Mastering The Boards and Clinical Examinations In Internal Medicine

Hepatology

A.B.R. Thomson

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THE WESTERN WAY

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Thank you

A. B. R. Thomson

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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 candida 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 360^0 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 forsight, 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

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, 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

GENERAL

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”).
  - Ca^{2+} 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)

- Hepatic stellate cells..
  - Control the diameter of the lumen of the sinusoidals
  - 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)
    - Kuppfer cells
      - Chemokines expression by HSC attracts kupffer cells
      - Kupffer cells secret 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

- Spaces of Disse
  - 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)
  - 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.

- 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.

Clinical

- Give the features of the history and physical examination of the patient with suspected chronic liver disease.
  - 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

- Give the clinical method to determine the 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
  - The umbilicus is common site of infiltration by cancer metastases

- Spider nevi are telangiectases
  - Leuconchyia-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

- Give cutaneous signs of chronic liver disease.
  - Eyes (sclera), mouth
    - Xanthelasma
    - Xanthomata
    - Jaundice
  - Skin, chest
    - Jaundice
    - Spider angiomata
    - Telangectasia
    - Hyperpigmentation
  - Hands
    - Dupuytren contracture
    - Palmar erythema
    - Loss of lunulae
    - White nails
    - Clubbing
    - Excoriations

- Give clinically significant extrahepatic manifestations of acute and chronic liver disease.
  - CNS
    - Depression
    - Anxiety
    - Hepatic encephalopathy (HE)
  - Lung:
    - Portopulmonary hypertension
    - Hepatopulmonary syndrome
    - Pleural effusion
    - 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
    - ↓ thrombopoetin
    - Immune mediated destruction
    - ITP (especially with use of interferon for HCV)
    - Direct effect of alcohol, cryoglobulinemia
  - GI
    - Esophagus
      - 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 (hemochromotosis)
- 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
  - 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 primay care which suggest the cause of underlying liver disease

- Give causes of chronically elevated aminotransferase levels with and without associated 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 metastic)
  - Medications
  - Diet
  - Drugs
  - Blood products
  - Infection

➢ ALT, AST
  - ALT, AST in liver, muscle, kidney
  - AST > ALT in ALD (mitochondria produce ↓ AST) fibrosis
  - R value
    - ALT/AP
    - >5, hepatocellular disease
    - <2, cholestatic disease

- Give 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

SO YOU WANT TO BE A HEPATOLOGIST!

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 than AST
  - When P5P↓, as in ALD, there will be less synthesis of ALT, so AST > ALT

- Give 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 uridyltransferase, 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 ↑ AP (normal ALT, AST; also normal GGT)
    - Renal cell carcinoma
    - Systemic mastocytosis
    - Paget disease
    - RA (rheumatoid arthritis; sometimes also ↑ GGT)
- ↑ AP plus GGT
    - Temporal arteritis
    - Metastatic CRC (colorectal) cancer
    - RA (rheumatoid arthritis; sometimes isolated ↑ 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 is persons with blood group B or O.
  - ↓ AP in fulminant Wilson disease and hemolysis

- Give causes of reduced serum **alkaline phosphatase** concentration.
  - Endocrine
    - Hyperthyroidism
    - Hypoparathyroidism
    - Hypophosphatemia
  - Stomach
    - Pernicious anemia (atropic 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

- Give 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

- 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 T½ 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 (intenational normalized ratio) in liver patients has been challenged.
  - Each lab measuring INR has their own standardization of the PT based on the thromboplastin eagent 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 access 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

Genetics

- 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 P4502EI (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)
- Cholelithiasis
  - ABC B4 gene (PC transporter)
  - ABC B11 gene (bile salt export pump)
  - CYP7AI (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 metallopeptidase 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.

Practical Tips For Liver Biopsy (LBx)

Peri-LBx management	Days to stop before LBx, (day 1)	Days to restart after LBx
○ Drugs		
– Antiplatelet drugs	10	2-3
– Anti-coagulants (warfarin)	5	1
– Heparin	1	
○ Restrictions		
– Food	No	
– Exercise	No	
– Sedation	No	
– Heavy lifting	Probably a good idea to restrict	

Peri-LBx management	Days to stop before LBx, (day 1)
○ 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 pre-LBx
    - Patients on chronic hemodialysis should be dialyzed before LBx.
- Consider real-time image guidance of LBx, or LBx by transvenous rate.

- CLINICAL GEM: before saying that the patient is resistant to the effect of diuretics to mobilize their ascites, measure urinary Na^+ and ensure that the daily excretion of Na^+ is > 88 mEq.
  - If the urinary Na^+ excretion is < 88 mEq / day, how do you know that the urinary collection is complete?
    The 24-hour excretion of creatinine per kg body weight is > 10 mg for women and 15 mg for men.
    If the urine contains less than this amount of creatinine, then the urine collection is not likely to be complete, and so the urinary Na^+ excretion may be underestimated.
- CLINICAL WHIZ KID: OK, but the urinary creatinine may be low if the cirrhotic patient is malnourished. How do you determine that the patient has diuretic resistance?
  - If the urinary spot sample has a ratio of Na^+ to K^+ > 1 (some "authorities" say $Na^+ / K^+ > 2.5$), then there is about a 90% likelihood for the 24-hour urine sample showing > 88 mEq Na^+ / day excreted
- CLINICAL CAUTION: overzealous use of diuretics, such as IV furosemide, may precipitate acute renal failure. As far as the use of diuretics, the rule of thumb is "go slow, go low".

Surgery and Liver Disease

- Give management considerations in the **pre- and post-operative care** of the patient with advanced liver disease (based on MELD score).
- Risk stratification
  - Child-Pugh classification
  - Model for end-stage liver disease (MELD)
  - Mayo preoperative score
- Diagnose and treat
  - Hepatic encephalopathy (HE)
    - Correction of reversible metabolic factors (eg. hyponatremia, hypokalemicmic alkalosis)
    - Oral lactulose administration, titrated to ~3-4 bowel movements per day
    - Administration of nonabsorbable antibiotics
    - Avoidance of nephrotoxic insult (eg. NSAIDs, narcotics, benzodiazepines, diuretics)
    - Supportive care
    - Correction of reversible metabolic factors
  - Esophageal varices
    - EGD +/- banding or non-specific β-blockers (NSBB;see current guidelines)
    - Do not start NSBB just before surgery (↑ risk of stroke)
    - Do not use NSBB in presence of ascites
  - 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
    - Paracentesis with analysis of ascitic fluid for evidence of infection
  - Coagulopathy
    - Vitamin K supplementation (oral or parenteral)
      - Fresh, frozen plasma transfusions
      - Intravenous administration of cryoprecipitate
      - Intravenous administration of recombinant factor VIIa
      - Platelet transfusions
      - Anticoagulation for thrombosis prophylaxis

- 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
- Follow patients after surgery to ensure introduction / maintenance of standard care program for
  - Immunization
  - Surveillance for
    - HCC (US q 6 mon)
    - HE for development of ascites and renal dysfunction

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

- 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.

- Give the **peri-operative mortality rates** (MR) in persons with cirrhosis, Child-Pugh classification (CPC).

CPC	Surgical MR (%)
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.

- 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.

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

Vivian Greene

NON-ALCOHOLIC FATTY LIVER DISEASE (NAFLD)

- Natural history

NAFL —20%→ NASH —~1% / year→ cirrhosis —~4% / 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 the Kleiner scoring system, also known as “NAS” (NASH activity score) (Kleiner DE, et al. *Hepatology* 2005;41:1313-21.)
    - Based on:
      - Simple steatosis
      - Steatosis plus inflammation alone
      - Steatosis plus ballooning
      - Steatosis plus fibrosis (Matteoni CA, et al. *Gastroenterology* 1999:1413-9.)
  - NAFLD worsens the prognosis of liver disease associated with HCV and HH (hereditary hemochromatosis).
  - Obesity (↑ BMI)
  - T2DM (type 2 diabetes mellitus)
  - Dyslipidemia
  - Metabolic syndrome

➢ Pathophysiology

- 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
    - Actvation of macrophages / immune system → ↑ lipoptosis
    - ↑ insulin-resistant adipocytes → ↑ FFAs
- 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-kB → ↑ 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-kB → 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 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

"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 mulprotein 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-1β 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-1β 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
    - PDF 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
    - TGFB 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

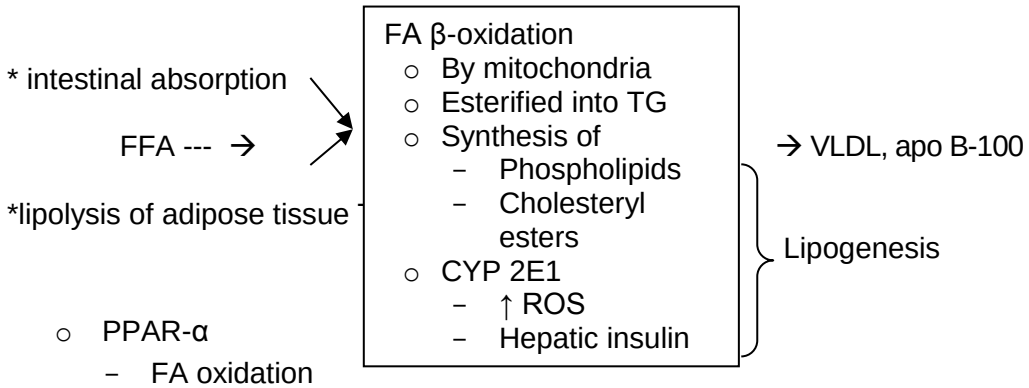
Abbreviations: NFkB, nuclear factor kappa B; ROS, reactive oxygen species; RNS, reactive nitrogen species

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-1β 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-1β 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)



  - PPAR-α
    - FA oxidation
    - Oxidative stress
  - Regulation by
    - Insulin
    - Catecholamines
    - Glucagon
    - Growth hormone
    - Leptin
    - Adiponectin

    - PPAR-γ are widely distributed among adipocytes, hepatocytes, and hepatic stellate cells, as well as macrophages and immune cells infiltrating adipose and liver tissue.
    - These may be targeted by PPAR-γ agonists during TZD therapy in patients with NASH.

- 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 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.
  - Progression

- Give the patient-related and laboratory-related **predictors of progression** of simple steatosis to NASH.

  - Patient
    - Age > 45 years
    - Female
    - Ethnicity (Hispanic, First Nations persons; Asian > Caucasian > Black)
    - Type II diabetes mellitus (even with normal LEs)
    - BMI > 35 (especially visceral obesity)
    - Insulin resistance
    - Hypertension
    - Metabolic syndrome (insulin resistance), even in young, non-obese persons
    - Comorbidity: alcohol, HCV infection
    - Stigmata of portal hypertension
  - Laboratory
    - ↑ ALT > 2x ULN
    - ↑ AST:ALT >1 [suggests fibrosis]
    - ↑ Triglycerides >1.5
    - ↑ INR
    - ↑ Bilirubin
    - ↓ Platelets
    - ↓ Albumin
    - Indexes of insulin resistance (HOMA, 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
- Curiosities of Investigation
  - ~25% of NAFLD have
    - ANA (antinuclear antibodies, title usually < 1:320)
    - ↑ serum ferritin

➢ Diagnosis

❖ Laboratory

- High risk groups (please see above)
- Unsuspected fatty liver on abdominal ultrasound → assess for causes of fatty liver:
  - Diabetes Type 2 / glucose intolerance
  - Obesity
  - Dyslipidemia
  - Drugs
  - Alcohol intake
  - HCV, genotype 3
  - HH (heretidary hemochromatosis)
  - WD (Wilson disease)
  - High titres of autoantibodies
  - Anti-tTG (tissue transglutaminase, suggestive of celiac disease)
- NAFLD fibrosis score / FibroScan)
- Liver biopsy for
  - Metabolic syndrome, ↑ Fibrosis score / FibroScan
  - Other causes of hepatic steatosis have been excluded (please see above)

- Detection of Hepatic Fibrosis
  - 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
      - α2-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, high cut-off (0.70)
      - PPV, 73%
      - Specificity, 98%
  - NAFLD and NASH may be distinguished using **Kleiner scoring system**, also known as “NAS” (**NASH activity score**) (Kleiner DE, et al. *Hepatology* 2005;41:1313-21.)
  - Based on:
    - Simple steatosis
    - Steatosis plus inflammation alone
    - Steatosis plus ballooning
    - Steatosis plus fibrosis (Matteoni CA, et al. *Gastroenterology* 1999:1413-9

- Gold standard
  - Liver biopsy
  - Only “bronze standard” because of considerable sampling variation (patchy changes)

- A panel of blood tests
  - α2-microglobulin
  - Apolipoproteins A-1
  - Haptoglobulin
  - Total bilirubin
  - GGT
  - ALT
  - To estimate
    - Hepatic fibrosis
      - First 5 test
    - Necroinflammatory activity
      - All 6 tests

- 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.

- 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%

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)
  - 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

- Special tests
  - ~Fibro Scan® (aka TE [transient elastography]) (> 20, cirrhosis)
  - Useful to identify advanced but not early cirrhosis from
    - HCV
      - PBC (primary biliary cirrhosis)
      - HH (hereditary hematomachrosis)
      - NAFLD
      - Recurrent chronic hepatitis after liver transplantation

➢ Histopathology

- 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
○ 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.

- Give the 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 (eosinophilic)
- ○ NAFLD Activity Score (please see material which follows)
- ○ Cirrhosis (7%-16% on index biopsy)
- ○ Glycogenated nuclei
- ○ Lipogranulomas
- ○ Stainable iron

- Focal Fatty Liver (FFL)
  - Patchy process of fat accumulation which may look like a hepatic mass on diagnostic imaging

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

- Give the **Grading and staging** of the biopsy lesions of NASH

❖ Grade I. Mild
- Steatosis: predominantly macrovesicular, involves > 33% < 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.)

