
 - Pancreas
- Yellow plaque

13. Give 2 GI causes of yellow plaques, the GI mucosa, or on the skin.

- In mucosa – cholesterol embolization
- On skin – PXE (pseudoxanthoma)

SO YOU WANT TO BE A GASTROENTEROLOGY!

- Give 2 GI causes of angioid streaks seen on fundoscopic examination of eyes.
 - PXE (pseudoxanthoma elasticum)
 - Paget disease (well, really above disease, but because serum alkaline phosphatase concentration is increased, your reflex might be to think of cholestatic liver disease)



Abbreviations

ACTH	Adrenocorticotrophic hormone
AIDS	Acquired immunodeficiency syndrome
ALP	Alkaline phosphatase
BMT	Bone marrow transplantation
CMV	Cytomegalovirus
CSS	Churg-Strauss syndrome
dDI	didanosine
EBV	Epstein-Barr virus
EGFR	Epidermal growth factor receptor
GH	Growth hormone
GI	Gastrointestinal
HSV	Herpes simplex virus
KS	Kaposi sarcoma
LES	Lower esophageal sphincter
LGV	Lymphogranuloma venereum
MAC	Mycobacterium avium complex
MCT	Medullary carcinoma of the thyroid
MCTD	Mixed connective tissue disease
MEN	Multiple endocrine neoplasia
NAAT	Nucleic acid amplification testing
PAN	Polyarteritis nodosa
PO	Orally
RPR	Rapid plasma regain test
SBP	Spontaneous bacterial peritonitis
SLE	Systemic lupus erythematosus
SOS	Sinusoidal obstruction syndrome
STI	Sexually transmitted infection
TMP- SMX	Trimethoprim sulfamethoxazole
TPHA	Treponema pallidum hemagglutination assay
TPPA	Treponema pallidum particle agglutination
VEGF	Vascular endothelial growth factor
VIP	Vasoactive intestinal polypeptide



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Available online at www.giandhepatology.com





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