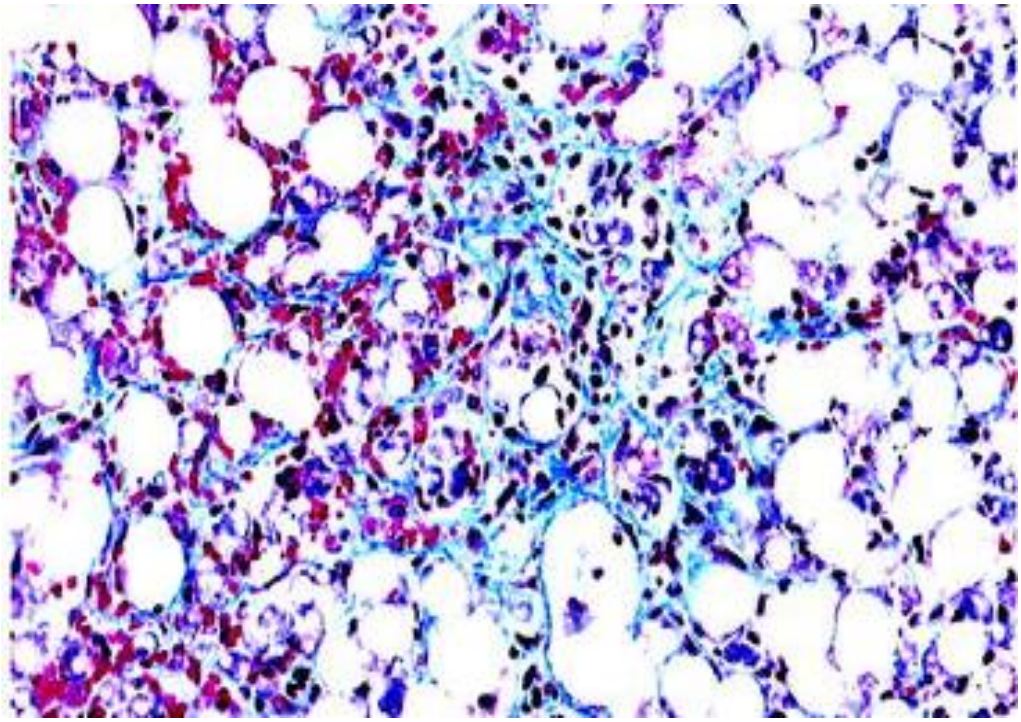
- Give the meaning of **Mallory bodies**, and with what hepatic conditions they are associated.
  - Mallory bodies
    - Cytoplasmic inclusions in hepatocytes
    - Red colour from
      - Cytokeratin intermediate filaments, and
      - Ubiquitins
    - "twisted rope" appearance
  - Associations
    - ALD (alcoholic liver disease) (~66%)
    - NAFLD (non-alcoholic liver disease)
    - PBC (primary biliary cirrhosis) (~25%)
    - WD (Wilson disease) (25% to 50%)
    - HBV (hepatitis B virus)
    - HCV (hepatitis C virus)
    - DILI (drug-induced liver injury), e.g.
      - Amiodarone

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

Grandad

Case. 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.



➢ Causes and associations

- 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.

- Give causes of **macrovesicular** steatosis.
  - Liver – Wilson disease, alcohol, NAFLD/NASH, HCV-3 (AFL 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
  - Ideopathic

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

- Give causes of **microvesicular** steatosis.
  - Pregnancy—Acute fatty liver of pregnancy (AFLP), HELLP syndrome
  - Infection – HBV, HCV, HDV
  - Drugs – Reye syndrome (salicylates), valoproic 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**B**V; H**C**V; **D**rugs; H**E**LLP-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 (α1-AT), and polycystic liver disease (PCLD)

- Give 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)

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).

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 misclasssificaion of histological grade
- Because NAFLD is a diffuse process, it is not clear how important an effect this sampling error would be

- Treatment
  - About 1/3 of persons with NAFLD and simple steatosis will progress to NASH
  - Patients with NASH will develop cirrhosis and portal hypertension (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.
  - Weight reduction and exercise
  - Associated conditions
    - Metabolic syndrome
  - Pioglitazone
    - Non-diabetic adults, biopsy proven NASH
    - ↓ steatosis (OR 4.05; 9% CI 2.58-6.35)
    - ↓ inflammation (OR 3.53; 95% CI 2.21-5.64)
    - Long-term safety and efficacy unknown
    - Not proven to be efficacy with chronic liver disease plus co-existing NAFLD or NASH
    - No ↓ in fibrosis (OR 1.40; 95% CI 0.57-2.24)
  - Possible use of high dose vitamin E (α-tocopherol, not yet consensus recommendation)
  - Vitamin E (α-tocopherol)
    - 800 IU/d
    - Non-diabetic adults with biopsy-proven NASH
    - Do not use with NASH cirrhosis or with cryptogenic cirrhosis

- Caution
  800 IU/d may ↑ all-cause mortality
  400 IU/d may ↑ prostatic cancer (absolute increase of 1.6 per 1000 patient years of vitamin E use)

- Alcohol intake
  - "non-heavy" alcohol intake acceptable
- Dyslipidemia
  - Safe to treat with statins, if /as indicated
- Screening in NASH cirrhosis
  - Esophageal varices (EV) (Gastroenterology 2007; 102: 2086-2102). Hepatocellular cancer (HCC) (Hepatology 2011; 53"1020-1022).
- Therapies which cannot be recommended at the present time to specifically treat NASH
  - Metformin (may be used for associated glucose intolerance to ↓ risk of developing diabetes)
  - Bariatric surgery
  - Abstinence from alcohol (mild-to-moderate intake is acceptable)
  - Statins (can be used for associated dyslipidemia)

Abbreviations: BMI, body mass index; IR, insulin resistance; SBP, systolic blood pressure

Tacrolimus is preferred to cyclosporin as the CNI for LT, but it does have a major impart 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.

Patients with NASH cirrhosis may come to liver transplantation (LT). Lifelong immunosuppression will be required

- NAFLD may recur post-LT, and the immunosuppression agents may worsen the hepatic steatosis, or worsen components of the metabolic syndrome.

For guidelines for the treatment of NSAID / NASH in children, please see Hepatology 2012; 55: 2005-2023.

- Give a clinical approach to the patient with suspected NAFLD / NASH.
  - Abnormal liver biochemistries and / or fatty liver on abdominal ultrasound
  - Assess 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 / portal hypertension
  - 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).

- Give the correction for fluid excess in body mass estimation 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.

ALCOHOLIC LIVER DISEASE (ALD)

- Definition: ALD is a disorder associated with the intake of ecessive 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 ---ADH---> Acetaldehyde

Acetaldehyde ---ALDH---> Acetate

  - Role of acetaldehyde
    - Acetaldehyde forms adduct with reactive residues (oxidatively modified proteins) on proteins or small molecules
    - Antibodies from against these adducts (e.g. MAA [malondialdehyde and acetaldehyde])

  - Methionine metabolism
    - Methionine is related upon by MAT (methionine adenosyltransforate) 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 and absorption and metabolism, including
    - ↓ 5-mTHF (5-methyltetrahydrofolate [THF])
- Hypoxia
  - Alcohol
  - ↑ O_2 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 superoxidase
  - 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-kB (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-kB → 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 actives T cell function
  - Hydroxyethyl radical from breakdown of alcohol modifies CYP 2E1
  - Modifies CYP2E1 plus CTTA-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 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

➢ Clinical Prognosis
- Alcohilic hepatitis
- Alcoholism
- Clinical signs of chronic liver disease (portal hypertension)
- Abnormal liver enzymes
- Complications of chronic liver disease

When to suspect

- Blood tests
  - Peripheral blood leukocytosis due to hepatitis (and not due to associated infection)
  - Impatient with ALD, fever and leukocytosis suggest AH
  - ↑ bilirubin and ↑ AP (alkaline phosphatase) occur in AH
  - In AH, ↑ ALT, ↑↑ AST
  - AST: ALD > 2 suggests
    - ALD / NAFLD, except when there is ALD or NAFLD-associated cirrhosis
    - Acute / muscle injury (check [creatinine kinase], since muscle injury caused ↑ ALD, ↑↑ AST)
- Liver biopsy
  - Hepatitis is defined by presence of
    - Hepatic neutrophils
    - Necrosis
    - Mallory hyaline bodies, quantitative

➢ Histopathology

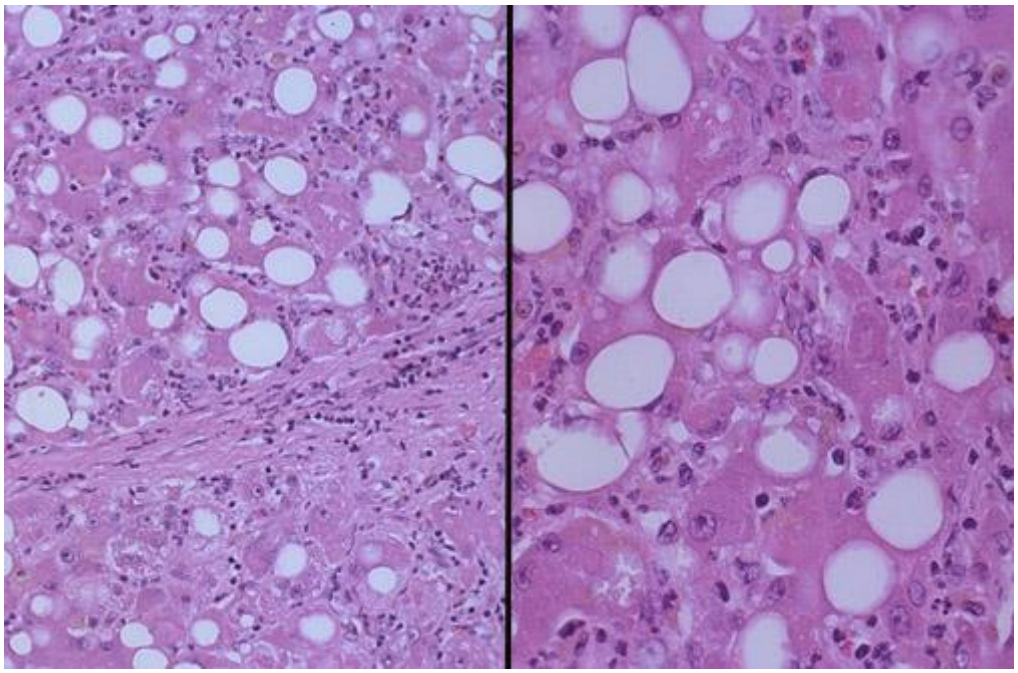
- Steatosis
  - Centrilobular
  - Perivenular
  - Microvesicular
  - If combination of macro- plus microvesicular, then there is an ↑ risk of cirrhosis
- Ballooning degeneration
- Mallory bodies in damaged hepatocytes
- Necroinflammatory reaction around damaged
  - Polymorphonuclear leukocytes
- Central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

Alcoholic Liver Disease

Case. 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.

SO YOU WANT TO BE A HEPATOLOGIST!

Alcohol abuse is associated with a 7% 5-year risk of developing cirrhosis, and a 5-year mortality rate of 17%. This outcome is beneficially affected by abstinence.

- Give the significance of **finding neutrophils** in the inflamed liver of a person with alcoholic hepatitis.
  - Inflammation, particularly neutrophils, are usually an indicator of poor prognosis.
    - For example, with abstinence, persistently elevated blood leukocytes (from hepatitis, not from associated infection) may be associated in with subfulminant hepatic failure.
  - When there are neutrophils in the patient with severe alcoholic hepatitis who is treated with steroids, this is a predictor of an improved prognosis.
- Give the histological features of the liver which suggest a poor prognosis.
  - The presence of both macro and microvesicular fat.
  - Perivenular fibrosis

- 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 stigamata
○ Laboratory (AST)	Variable	< 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 -

- Give histopathological factors which **predict the prognosis** of ALD (alcoholic liver disease).

Histopathology	Cirrhosis	5-year Mortality rate
ALD-fatty liver (no steatohepatitis)	16%	0.7%
ALD-steatohepatitis	25%	17%

Histopathology	Mortality Rate 1-year	5-year
ALD-hepatitis	27%	47%
ALD-no hepatitis	7%	31%

Clinnical Gem

- Remember that ingestion of alcohol may transiently ↑ portal pressure, so complications of portal hypertension may develop in ALD, even in the absence of cirrhosis.

➢ Risk assessment

- Give **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 = 4.6 (patients PT – control PT) + total bilirubin (mg / dL)	≥ 32
MDF, modified Maddrey discriminant function	Used on admission	Prednisone, pentoxifylline
○ 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

- Performs as well as MDF to predict 30- and 90- day mortality from alcoholic hepatitis.
  - MELD=21 predicts 90-day mortality
- Sensitivity, 75%
- Specificity, 75%
  - Δ MELD ≥ 2 points lower first hospital week predicts mortality from alcoholic hepatitis

- **GAH** (Glasgow Alcoholic Hepatitis) Score
  - Obtained from PT, bilirubin (day 1 and day 6 to 9), BUN (blood urea nitrogen), and peripheral WBC count
  - Mortality rate in severe alcoholic hepatitis (MDF > 32, GAH ≥ 9), no steroids

GAH score	Mortality rate (MR)	
	1-month	3-month
≥ 9	48	62
< 9	22	41

  - GAH score less sensitive to predict 3-month mortality (not clear if GAH is better or worse than MDF to predict 1-month mortality)

- **Lille model**
  - Obtained from PT, serum bilirubin (day 1 and day 7), creatinine (> 1.3, or Cr clearance < 40), albumin concentrations, as well as, patient's age
  - Comparison with MDF, GAH, Child-Pugh score
  - Lille model better to predict 6-month MR (mortality rate)

- **Doppler ultrasound (DUS)**
  - Assessment of amount of hepatic steatosis, and blood flow in portal trunk and/or intrahepatic branches of portal vein
  - Predictor of high mortality rate (MR) in severe alcoholic hepatitis if steatosis < 20%, if blood flow is reversed, or is alternating back and forth.

DUS signs	90-day MR
Yes	65%
No	7%

- **ABIC score**
  - Determined from INR, serum concentration of bilirubin and creatinine, as well as patient's age
- Child-Pugh class A, B, C
- Obesity ("political correct" term, ↑ BMI !)

- Give the comparison of the use of various determinants of Prognosis (Mortality Rate) of Patients with Alcoholic Hepatitis.

Determinants	MDF	MELD	GAH	Lille	ABIC	CP
PT / INR	+	+	+	+	+	+
BILI	+	+	+	+	+	+
Cr		+		+	+	
BUN			+			
WBC			+			
ALB				+		+
Age				+	+	

Abbreviations: ALB, albumin; BILI, bilirubin; BUN, blood uea nitrogen; CP, Child-Pugh; Cr, creatinine; GAH, Glasgon alcoholic hepatitis score; INR, international normalized ratio; MDF, modified Maddry discriminant function; MELD, model of end-stage liver disease; PT, prothrombin time; WBC, white blood cell count

	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

➢ Prognosis

- Give 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

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

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

"We learn something from everyone who passes through our lives. Some lessons are painful, some are painless… but, all are priceless."

Unknown

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.
    - ↑ SHBC (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

- Give 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

SO YOU WANT TO BE A HEPATOLOGIST!

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 T½, 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

- Give the treatment of alcoholism.
  - Abstinence, or at least a reduction in heavy drinking ("abuse")
    - Men > 5 drinks of alcohol per day
    - Women > 4 drinks o alcohol per day
  - Psychosocial interventions
    - AA, 12-step programs
    - Support systems
    - Motivational interviewing
    - CBT (cognitive behavioral therapy)
    - These interventions do not work for everyone, and are associated with a recurrence rate of ~70%
  - Pharmacotherapy
    - Useful to treat associated psychological problems e.g.
    - Depression
    - Anxiety

- Give the treatment algorithm of ALD.
  - Suspect diagnosis of alcoholism
  - Include questions about alcohol use in every patient as part of the social or drug history

Significant alcohol consumption:

↓

  - Any suspicion about overuse of alcohol (> 21 drinks per week in men, > 14 / week in women),
    - Perform a structural questionnaire (e.g. CAGE, or Audit questionnaire), and
    - Perform serum liver enzymes (LAT, AST, AP) and liver function tests (INR, bilirubin, albumin, globubins)
    - Review history and physical examination for dues to liver diseases, including alcohol, risk behaviour, complications of possible portal hypertension (jaundice, ascites, hepatic encephalopathy [end organ damage])
  - Treat the patient's alcohol abuse and dependence.
  - Drugs to achieve and maintain abstinence [↓ recidivism]
    - Nalfrexome
    - Opioid antagonist
    - Acamprosate, (acetylhomotaurin analog to the inhibitory neurotransmitter GABA [gamma amino butyric acid]) maintenance to ↓ alcohol craving
    - Baclofen (GABA receptor agonist)
  - Abstinence – total and life-long
  - Nutritional support
    - Consider enteral nutrition, 200 kcal/day, or supplements of protein, 1.2 to 1.5 g/kg per day, and energy, 35% to 40 kcal/kg per day.

↓

  - If the presence of liver disease is supported, excluded treatable causes (e.g. HAV, HBV, HCV, hereditary hemochromatosis [HH], autoimmune hepatitis [AIH], primary biliary cirrhosis [PBC], primary sclerosing cholangitis [PSC]) with further blood tests and abdominal ultrasound, nutritional assessment and intervention (protein-calorie malnutrition, deficiencies of vitamins and mineral

↓

  - Percutaneous or transjugular liver biopsy and / or Fiber Scan®

↓

  - Determine stage of ALD, including alcoholic hepatitis (AH)
    - For AH, calculate Maddrey Discriminant Function (MDF) score on day 1 and 7, and serial calculations of MELD score.

- See section “Treatment of alcoholic hepatitis”
- Treat complications of portal hypertension and or cirrhosis
- Prognosis
  - 5-year survival rate (SR) from time of diagnosis of ALD, 15% to 42%
  - 1-year SR from HE (hepatic encephalopathy), 36%
  - Admitted to ICU decompensation plus easier alcoholic hepatitis, MR is > 90%
  - Abstinence, hepatic histopathology, and laboratory findings are predictive of the prognosis
  - Benefits to the liver of abstinence in the person with alcoholism
    - ↓ fibrosis
    - ↓ portal hypertension
    - ↓ risk of complications, e.g. ascites, EV (esophageal varices)

Useful trivia: A biological marker of alcohol intake is the plasma concentration of GGT (gamma glutamyl transferase)

Treatment Cautions

- Do **not** use in pregnancy
- **Topiramate**
  - Use ↑ abstinence
  - 50 mg po od, increasing by 50 mg every 2 weeks to max of 150 mg bid
    - ↓ heavy drinking days
    - ↓ number of drinks per day
  - Do **not** use in pregnancy

Source: Johnson BD. Pharmacotherapy for alcohol abuse and dependence. UpToDate, 2012.

- Drugs for AH (if MDF ≥ 32, MELD ≥ 18, or presence of HE
  - Prednisolone / prednisone (40 mg / day for 4 weeks followed by 2 weeks taper or discontinuation)
  - Pentoxifylline (400 mg po tid for 4 weeks) if corticosteroids are contraindicated (sepsis, hypoglycemia, HE, active bleeding), or if there is early renal failure (possible beginning of HRS [hepatorenal syndrome]).
  - Combination of corticosteroids plus pentoxifylline may be superior to corticosteroids alone
- For poor prognosis, based on score (e.g. MDF > 32, MELD ≥ 32)
  - Evidence for benefit for MELD ≥ 32
  - A 7-day drop in serum bilirubin concentration ("early responders") suggests the reasonable possibility of continued improvement of severe alcoholic hepatitis hepatitis using steroids.
  - While there appears to be benefit from steroids for MDF > 32, the benefit is not present for MELD > 54 (in fact, MR was increased by steroids, in part due to high risk of infection [alcoholic hepatitis by itself is associated with a risk of infection, and this risk increased (11%) in these received steroids]).
  - Curiously, patients with severe alcohol hepatitis (MDF > 32) who respond to steroids, have a lower risk of infection than do these who do not respond (11% vs. 43%, respectively).
- Liver transplant
- Consider assessment for liver transplantation (LT) if Lille score ≥ 0.56 at day 7
- Survival benefit for LT in MELD ≥ 15, or Child-Pugh C

- Give the mechanism of action of pentoxifylline in AH +HRS.
  - Phosphodiesterase inhibitor
  - Anti-TNF activity

- Give 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

- Metadoxine
  - In alcoholics with ultrasound-demonstrated fatty liver, 3 month of metadoxine reduced steatosis by 72%, vs. 30% for placebo; relationship to overall mortality unclear.
- Alter the CMDA (cortimesolimbic dopamine system, to reduce the reinforcing pleasurable effects of alcohol use)
  - Opioids
  - Glutamate
  - GABA (gamma amino butyric acid)
  - 5-HT

- Give the mechanism (s) of action of 6 pharmacotherapeutic agents used to treat alcohol abuse ("heavy drinking") and dependence.

Name	Method of Action
Naltrexone	Blocks mu-opioid receptors
Acamprosate	Modifies glutamate expression at glutamate receptors
Disulfiram	↑ blood aldehyde by ↓ aldehyde dehydrogenase
Topiramate	Inhibits ▪ Kainate glutamate receptor ▪ Alpha-amino-3-hydroxy-5-methylisoxazole-4-pr onic acid receptors Stimulates ▪ Inhibitory GABA(A)-mediated currents at non-benzodiazepine sites on the GABA(A) receptor
Baclophen	GABA receptor agonist Modulator of CMDA system
Nalmefine	Opioid antagonist
SSRIs	Selective serotonin reuptake inhibitors
Ondansetron	5-HT3 receptor antagonist

Historical Curiosities

In the past and in the context of ALD, there was enthusiasm for the now abandoned use of PTU (propulthiouracil), colchicine, soybean polyunsaturated lecithin, SAM (S-adenosyl methionine), infliximab, etanercept, insulin or glucagon.

- Choices
  - While still drinking
    - Naltrexone
  - For maintenance of abstinence
    - Disulfiram
    - Acamprostate
  - Naltrexone
    - Blocks the mu-opioid receptors
    - More likely to be effective in persons
      - Who are heterozygous for the Asp variant of the OPRMI gene
      - Family history of alcoholism
      - Who have strong cravings for alcohol (still drinking)
    - Naltrexone 5 mg per day
    - ↓ risk of relapse
      - RR 0.64, NNT = 7
    - ↓ time to first drink
    - Deposit naltrexone Vivitrol 380 mg IM q 4 wks
      - ↓ rate of heavy drink after 24 wks, HR 0.75
    - Depot Naltrel ↑ mean number of abstinent days
    - Contraindications
      - Persons who must take an opioid
      - Acute hepatitis
      - Liver failure
    - Do **not** use in pregnancy (use may induce withdraw syndrome and harm the fetus if mother takes opiates)
    - ↓ rate of return to heavy drinking (RR 0.86, NNT = 9)
      - ↑ maintenance of abstinence

- Acamprostate
  - Modifies glutamate expression at glutamate receptors
  - Acampostate 666 mg po tid
  - Predictors of success
    - Late onset alcoholism
    - Anxiety
    - Severe withdrawal symptoms
    - No family history of alcoholism
  - Contraindication
    - Renal failure
    - Not to be used to achieve abstinence in heavy drinkers, but instead to maintain state after heavy drinking is controlled
    - Do **not** use in pregnancy
- Disulfiram
  - Use ↑ maintenance of abstinence
  - ↓ aldehyde dehydrogenase → ↑ blood aldehyde → "disulfiram effects"
    - CNS
      - Headache
      - Sweating
    - CVS
      - Dyspnea
      - Palpitation
      - Hypotension
  - Dose: 500 mg po per day for 1 week to 2 week, then maintain at ~ 250 mg per day
- AEs
  - Hepatitis
  - Hepatic failure
  - Depression
  - Psychosis
  - Low compliance
    - Cleft lip
    - Cleft palate
  - Clinical efficacy is questioned

- Give which of these drugs should not be used in pregnancy.
  - Naltrexone
  - Acamprostate
  - Disulfiram
  - Topiramate
  - Baclofen

From: Johnson BA. UpToDate, Pharmacotherapy for alcohol abuse and dependence. 2012

- Baclofen
  - GABA receptor agonist
  - Modulator of CMDA system
  - Baclofen 10 mg potid, for 12 weeks
    - ↑ abstinence OR = 6.3 vs placebo
    - ↑ duration of abstinence
  - Do **not** use in pregnancy
- Nalmefene
  - Opioid antagonist
  - Nalmefene 10 mg po tid
  - ↓ relapse rate RR 0.62
- SSRIs
  - Selective serotonin reuptake inhibitors
  - Effective only if there is associated depression
  - More effective for subtype of late onset
- Ondansetron
  - 5-HT3 receptors antagonist
  - Useful for
    - Early onset alcohol dependence
    - Persons with 5-HTT gene (a variant of the 5-HT receptor), LL rather than LS or SS genotype
  - 4 mcg po per kg per day

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

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 ~ $2/10^5$ / year; prevalence ~ $17/10^5$

- Types

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

- 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

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”.

➢ Pathophysiology

- 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-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

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 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".

➢ Causes / associations

- Give 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
    - Chapannal 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.

- Give immune diseases/disorders which are associated with AIH.

  - Skin, eye
    - Iritis
    - Gingivitis
    - Dermatitis herpetiformis
    - Erythema nodosum
    - Lichen planus
    - Pyoderma gangrenosum

o CNS/PNS	– Peripheral neuropathy – Myasthenia gravis
o Thyroid	– Autoimmune thyroiditis – Graves' disease
o Heart, lung	– Pleuritis – Fibrosing alveolitis – Pericarditis
o Pancreas	– Insulin-dependent diabetes – Autoimmune pancreatitis
o Gut, liver	– Celiac disease – Ulcerative colitis – Autoimmune sclerosing cholangitis – Pernicious anemia (PA) – Autoimmune cholangitis (PSC)
o Kidney	– Glomerulonephritis (immune complex)
o Blood	– Coombs- positive hemolytic anemia – Cryoglobulinemia – Idiopathic thrombocytopenic purpura (ITP) – Pernicious anemia + ITP (Evan syndrome) – Neutropenia
o MSK	– Rheumatoid arthritis – Sjögren syndrome – Synovitis – Systemic lupus erythematous – Focal myositis

Abbreviation: MSK, muscoluskeletal

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 refect 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).

- Clinical
  - Type I (F, 50) ANA+ ASM+ IgG↑
  - Type II (children) ALKMI+
  - Clinical Course
    - Asymptomatic ~ 40% (70% later become symptomatic)
    - Spontaneous resolution ~ 15%
    - Compensated cirrhosis ~ 40%
    - Esophageal varices (EV) ~ 55%

- Give clinical presentations of AIH.
  - Acute hepatitis
  - Fulminant hepatitis (acute liver failure)
  - 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 (please see below)
  - Hepatocellular cancer (HCC)

- Differential

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 variation	Worldwide	Worldwide
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-mitochondral 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.

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

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

Definite AIH	Probable AIH
○ Exclude other causes of chronic liver disease	– Partial AAT deficiency
○ Normal AAT phenotype	– Abnormal copper or ceruloplasmin level but Wilson disease excluded
○ Normal ceruloplasmin level	– Nonspecific iron or ferritin abnormalities
○ Normal iron and ferritin levels	– No active hepatitis A, B, or C infection
○ No active hepatitis A, B, or C infection	– Daily alcohol <50 g
○ Daily alcohol < 25 g	– No recent hepatotoxic drugs
○ No recent hepatotoxic drugs	– Predominant serum aminotransferase abnormality
○ Predominant serum aminotransferase abnormality	
➢ Suggestive laboratory tests	
○ Globulin, γ-globulin, or IgG level ≥1.5 times normal	– Hypergammaglobulinemia of any degree
○ ANA, SMA, or anti-LKM1 ≥1:80 in adults and ≥1:20 in children; no AMA	– ANA, SMA, or anti-LKM1≥1:40 in adults; other autoantibodies

Definite AIH	Probable AIH
➢ Liver biopsy	
○ Interface hepatitis–moderate to severe	○ Interface hepatitis–moderate to severe
○ No biliary lesions, granulomas, or prominent changes suggestive of another liver disease	○ 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
○ Smooth muscle antibodies	- >1:80	+2
○ Antibodies to liver kidney microsome type 1	- >1:40	+2
○ 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.

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.

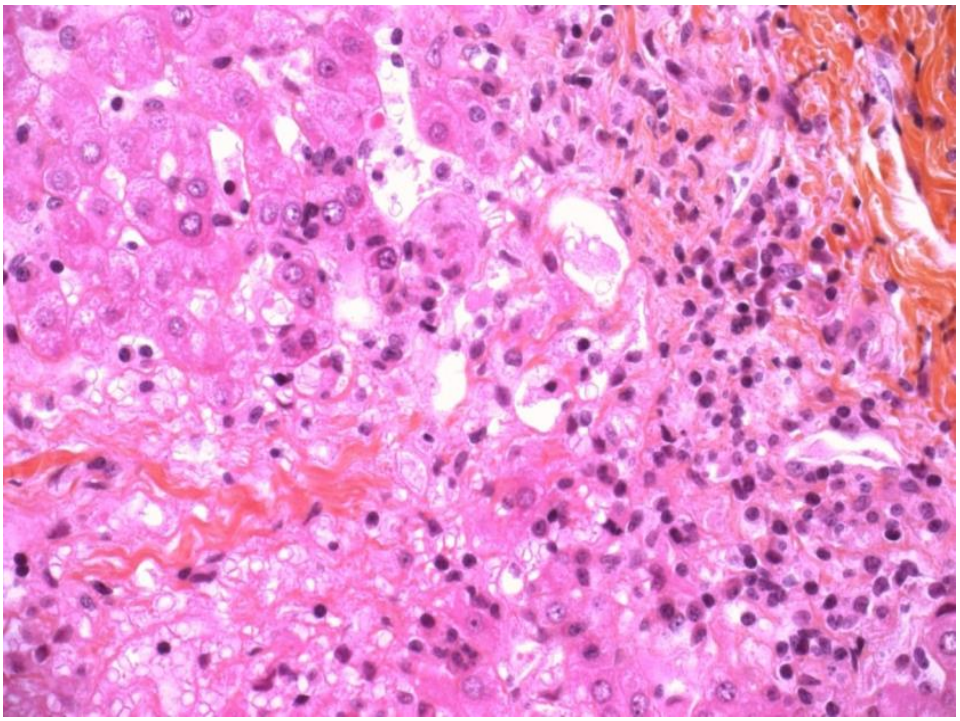
- Give predictors of response to treat in autoimmune hepatitis type 1.
  - Low levels of anti-α-actinin at baseline are independent predictors of response.
  - Autoantibodies against filamentous-actin and α-actinin.
  - HLA-DR3 (poor response)

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".

Case. 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.

- Give 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 High serum globulin LKM antibody positive SLA/LP positive or no immune markers	Low serum albumin and coagulopathy Confluent necrosis on biopsy	Females African-American men Type 2 AIH and SLA positive AIH Cirrhosis 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.

- Therapeutic choices

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	
	1st choice	2nd choice	3rd choice	4th choice
○ 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 Mycophenoate mofetil (2 g daily)	Tacrolimus (4 mg twice daily)
○ 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)

Clinical event	Conventional treatments		Possible empiric treatments	
	1st choice	2nd choice	3rd choice	4th choice
○ Incomplete Response	Prednisone maintenance (≤ 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 (≤ 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 aid

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

- Give the **therapy of AIH** (autoimmune hepatitis).
  - Initial therapy
    - Prednisolone 60 mg/day monotherapy, reducing to 20 mg/day over 4 weeks
    - Prednisolone up to 1 mg / kg / day, or 30 mg / day with slow taper to 10 mg / day over 4 week; plus
    - Azathioprine 2 mg / kg / day
    - Budesonide may de used in place of prednisolone
    - Tacrolimus or mycophenollate may be used in place of azathioprine
  - Continued therapy
    - Prednisolone 5-10 mg / day plus azathioprine 1 mg / kg / day for
      - At least 2 years, or
      - At least 2 years after normalization of transaminases, or
      - Continue maintenance therapy with prednisolone plus azathioprine, or
      - Switch to other immunosuppressants
      - Continue azathioprine alone at 1 mg / kg / day
      - Stopping rules:

- Stable response
- Biopsy with no interface hepatitis
- Type 2 (LKM antibody positive or SLA-positive), or younger patients
  Continued azathioprine therapy

- Relapse after withdrawal of prednisolone and azathioprine (70% relapse within 1 year)
  - Retract as done with prednisolone plus azathioprine (2 mg / kg / day), plus
  - Maintenance with azathioprine (1 mg / kg / day)
- Vaccination
  - HAV
  - HBV
- Bone health
  - Daily calcium plus vitamin D supplements
  - Yearly DEXA scans
- AIH-cirrhosis
  - Screening for
    - HCC every 6 months and
    - Esophageal varices every 1-2 years
- For AIH plus PBC / PSC overlap diseases, treat AIH as per usual, plus the component diseases.
- Consideration for liver transplantation (LT) for
  - Continued non-response
  - Continued ↑ ALT, or
  - Decompensation

➢ Continue corticosteroids 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
- Liver transplantion
  - 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

- 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.

- **AIH overlap (variant) syndromes**

- Demography
  - About 10% of persons with AIH also have HCV infection, and about half of HCV patients have features suggestive or AIH, such as
    - Autoantibodies
    - Other immune diseases, or
    - Both of above

- Types
  - 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

➢ Differential

- 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	

➢ Treatment

- ○ 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.

- 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 ≤ twice ULN ▪ Add ursodeoxycholic acid (UDCA) if serum ALP is > twice ULN and/or florid duct lesions in liver tissue

Variant syndrome	Salient features	Empiric treatment strategies
○ AIH and primary sclerosing cholangitis (PSC)	– Ulcerative colitis – Pruritus – Cholestatic and hepatic tests – ALP:AST>1.5	▪ Corticosteroids
○ 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, budesonide, 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.

Hereditary AIH

- 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, alering AIRE (autoimmune regulator)
  - AIH is usually severe, and responds poorly to usual effective therapy

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

- General
    - Monitor for weight gain
    - Supplement with calcium, vitamin D, +/- bisphosphonates; or regular DEXA scans (bone marrow density [BMD])
    - 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
    - Standard 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 influences 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 on 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 ≥ 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".

- Give the complications of **liver transplantation** (LT) which are more common for AIH than compared with non-autoimmune liver disease.
  - Rejection
    - Acute
    - Chronic
    - Steroid-resistant rejection
  - Difficulty in stopping steroids

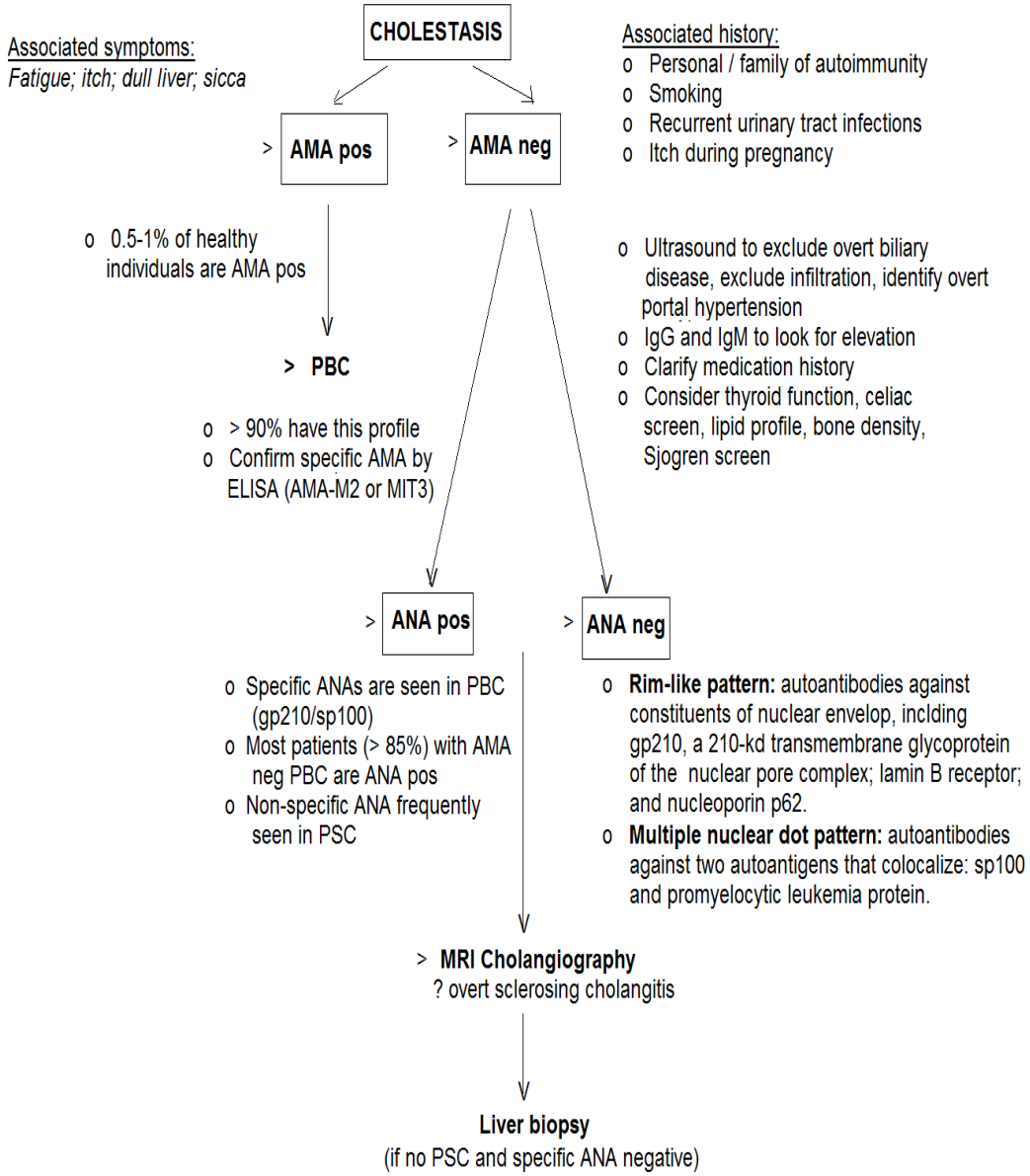
Total Trivia

○ Autoimmune polyendocrinopathy	– Candidiasis – Ectodermal dystrophy APECED
○ Polyendocrinopathy	– Failure of ▪ Parathyroids ▪ Adrenals
○ Candidiasis	– Mucocutaneous
○ Ectodermal dysplasia	– AIH (autoimmune hepatitis)

CHOLESTATIC LIVER DISEASES

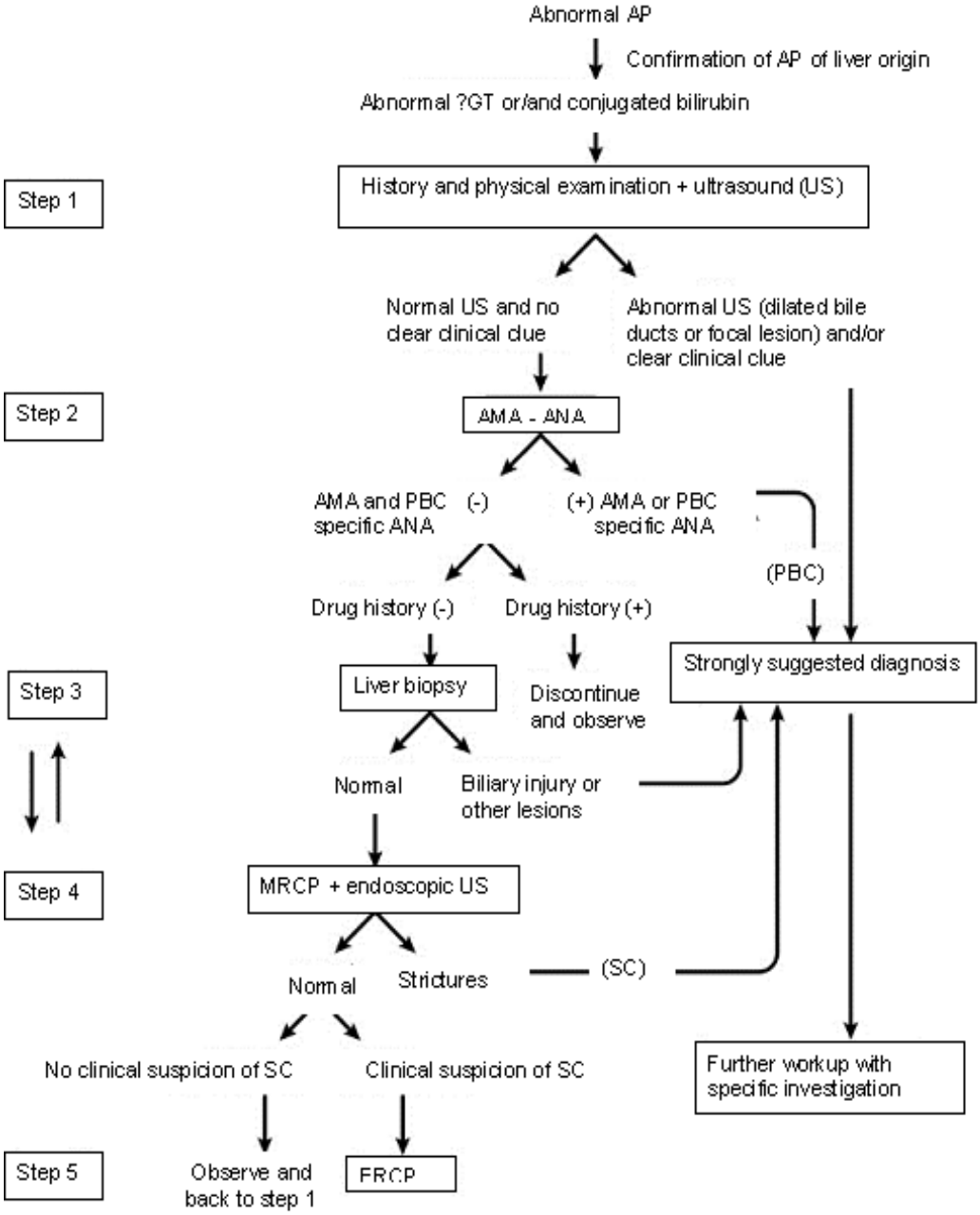
- Laboratory

Suggested flow chart for investigating cholestatic patients



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

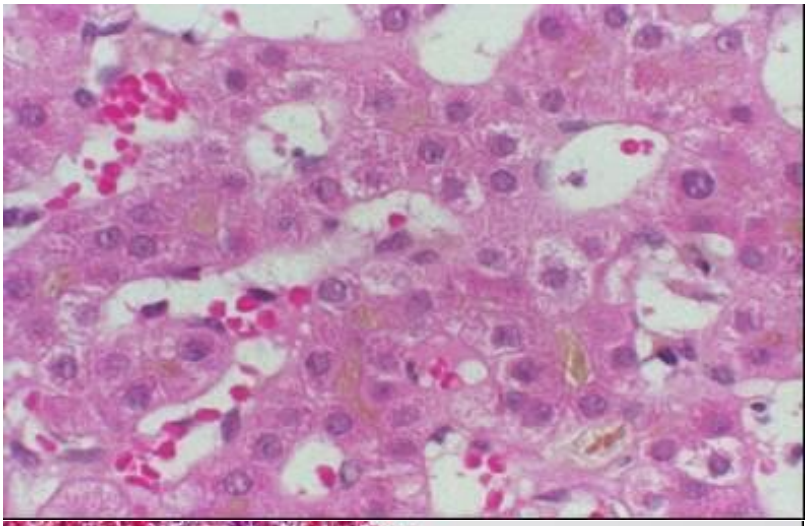
Suggested Algorithm for management of cholestatic liver diseases

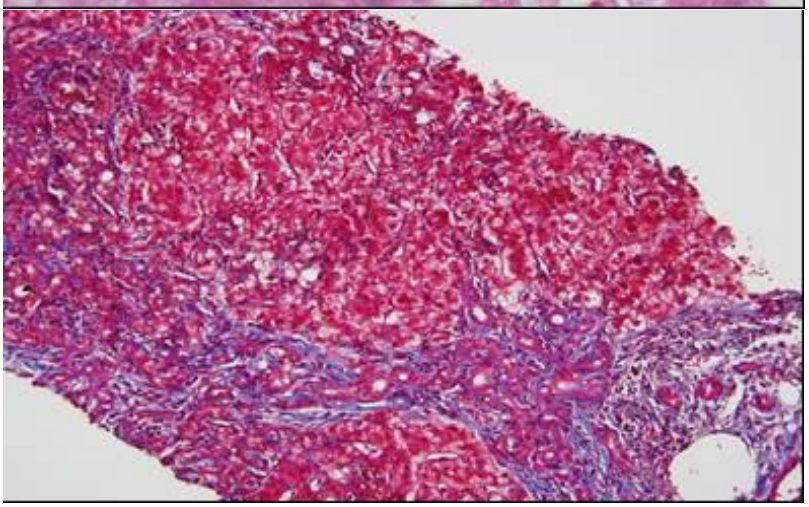


Printed with permission: European Association for the Study of the Liver. EASL Clinical Practice Guidelines. J Hepatol 2009; 51(2), Figure 1: 237–260.

Case: 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.





SO YOU WANT TO BE A GASTROENTEROLOGIST!

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

Primary Biliary Cirrhosis (PBC)

- Definition: PBC is an autoimmune liver disease characterized by specific antibodies, a characteristic liver biopsy (inflammatory distraction 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
        - $3/10^5$
    - Prevalence
        - $40 / 10^5$

- Pathogenesis

- 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

- 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

MCQ ALERT

- 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
- 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 f artherosclerosis 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 decreases survival" (Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier, Philadelphia, 2010, page 1487).

➢ Laboratory

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+, ↑ AP > 1.5 x ULN + ↑ AST < 5 x ULN
- "….a liver biopsy is not necessary to confirm the diagnosis in most patients with PBC and should be performed in only the mimicrity 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).

➢ Histopathology

- 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 μm 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 GEM

- Give the causes of serum transaminases (ALT, AST) > 1000 IU.

○ Infection	– Acute viral hepatitis
○ Immune	– Autoimmune hepatitis (AIH)
○ Ischemic	– Ischemic hepatitis ▪ Vascular ▪ Common bilr ducts
○ Iatrogenic	– Drugs

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

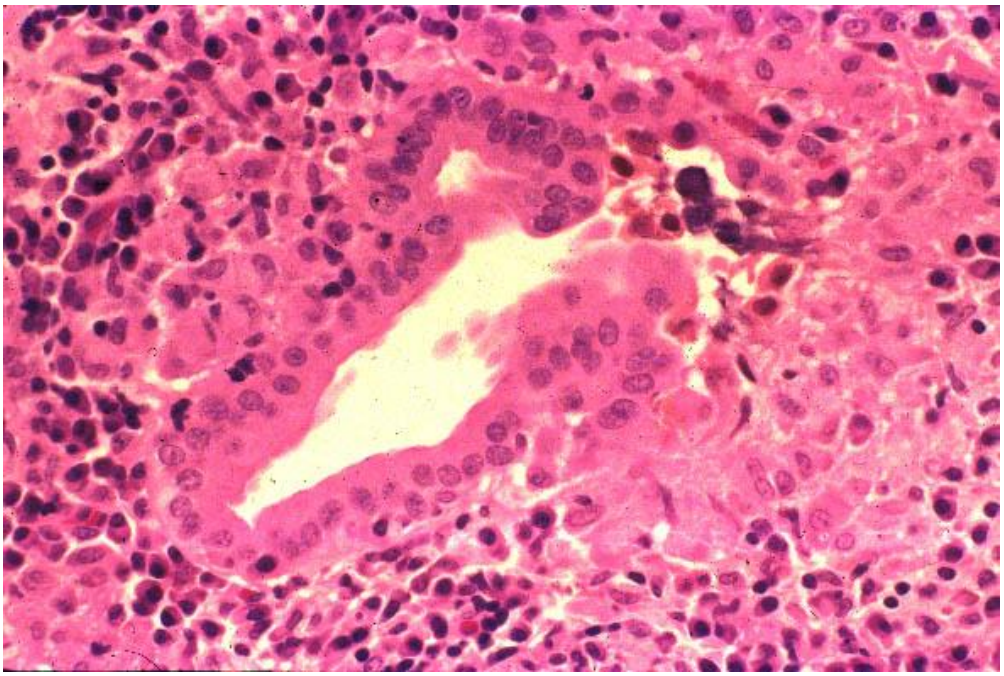
Don't believe it:TRUST, BUT VERIFY.

Grandad

Case: 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.

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

- Give 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 hemoglobulinuria (PNH) – Vasculitis – Henoch-Schōnlein – 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 hemoglobulinuria; TPN, total parenteral nutrition

- 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

- 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 inti 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

- Give the treatment of pruritus in hepatic cholestatic syndromes.
  - Treat the underlying cholestatic condition, including
    - Deficiencies of calcium, fat soluble, vitamin (A, D, E, K)
    - Cholestyramine 4 g po q AM, increasing to tid, taken 2 hr before or after other medications
    - UDCA may help to ↓ pruritus in PBC

- Skin care
  - Skin moisturizing emollient lotions
- Anti-histamine
  - Hydroxyzine 25 mg – 50 mg tid po
  - Cimetidine 300 mg tid
- Naltrexone
  - Opiate receptor antagonist – naltrexome 12.5 mg – 50 mg / day po
- SSRI
  - Sertraline (Zoloft®) 50 mg -100 mg / day
- Rifampin
  - 150 mg / day po in doses increasing to 10 mg / kg / day in 2 divided doses

- Give 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

- All of following are reduced by 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

- 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.

➢ **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 (ASM) antibodies
  - – 50% have anti-gp 210

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

- Give serum autoantibodies which are most prevalent in PSC.

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

Clinical Pearl

When considering issues related to ethics problems in medicine, such as the allocation of donor livers for transplantation into a questionable recipient, frame your thoughts around the “pillars of ethics”

- Do good (beneficence)
- Do no bad (harm)
- Be fair (justice)
- Ensure patient gives informed consent (autonomy)

➢ Diagnostic Imaging

- 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 ▪ ILymphocytic 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

➢ Histopathology

○ Types

– Large-duct PSC (95%)80% are associated with IBD.

▪ If large-duct PSO 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 induced.

▪ 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

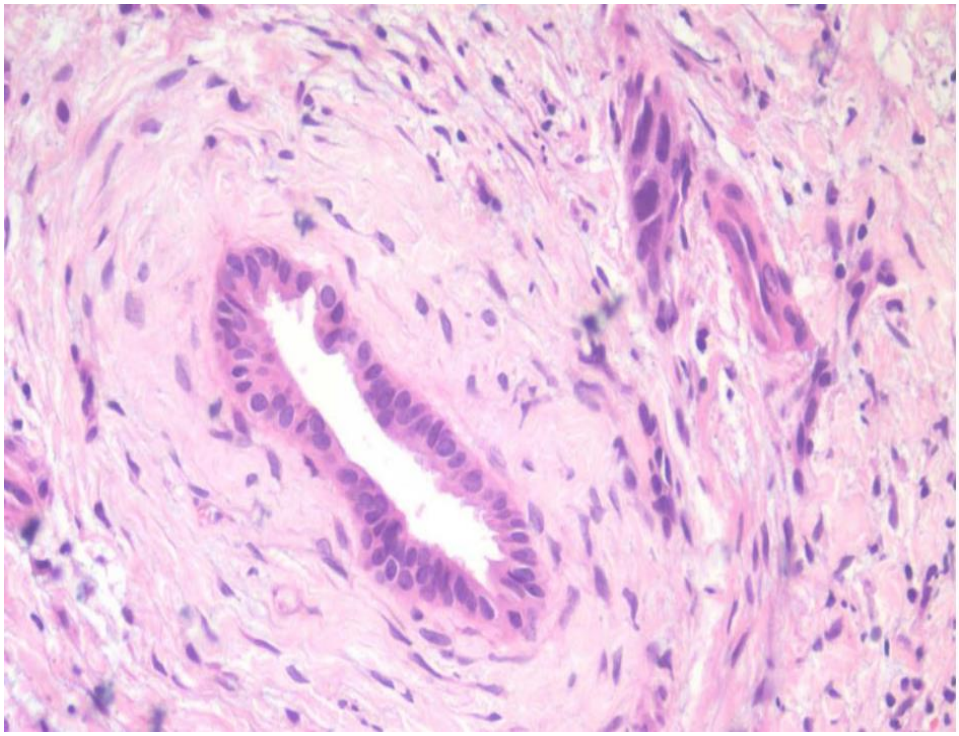
- PSC + gallbladder polyps → elective cholecystectomy for high risk of malignant degeneration of even small gallbladder polyps
- Findings
  - Medium-sized bile ducts:
    - "onion skin" lesion: (fibro-obliterative process)
    - Small interlobular / septal bile duct branches: fibro-obliterative cholangitis
  - 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)

Case: 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.

➢ Causes / associations

- 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
      - Post-liver transplantation (fibrointimal hyperplasia)
      - 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
  - Systemic diseases with fibrosis
    - Retroperitoneal fibrosis
    - Riedel 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 syndrome
  - Autoimmune hemolytic anemia

- Kidney
  - Membranous nephropathy
  - Rapidly progressive glomerulonephritis

- Infections
  - Biliary TB
  - HIV (CD4+ T lymphocytes < 100 / mm^3)
    - 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 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.

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

SO YOU WANT TO BE A GASTROENTEROLOGIST!

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 negatives
            - Negative Lewis antigen status
        - False positives
            - Choledocholithiasis
            - Bacterial cholangitis
    - PET scan
        - False positive
        - Bacterial tract inflammation

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)

- The high mortality in PSC (medial 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).

- Give **biliary tract complications** in PSC.
  - Cirrhosis, and its complications
  - Choledocholithiasis (in ~25%)
  - Cholangitis
  - Multiple strictures
  - Single / strictures
  - "dominant" stricture
    - Intrahepatic > 10 mm in length
    - Extrahepatic, > 15 mm in length
  - Cholangiocarcinoma (in ~ 10%)
  - Gallbladder tumors (~ 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%)
  - 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 (medial 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.

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

- Clinical

- Give characteristics of inflammatory bowel disease (IBD) associated with primary sclerosing cholangitis (PSC).
  - Distribution
    - More R-sided colitis and rectal sparing
    - Rectal sparing
    - Extensive colitis
    - Right-sided predominance of inflammatory activity
    - ↑ backwash ileitis
  - Clinical course
    - Independent
    - Colectomy does not affect PSC
    - Often mild or quiescent course
  - Complications
    - ↑ risk of colorectal neoplasia
      - Perform annual colonoscopy
    - ↑ risk of pouchitis in patients undergoing proctocolectomy with IPAA
    - ↑ risk of peristomal varices in patients undergoing proctocolectomy with ileostomy
  - Post-transplantation
    - 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.

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.

	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. 9th Edition. Saunders/Elsevier, Philadelphia, 2010, page 1159).
- ○ Prognostic models (multivariant)
  - See Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th 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
  - Suppportive 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)

- 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.

- Give 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 (↑ ALT, ↑↑ LDH)
        - ↑ AP (AP increased more than in most patients with hepatitis)
        - ↑↑ 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.

- 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

- 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)

- 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% Preschoolers 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 superinfection with HBV; rare by itself

* Also perinatal

** Pre-1990 blood transfusion

Abbreviation: MSM, mem who have sex with men

- Give which two of the viral causes of hepatitis have a higher mortality during pregnancy.
  - HEV
  - HSV

- 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)

- 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)

- Clinical

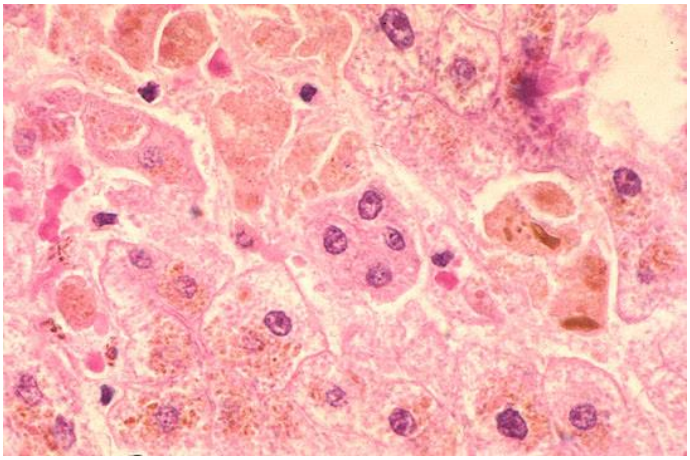
- Modes of clinical presentation
  - Acute hepatitis
  - Fulminant hepatitis failure (FHF)
    - Week 1 of HAV, 55%
    - Week 4 of HAV, 90%
  - Relapsing or “prolonged”, but not chronic course
  - HAV may trigger onset of AIH (autoimmune hepatitis)

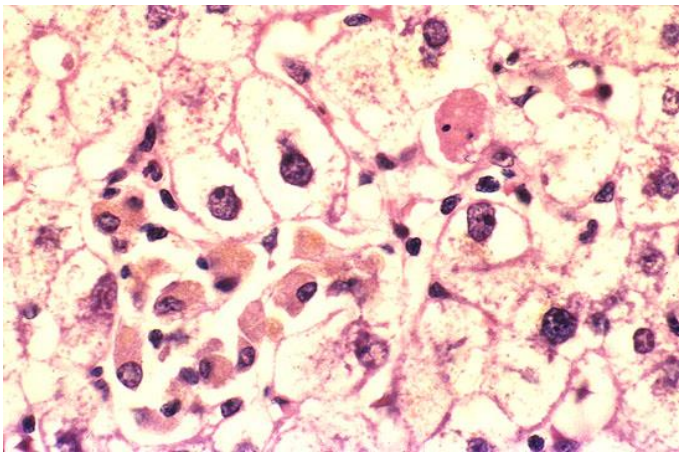
➢ Histopathology

Case: 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.





- 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 / mm^3
  - 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

- 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

- 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%

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- Give the rate of vertical transmission of HBV from (HBs-Ag)-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 explaination for the high rate of transmission of HBV from HBsAg-negative but HBc-positive blood donors.
  - HBV may replicate in many body tissues other than liver
  - These extrahepatic tissues act as reservoirs for HBV DNA

➢ Pathogenesis

- 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.
- 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.

- 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

- 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.

- 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 HBV
  - Survival
    - Spontaneous, 20%
    - Liver transplant, 50%
  - 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 $<10^5$ copies/mL (<20,000 Ik, 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 hepatotrophic viruses (A, C, D)
  - Extrahepatic manifestations
    - Fever, arthralgias (proximal interphalangeal pints), angioneurotic edema
    - PAN (polyarteritis nodosa)
    - HBV-associated renal disease
      - Glomerulonephropathy
      - Membranous glomerulonephritis
      - Membranoproliferative glomerulonephritis
      - Immune-complex glomerulonephritis
      - Nephrotic syndrome
      - Renal failure
      - Cryoglobulinemia

➢ Laboratory

- 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.

- Give 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

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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.

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

Stage	HBeAg	HBV DNA	ALT / AST	progression to fibrosis
○ Immune tolerant	+	↑↑	N / low	Very low
○ Immuno-reactive (HBeAg - positive netcro-infllammation	+	↑	↑ / 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

- 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
○ ALT	– Normal	▪ 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 recom-mended	– No progression of disease for about 3-6 months	▪ HBeAg sero-conversion with treatment		8-10% develops cirrhosis each year, compared with 2-6% of HBeAg positive patients
○ Liver biopsy	– Inactive	▪ Active/+ fibrosis	- Inactive	Active/+ fibrosis
○ Treat-ment	– Not recom-mended	▪ Recom-mended	- Not recommended	Recommended

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

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

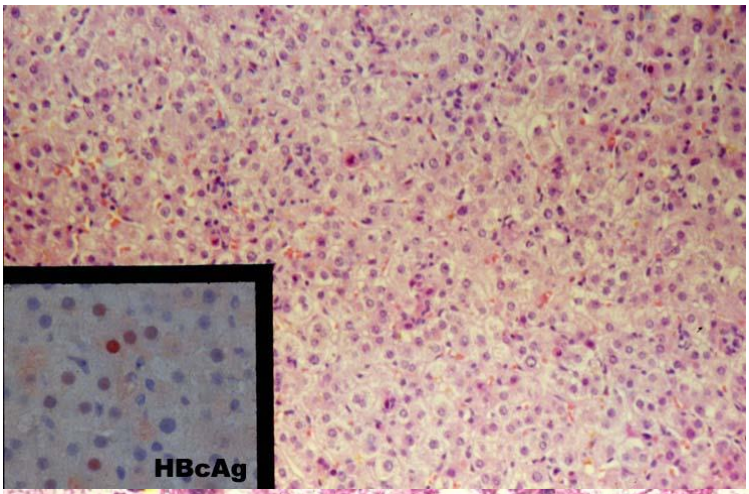
- Give reasons for anti-HBe being in the serum.
  - Acute HBV – IgM anti-HBe
  - Recovery from acute HBV
  - Exacerbations of HBV in chrnic carrier
  - Progression of acute HBV
  - Chronic HBV → HBsAg is undetectable
  - Acute HBV window period, IgM anti-HBe (HBs Ag^+ → $HbsAg^-$, and development of 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

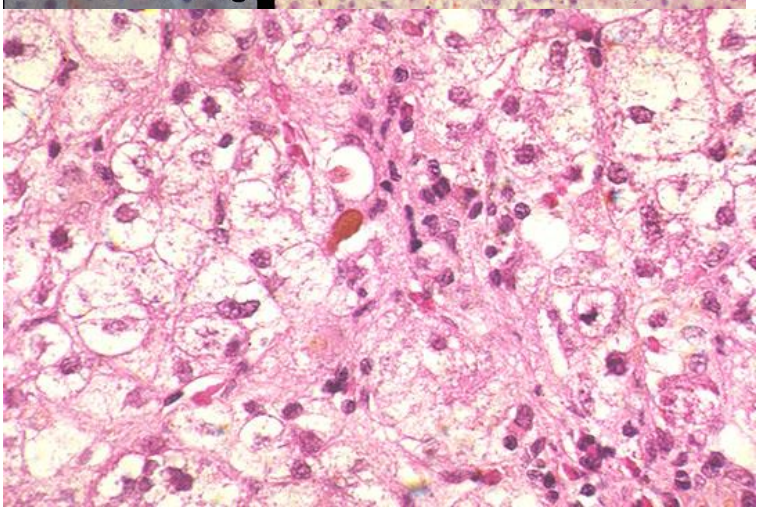
➢ Histopathology

- Give the hepatic histopathological features of HBV infection.
  - Ground-glass hepatocytes
    - HBsAg in the ER of infected hepatocytes
    - Cysteine 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

Case: 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.





➢ Causes / associations

- Give **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.

➢ Prevention

- Give who needs HBV vaccination.
  - The patient
    - Age (infants, pre-adolescents)
    - Renal failure / dialysis
    - Clotting disorders
    - Who are likely to require multiple transfusions with blood or blood products
    - Chronic liver disease
    - Potential organ transplant recipients
    - Co-infection
    - HCV
    - HIV

○ Their habits	– Sexually active heterosexual men and women, if they have more than one partner – Multiple sex partners (MSP) – Men who have sex with men (MSM) – IV drug user (IVDU)
○ The family	– Household contact – Sexual contact – Household contacts and sexual partners of HBV carriers or patients with acute hepatitis B
○ Traveller	– International travellers to areas endemic for HBV who may have intimate contact with the local population or take part in medical activities
○ Worker	– Healthcare workers – Public safety workers with likelihood of exposure to blood – Correctional facility – Staff and clients of institutions for developmentally disabled

*hepatitis A vaccination also recommended

Printed with permission: *Sleisenger and Fordtran's Gastrointestinal and Liver Disease: Pathophysiology/ Diagnosis/ Management*. Ninth edition, 2010, Table 78.6, page 1308.

Vaccination for HBV

- Give reasons for failure of the usual expected antibody response to HBV vaccine.
    - Age > 50 years
    - Underlying disease (chronic renal failure, esp. hemodialysis)
    - Immunosuppressed, immunodeficient
    - HIV positive
    - HCV co-infection
    - Genetics (HLA-B8)
    - Buttock injection

- Frozen vaccine
- Wrong timing or dose of injections
- Smoker
- Obese
- Immunoglobulin, HBIG

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.

Important, but "Not yet proven"

- Giving pregnant HBV mother HB Ig plus a nucleos(t)ide analogue to ↓ vertical transmission
- Nucleos(t)ides used for HBV treatment are excreted in milk.
  - Safety to child is unknown
- Vertical transmission of HBV from mother to baby is reduced with lamivudine plus HBIg in late pregnancy, but longterm safety is not yet proven.

Clinical Gems

- When starting any patient on prednisone, immunosuppressants, biological or chemotherapy, check the HBV status.
- These drugs may cause seroconversion from anti-HBe (HBe Ag – negative) → HBeAg – positive with an acute flare, both when on these medications, as well as upon their withdrawal.
  - HBIg (hepatitis B specific immunoglobulin), plus
  - Hepatitis B surface antigen vaccine
  - Some success with lamivudine plus HBIg multiple injections late in pregnancy, but long-term safety data not yet available.

Please see the following useful tables in Adapted from: Peltekian K and Hirsch G. Chapter 59. In: Therapeutic Choices. Grey J, Ed. 6th Edition, Canadian Pharmacists Association: Ottawa, ON, 2011, page 782-802.

- 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 litre 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 Laiver 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.

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- Give 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

- 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

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 $\log_{10}$ 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.

- Give **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 patent 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

The importance of HBeAg status

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

- Give **goals (endpoints) of treatment** of $HBeAg^+$ and $HBeAg^-$ HB.

  - Loss of E-antigen
    - 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)
  - Conversion to inactive status
  - Loss of detectable HBV DNA
    - Undetectable HBV DNA (< 2000 IU/mL at 12 mon after end of long-term antiviral therapy)
  - Appearance of anti-E
    - HBcAg-positive → anti-HBe, seroconversion, off-therapy
  - Conversion to inactive status
  - Normal serum
    - ALT at least 1 yr off-treatment post-treatment, with ALT measurements q 3 mon
  - Improvement in liver histology
    - Advance resolution of hepatic necroinflammation
  - ↓ risk of developing portal hypertension
  - ↓ risk of developing decompensated cirrhosis

- Loss HBs Ag
  - HBsAg seroconversion (occurs in < 10%, and is often not seen for 4-5 years after therapy has been completed and e-Ag has occurred
- ↓ risk of hepatocellular carcinoma (HCC)
- Improve patient quality of life
- Please refer to J Hepatolol 2012; 57:167-185 for details re virological responses on therapy (IFN [interferon}) PEG [pegylated] IFN or NAs [nucleoside / nucleotide analogs])

- 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
○ 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

Clinical Tips

- The treatment of HBV infection requires longterm therapy, whereas the treatment of HCV infection provides high rates of viral eradication (sustained virological response).
- Because the treatment of HBV is longterm and only suppressive, not all patients will be treated at the time of their first medical encounter.

- 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

SO YOU WANT TO BE A HEPATOLOGIST!

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

- 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 ($HBeAg^+ \rightarrow HBeAg^-$, anti-HBe) usually associated with ↓ HBV DNA

- 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 Iμ/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.

SO YOU WANT TO BE A HEPATOLOGIST!

- 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

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

  - 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%

  - 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 Rx

- 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 ≥ 2 $\log_{10}$ IU / mL, and no ↓ HBsAg
    - Stop PEG-IFN (especially genotype D)

➢ NA (nuceos[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**

- 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

Printed with permission: Keeffe EB. *2007 AGA Institute Postgraduate Course*: 75.

- 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

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- Give 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: Keeffe 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

- Give 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
○ 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)

Agent	Advantages	Disadvantages
○ 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-IFNα), and at 48 all 52 weeks of nucleos(t)ide analog (NA) therapy.

HBeAg positive	PEG-IFN		Nuclesoside analogs			Nucleotide analog	
	PEG-IFN-2a	PEG-IFN-2b	LAM	TEL	ENT	ADE	TEN
Dose	180 µg	180 µg	100 µg	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		Nuclesoside analogs			Nucleotide analog	
	PEG-IFN-2a	PEG-IFN-2b	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 µg	100 µg	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, telbividine; 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

[a]Cumulative 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, entercavir 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.

- Give the overview of **response rates** in HBeAg positive and HBeAg negative patients with currently available antiviral drugs.

Antiviral therapy	HBeAg positive HBeAg seroconversion		HBeAg negative Undetectable HBV DNA	
	End of therapy	Post treatment	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.

- 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 Iμ/ml	Normal	- No treatment - Monitor every 6-12 months - Consider therapy in patients with known significant histological disease even if low-level replication
○	≥ 20,000 Iμ/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.
○	≥20,000 Iμ/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

- 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 Iμ/ml	Normal	- No treatment: majority inactive HBsAg carriers - Monitor every 6-12 months
○ ≥2,000 Iμ/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.
○ ≥2,000 Iμ/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

- 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.

- Give **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)

- Give **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 (Lam)
    - 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) < enterocovir < telbivudine (Tel) < tenofovir (Ten)
  - HBV resistance
    - Ten > The > Ent >Ade
    - Rate of resistance
      - Lam 69% / 5 yrs
      - Ade 30% / 4 yrs
      - Ten rare

      ] don't use
  - Adefovir dipovoxil
    - Acyclic phosphate nucleotide analog of adenosine monophosphate
    - ↓ HBV polymerase and reverse transcriptase
  - Entercavir
    - 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.
  - Telebuvidine
    - 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

Approximate response rate (%) for chronic hepatitis B at 12 months

Endpoint	PEG-IFN PEG-IFN-2a PEG-IFN-2b	Nucleoside analog LAM, TEL, ENT	Nucleotide analog, ADE, TEN
○ HBeAg-positive			
○ Anti-HBe seroconversion	30	20	15
○ HBV-DNA < 60 to 80 IU/mL	10(20)	65(70-90)	21-76 (60-90)
○ Normal ALT	35(60)	65(75)	60(75)

Note: Approximate the result for HBeAg-negative patients is given in brackets
The PEG-IFN data in HBeAg-negative is for PEG-IFN-2a
The one and five year HBV resistance rates are LAM, 24% and 70%, ADV and 29%

Abbreviations and daily doses:
PEG-IFN, pegylated interferon 2a – 180 mcg
2b – 100 mcg
LAM, lamivudine – 100 mg
TEL, telbivudine – 600 mg
ENT, entecavir – 0.5 mg
ADE, adefovir – 10 mg
TEN, tenofovir – 245 mg

Adapted from J Hepatol 2012; 57:167-185.

❖ Predictors of response

- IFN / PEG IFN based treatment

❖ Pretreatment

- HBeAg-positive → predictors of anti-HBe seroconversion
  - HBV DNA < 2 x 10^8 IU/mL
  - ALT > 2 to 5x ULN
  - HBV genotypes A and B
  - Activity scores high (≥ A2) on liver biopsy
  - Note: inadequate data to predict pre IFN / PEG-IFN response in HBeAg-negative CNB

- During treatment
  - HBeAg-positive → predictors of anti-HBe seroconversion
    - HBV DNA
      - ↓ to < 20,000 IU/mL at 12 wk
      - ↑ ALT followed by ↓ HBV DNA
    - HBsAg
      - ↓ to < 1500 IU/mL at 12 wk
    - HBeAg at 24 wk
  - HBeAg-negative
    - HBV DNA ↓ to < 1500 IU / mL at 12 wk
    - No HBsAg ↓ and ↓ HBV DNA < 2 $\log_{10}$ IU/mL
    - HBsAg
  - Nucleoside / nucleotide treatment

Note: HBV genotype does not alter virological response to NAs

  - ↓↓ HBV DNA (undetectable) after 24 (LAM, TEL) and 48 wk (ADE) treatment
  - ↓ HBsAg in HbeAg-positive
  - Finite duration
    - PEG-IFN
      - Higher rates of anti-HBE and anti-HBS seroconversion with 12 mon therapy, with no risk of resistance, in HBV infected persons with CHB and no decompensated
      - Usually 48 wk treatment, with risk of AEs
  - NAs
    - HBeAg-positive seroconvertors (use more potent NA for durable seroconversion)
    - 48 wk treatment to ↓ risk of loss of seroconversion (~66%)
    - Continence until clearance of HBsAg +/- HBsAg antibody
  - Long-term treatment with NAs
    - Ideal for persons who are
      - HBeAg-positive persons who are unlikely to seroconvert (please see predictors above)
      - HBeAg-negative persons
      - Cirrhosis
    - Tenofovir or entecavir monotherapy for ≥ 3 yr

- Treatment failures
  - Note: conform adherence to treatment recommendations
  - Primary non-response
    - Suboptimal anti-viral effect
    - Adefovir (10%) → switch to
      Tenofovir, or
      Entecavir
  - Partial virological response
    - Lamivudine or telbivudine → switch to
      - Tenofovir, or
      - Entecavir
    - Tenofovir or entecavir use both drugs
  - Virological breakthrough
    - If available, determine genotypic resistance to choose appropriate alternate NA

Resistant NA	Therapeutic strategy
Lamivudine	– Switch to tenofovir, or – Add tenofovir to lamivudine or adefovir
Adefovir	– NA naïve switch to enterocavir or tenofovir – Switch to tenefovir plus emtricitabine not NA naïve, i.e lamivudine resistance before developing adefovir resistance) – Switch to or add tenofovir, or – Add adefovir to telbivudine
Entecavir	– Switch to or add tenofovir, or – Add adefovir
Tenofovir	– Add entecavir, telbivudine, lamivudine, or emtricitabine

- Monitoring during treatment

- Finite duration – PEG-IFN

q 1 mon	CBC, ALT	for 12 mon of Rx
q 3 mon	TSH	

- HBeAg-positive
  - q 6 and 12 mon on treatment, plus q 6 and 12 mon off treatment
    - HBeAg
    - Anti-HBe antibodies
  - HBeAg-positive patients who seroconvert may develop HBeAg seroconversion or develop HBeAg-negative CHB, and this need to be followed long-term
  - Including HBsAg q 12 mon, and if HBeAg becomes negative, follow for anti-HBs
- HBeAg-negative
  - q 6 and 12 mon on treatment, plus 6 mon and 12 mon off treatment HBV DNA
  - HBsAg q 12 mon, and if HBsAg becomes negative, follow for anti-HBs
  - Continue long-term follow up for possible reactivation
  - NAs

q 3 to 6 mon	HBV DNA
q 6 mon	HBeAg and anti-HBe
q 12 mon	HBsAg

- Long-term NAs
  - q 3 mon HBV DNA, then q 3 to 6 mon after virologic response
  - Serum creatinine and phosphate, creatinine clearance test
  - Renal function assessment
    - Low renal risk
      - q 3 mon for 1 yr then if no deterioration, q 6 mon
    - High renal risk
      - q 1 mon for 3 mon, then if no deterioration, q 3 mon for 9 mon, then q 6 mon
  - Cirrhosis
    - Compensated
      - Use PEG-IFN; tenofovir or entecavir
      - q 3 mon HBV DNA (if resistance occurs, CHB may exacerbate and must be quickly treated
      - Continue long-term HCC monitoring

- Decompensated
  - Transfer patient to specialized liver unit
  - Do not use PEG-IFN
  - Entecavir 1 mg/day or tenofovir 245 mg/day
    - Monitor for possible lactic acidosis
    - Reduce dose of entecavir or tenofovir if creatinine clearance rate < 50 mL/min
  - Therapy successful
    - Life-long treatment
  - Therapy not successful
    - Consider liver transplant, using usual MELD criteria
    - or ideally HBsAg loss and anti-HBs seroconversion and in HBeAg-negative patients if they achieve confirmed HBsAg loss and anti-HBs seroconversion"

Source: J. Hepatology 2012; 57:167-185.

- 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

- 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

- 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, resitance to LAM

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

- Give the treatment of anti-viral resistant HBV.
  - Lamivudine or telbuvidine 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

Mutants

- HBsAg mutants
  - Vaccine escape
    - In persons for whom HBIG does not present 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.
- 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).

❖ Special conditions in treating HBV infection

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 $\log_{10}$ (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 > 10^5 (20,000 IU/mL)

OSCE and Boards Alert

- 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

- 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 IU/mL	Normal	– No treatment – Monitor every 6-12 months – Consider therapy in patients with known significant histological disease even if low-level replication
≥ 20,000 IU/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.
≥20,000 IU/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
HBV Lam < adefovir (Ade) < enterocovir < telbivudine (Tel) < tenofovir (Ten) viral suppression

❖ When **immune tolerant**, then no liver damage and no Rx needed

In HBV, "Be patient and wait" – 50% become acute over 5 years, and should then be treated

❖ When **HBV DNA** > 10^5, then ↑ risk of HCC

"AT", aminotransferases AP, alkaline phosphatase

Peginterferon 180 µg/wk - 35% $E^+ \rightarrow E^-$ seroconversion
Genotype A 50%
B, C, D 30%
TEN > THE > ENT >ADE
Rate of resistance
LAM 69% / 5 yrs] don't use
ADE 30% / 4 yrs]
TEN rare

Clinical Reminder

- HBV anti-core$^+$ can reactivate with Prednisolone, azathioprine, anti-TNF therapy

- PEG-IFN or NA (NTs and NSs) monotherapy for finite duration
- NA for longterm duration

❖ PEG-IFN or NA **monotherapy** for finite duration

- PEG-IFN (in the absence of contraindications) for HBeAg- positive and -negative patients for 48 weeks

Treatment 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 **longterm duration**

- Entecavir or tenofovir monotherapy for
  - HBeAg-positive patients who failed to seroconvert or HBeAg-negative patients
  - All HBV cirrhosis

- For resistance to NA
  - Switch NT → NS, or NS → NT
- Lamivudine, telbivudine, entecavir → tenofovir or adefovir (nucleotide analogues; note: nephrogenic potential is adefovir > tenofovir; in fact, tenofovir may actually improve renal function)
- 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

- Give the treatment in the following special clinical aspects 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, entercavir 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-method 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 an 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 > 10^{-7} IU / mL
    - HBIG plus HBV vaccination
  - Safety of NA for mother who wishes to breast feed is unknown

"FLARES"

- Give causes of "flares" of acute hepatitis (reactivation, decompensation) in persons with chronic HBV.

Cause of flares	Comment
❖ Virus	
○ Spontaneous	- Seroconversion HBeAg+ →HBeAg- - Reappearance of IgM anti-HBC
○ YMDD mutant	- Can have severe consequences in patients with advanced liver disease
○ Genotypic variation – Precore and core promoter mutants	- Fluctuations in serum ALT levels are common with precore and core promoter mutants
❖ Treatment	
○ During treatment	- Flares are no more common than with placebo
○ 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	
○ Adefovir, entecavir	- On withdrawal, flares are caused by rapid reemergence of wild-type HBV; can have severe consequences in patients with advanced liver disease
❖ Superimposed	
○ HIV treatment	- Flares also can occur with immune reconstitution or secondary to antiretroviral drug hepatotoxictity
○ Superimposed infection with other hepatitis viruses (HDV, HEV)	- HAV, HCV, HDV may be associated with suppression of HBV replication
○ Alcohol use	

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

- 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.

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- A flare of HBV may occur with a superinfection with a hepatotrophic 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 hepatotrophic viral superinfection in chronic HBV, the non-PCR tests for HBV DNA and for HBeAg may be 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**

- Give the reason why ALF may occur during steroid withdrawal for treatment of polyartritis 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.

- Give the explanation for this immune rebound which ccurs 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% $E^+ \rightarrow E^-$ seroconversion

      Genotype A 50%

      B, C, D 30%

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

Peter F. Drucker

HBV Infection and Hepatocellular Cancer (HCC)

- Give 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 (at age of diagnosis of cirrhosis, ultrasound every 6 mon)
    - *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.
  - Family history of HCC
  - Co-infection with HCV, HIV
  - HBe Ag negative

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

HBV in an oncogenic virus (risk of hepatocellular cancer [HCC]).

- Give 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
    - Reversion of anti-HBe to $HBeAg^{+}$
    - HBV DNA > 10^{5}
    - Cirrhosis

Clinical Alert! Clearance of HBsAg and HCC

- Even HBsAg clearance, … is not on 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.

Clinical Alert ! HBeAg and HCC

- HCC may develop in HBV
  - In the absence of cirrhosis
  - Even after seroconversion ($HBeAg^+ \rightarrow HBeAg^-$, anti-HBe-positive)
  - Even after loss of HBsAg
  - This is whyscreening is so important
- A normal ALT is not a good marker for disease activity
  - ~25% of HBV carriers with normal ALT an serum HBV DNA > 10^4 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

For more detail regarding treatment of chronic hepatitis B: definitions of response to antiviral therapy, please 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 > 10^8 copies/mL
  - Percutaneous
    - Blood products ($1/2x10^6$)
    - IV drug use (60% to 90% HCV infected)
    - Nucleotide accidents
    - Hemodialysis
  - Non-percutaneous
    - Sexual contact
    - Intercourse
      - Per rectum
      - During menstruation
  - Usually seen in
    - Cirrhosis
    - Non-cirrhotic or cirrhotic HBV infection
    - HCV with cirrhosis and non-cirrhotic HCV infection (in Japan)
    - Hemochromatosis
    - NAFLD (non-alcoholic fatty liver disease)
  - Hepatocellular carcinoma (HCC) is one of the most common malignant tumours worldwide and its incidence is increased in industrialized countries
  - About 80% of HCC worldwide are due to HBV and HCC, and most cases are associated with cirrhosis.
  - Because of the high mortality rate of HCC, the prevalence approximately equals the incidence
  - Overall median survival of HCC - 6 to 12 months
  - The epidemiology of HCC varies in different parts of the world
    - High incidence
      - $15/10^5$
      - Asia (except Thailand and Indonesia), sub – Saharan Africa
      - M > W 3.7 : 1

– Medium incidence	▪ Asia	Thailand Indonesia
	▪ Austrasia	New Zealand First Nations people (Maoris)
	▪ North America	Alaskan Inuit ("Eskimos)
– Low incidence $< 3/10^5$	▪ North America* ▪ South America ▪ Europe ▪ Middle East ▪ Australia	Males-to-females 2 to $7/10^5$

*Note racial variation in incidence (per 10^5) within America

o Asians	11
o Hispanics	6.8
o African Americans	4.2
o Caucasians	2.6

- 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

- 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)

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

Groups at risk	Estimated prevalence (range %)
Injection drug users	35-90
Hemophiliac treated before 1990/91	50-90
Thalassemics	42-83
Hemodialysis patients	10-45
People who received a blood transfusion before 1990/91	5-10
Children born from HCV positive mothers	3-10
Incarcerated persons	30-80
Migrants coming from endemic regions	Related to country of origin
Health care workers	Related to country of origin
HIV infected persons	25-35
Persons with unexplained persistently elevated ALT	15

- Give 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 behaviors
    - 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

- At risk occupations
  - Needle stick injury
  - Inmates
- 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.

➢ Screening

- 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.

- 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 contents of HCV-infected persons need to be tested for anti-HCV.
- Test the children of HCV-infected mothers for HCV RNA when 1 mon old.

➢ Major Etiologies

- Chronic hepatitis B, C or D
- Toxins (e.g. alcohol, tobacco, aflatoxins)
- Hereditary metabolic liver diseases (e.g. hemochromatosis, a1-antitrypsin deficiency)
- Autoimmune hepatitis
- Obesity (males)
- Diabetes mellitus
- Nonalcoholic steatohepatitis (NASH)
- Nonalcoholic fatty liver disease (NAFLD)

Printed with permission: Macmillan Publishers Ltd: Spangenberg et al, Nat.Rev. *Gastroenterol Hepatol* 2009;6: 423-432.

- Give risk factors for developing hepatocellular cancer (HCC) in persons with HBV infection.
  - Patient
    - M:F 2:1 – 4.1
    - Africans > 20 years (HBV^+)
    - Asian males> 40 years / females >50 years (HBV^+)
    - Family history of HCC
    - Dietary aflatoxin exposure
    - Alcohol intake > 50 g/d
    - Obesity (↑ BMI)
    - Tobacco, marijuana smoking
    - Oral contraceptive pill (OCP)
    - Androgenic hormones
  - Without cirrhosis
    - Chronic HBV infection (even without cirrhosis)
    - Chronic HCV infection (Japan; all others, HCV cirrhosis)
    - Hepatic adenoma
    - Hemochromatosis (HH)
    - Aflatoxin BI
    - 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
  - Medications
    - Exposure to OCAs (oral contraceptives)

- Infection
  - HCV infection for > 25 years
  - Failure of HCV to respond to IFN (interferon)
  - Older age of HCV treatment
  - Absence of previous HCV treatment
  - HBV coinfection
  - HIV co-infection
  - Long duration of active disease

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.

- Environmental factors
  - Alpha toxin
    - Mycotoxin contamination of corn, soybeans and peanuts
    - Causes of the p53 tumor suppressor gene which leads to HCC
  - Dirty drinking water
    - Especially contamination of blue-green algae toxin microcystin
  - Betal nuts
    - Chewing these nuts increases the risk of
      - Cirrhosis
      - HCC
      - Squamous cell cancer
        - Esophagus
        - Head/neck
  - Red meat/saturated fats ↑ risk of HCC approximately 50%

- Blood group (vs. blood group O)
  - Males - A or B
  - Females - AB or B

- HBV Serology
  - 20% of HBV with HCC are only carriers
  - 80% of HBV developing HCC have cirrhosis
  - Of those with HBV chronic hepatitis, risk factors include
    - HBeAg
    - HBsAg
    - Reversion of anti-HBe to $HBeAg^+$

Virology	Incidence per 10^5 person years
– HbsAg-neg plus HBeAg-neg	39
– HBsAg-pos	196
– HBsAg-neg	35
– HBsAg-pos; HBeAg-neg (inactive carriers)	324
– HBsAg-pos, plus HBeAg-pos	1169

  - Note: Clearance of HBV (i.e. HBsg-pos → HbsAg-neg does) dose not preclude development of cirrhosis or HCC; it just reduces the risk)
  - Example re HBV DNA

(copies /mL)	Incidence (per 10^5 person-years)	cumulative incidence
< 300	108	1.3%
> 10^6	1152	14.9%

- Coinfection
  - HCV plus HBV, especially when HBeAg-pos
  - HDV plus HBV

Anti-HDV	HBeAg	5 yr risk of HCC
-	+	2%
-	-	4%
+	-	13%

HDV infection	SIR for HCC
- Acute	6.1
- Chronic	3.9

- Co-infection with HIV
  - HBV or HCV plus HIV
- Active hepatitis (↑ ALT)
  - ↑ ALT reflects active inflammation, and this is especially a risk for HCC in HCV.

- HBV mutations
  - Core
  - Precore

Abbreviation: SIR, standardized incidence ratio

- ↑ AFP (alpha-fetoprotein > 2 mcg/L)
- Diabetes/metabolic syndrome

Associated conditions	RR of HCC	Incidence (per 10^5 person-years)
Metabolic syndrome	2.1	-
Diabetes	2.2	210
Metabolically normal	-	104

Abbreviation: RR, relative risk

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

Apoorve Dubey

➢ Case finding

- All persons having a medical encounter ("comprehensive health evaluation") require inquiry
- Possible at-risk-behaviour which ↑ risk of HCV

↓ risk behavior

- Test anti-HCV, HCV-RNA for HCV infection
  - Anti-HCV positive Rx considered
  - Anti-HCV negative but immunocompromised or suspected as having HCV

↓ Anti-HCV positive

HCV positive → interpret HCV → HCV genotyping

↓ Access for possible

- Give advice re **measures to avoid transmission** of HCV.

↓ Fibrosis, FibroScan, or Liver biopsy

- Access for treatment
  - Indications
  - Contraindications
  - Individualized therapy

↓

- Not determined by ALT value
- Individualized decision to treat based on
  - Severity of liver biopsy
  - Likelihood of severe AEs
  - Likelihood of response
  - Comorbidities

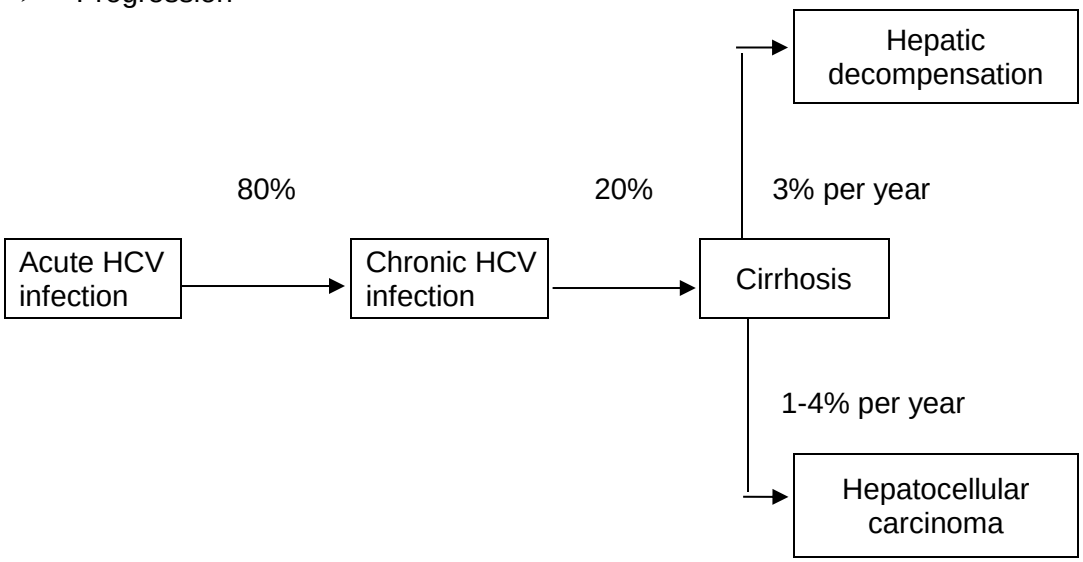
PEG IFN plus Ribavarin (RBV) (for 12-72 wk, depending on genotype and response, shown below), or non-PEG IFN protease inhibitors if available

Note:

- HCV Rx is usually withheld if baseline absolute neutrophil count ≤ 1500 mm^3, but this should not be an exclusion in persons of African origin
- Use growth factors for treatment associated anemia or leukopenia

- Drug users
  - PEG IFN plus RBV if drug user (active, or methadone program)
    + wishes treatment, and
    + willing to be
      - Closely monitored
      - Take contraception
      - Take addiction counselling including mental health support

➢ Progression



➢ 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

SO YOU WANT TO BE A HEPATOLOGIST!

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

- Give **paraneoplastic syndromes** associated with hepatocellular carcinoma (HCC).

o CNS	– Neuropathy
o Endocrine	– Sexual changes- isosexual precocity, gynecomastia, feminization
	– Hypoglycemia
	– Hypercalcemia
	– Thyrotoxicosis
o MSK	– Carcinoid syndrome
	– Hypertrophic osteoarthropathy
	– Osteoporosis
	– Polymyositis
	– Thrombophlebitis migrans
o CVS	– Systemic arterial hypertension
o Skin	– Porphyria
o GI	– Watery diarrhea syndrome
o Hematology	– Polycythemia (erythrocytosis)

Adapted from: *Sleisenger and Fordtran's Gastrointestinal and Liver Disease: Pathophysiology/ Diagnosis/ Management*. 9th edition, 2010, Table 94.2: page 1571.

SO YOU WANT TO BE A GASTROENTEROLOGIST!

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
o Hypoglycemia	– Pre-IGF II (insulin-like growth factor)
o Polycythemia	– Erythropoietin (or erythropoietin-like substance)
o 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.

- Give **dermatological manifestations** in untreated or treated patients with patients with HCV infection.
  - PCT (porphyria cutanea tarda)
    - Sporatic 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

- Give non-dermatological **extrahepatic manifestations** of Hepatitis C (HCV) infections.
  - Skin
    - Vitiligo
    - Lichen planus
  - Lung
    - Idiopathic pulmonary fibrosis
  - Endocrine
    - Diabetes mellitus
    - Autoimmune thyroiditis
    - Thyroid cancer

- 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,

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

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

- Give the clinical feature of acute HCV infection which 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.

➢ Laboratory

Useful Reminders

- In acute HCV infection, HCV RNA appears before anti-HCV antibodies.
- The presence of HCV RNA plus anti-HCV antibiotics 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 antibiotics.

- 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

- Give the **interpretation** of anti HCV serological 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

[a]Anti- HCV does not necessarily indicate current hepatitis C infection

- Give the reasons why the ALT or AST are not a useful markers 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.

➢ Pathology

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

- Give the methods of **assessment of severity of HCV liver disease.**

❖ Invasive

  - Liver biopsy-based structured semi-quantitative scoring systems
    - More reproducible
      - METAVIR
      - Scheuer
    - More discriminant
      - Ishak
      - Knodell HAI
    - These scores report
      - Grade of necroinflammation
      - Stage of fibrosis

❖ Non-invasive

- 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

Clinical Pearl

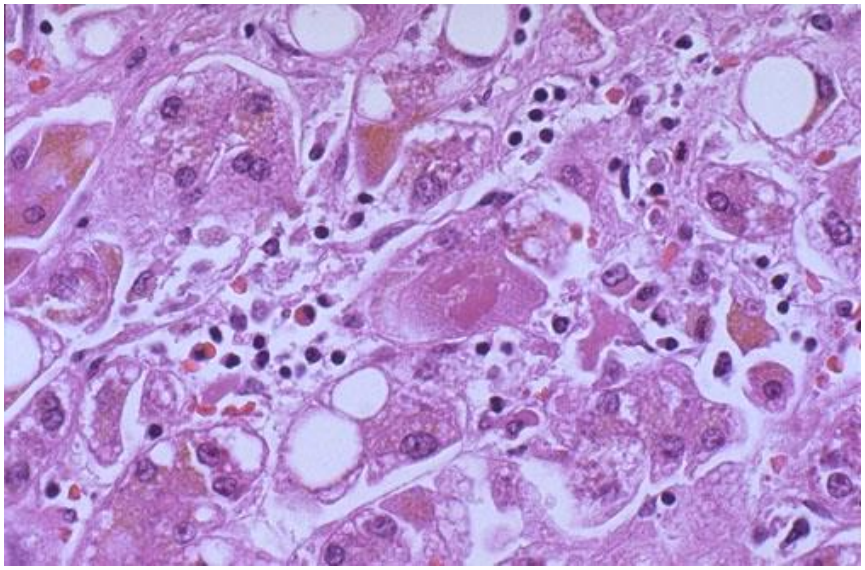
- Serum ALT may be normal in the presence of fibrosis
- Therefore, perform serial tests for severity of liver disease (such as TE [transient elastography] plus blood test) even if ALT is normal.

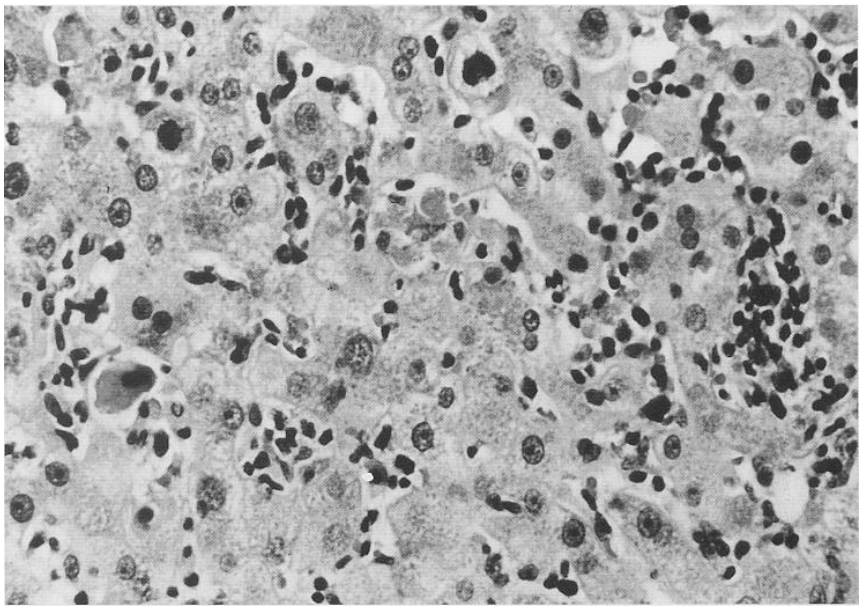
➢ Histopathology

Case: 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.





- 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

- Give 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

- 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

- 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.

- Give 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 Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier, Philadelphia, 2010, 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
- Laboratory / 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.

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

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

SO YOU WANT TO BE A HEPATOLOGIST!

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

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

Abbreviation: TJ, tight junctions

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

- Give the management principles of persons with HCV infection.
  - Prevention, screening, vaccination (none), prophylaxis on exposure
  - General management strategy
  - Objective of therapy
    - Eradicate HCV
    - SVR (sustained viral response)
    - Absent serum HCV RNA 6 months after
  - Assessment of factors predictive of viral response
  - Specific treatments
  - Select optimal agent
  - Reassess therapy
  - Screen for HCC

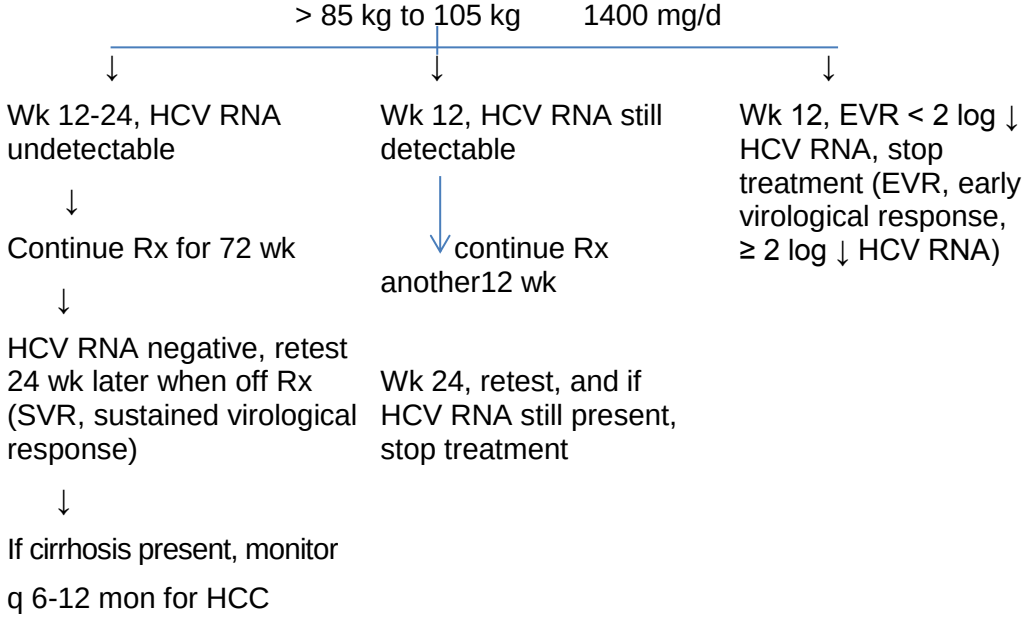
Adapted from: Berenguer M, and Wright TL. Hepatitis C. *Sleisenger & Fordtran's Gastrointestinal and Liver Disease: Pathophysiology/ Diagnosis/ Management* 2006. pg. 1681-1712.

Treatment Alert!

The guidelines for best practice are changing rapidly and the reader is encouraged to refer to online sources sponsored by subspecialty societies such as the American / Canadian Association for the Study of Liver disease

  - Follow patient with a multi-disciplinary team, including mental health experts
    - Psychiatric disorders
      - PEG IFN plus RBV, undertaken by multidisciplinary team including mental health experts

- General management
  - No alcohol consumption for HAV and HBV
- Genotype I, or 4 HCV
  - PEG IFN-α 2a, 180 mcg SC per wk, plus
  - RBV ≤ 75 kg BW 1000 mg/d
    > 75 kg 1200 mg/d, or
  - PEG IFN-α 1.5 mcg/kg SS per wk, plus
  - RBV < 65 kg 800 mg/d
    > 65 to 85 kg 1000 mg/d
    > 85 kg to 105 kg 1400 mg/d



➢ Terminology

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
- Partial EVR (pEVR)
  - EVR at week 12, HCV RNA up to week 24, but no HCV RNA after week 24
  - 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.

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.

- 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.

- ○ 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.

- Give 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	– HIV coinfection – Poor adherence to anti-HCV treatment
○ Co-morbidities	– Insulin resistance – Diabetes – Obesity (↑ BMI) – 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 ↑ 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
  - Genotypes1, 4
  - High HCV load
  - No IL-28 B CT, TTgenotype
  - Viral genotype: Genotype 1&4 (42-46%), Genotype 2, 3 (76-82%)
  - Lower viral levels: >2 x 10^6 (42-53%), <2 x 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 inferon 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)

- Pregnancy
  - 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

- Vaccination
  - 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.

- Before protease inhibitors

- Give the lifestyle recommendations for the patient with HCV infection.
  - 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 donatation of body organs, other tissue, or semen

Ribavirin (RBV)

- Give 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

- 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/μL	– Reduce peginterferon by 50%	– Monitor more closely
	1000/μL	– Stop treatment	– Monitor more closely; consider G-CSF
○ Absolute neutrophils	750/μL	– Reduce pegIFN by 50%	– Monitor more closely
	500/μL	– Stop pegIFN	– Monitor more closely

Laboratory	Level	Other clinical considerations
○ Platelets	50,000/μL – Reduce pIFN by 50%	– Individualize dose adjustment
	25,000/μL – Stop IFN	– Consider platelet transfusion or platelet stimulating factor

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- Overall dose reduction of ribavirin in19% of Ribavirin-treated persons, with discontinuation of Ribavarin in 10%

- 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 μg PEG alfa-2a or 1.5 μg/kg PEG alfa-2b	800-1400 mg/day weight-based	48	41-42%
2	180 μg PEG alfa-2a or 1.5 μg/kg PEG alfa-2b	800 mg/day	24	66-75%
3	180 μg PEG alfa-2a or 1.5 μg/kg PEG alfa-2b	800 mg/day	24	66-75%
4	180 μg PEG alfa-2a or 1.5 μg/kg PEG alfa-2b	1000-1200 mg/day	48	55%
5	180 μg PEG alfa-2a or 1.5 μg/kg PEG alfa-2b	1000-1200 mg/day	48	64%
6	180 μg PEG alfa-2a or 1.5 μg/kg PEG alfa-2b	1000-1200 mg/day	48	63%

Abbreviation: SVR, sustained viral response
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- 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			

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- 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: the paradigm shift in HCV treatment

- 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 and direct acting agents, the hope for the sustained eradication of HCV has gone from dismall 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 revolutional 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/

- Pharmaceutical therapy recommendations, genotypes and interferon eligibility

Interferon (IFN) eligibility

Eligible	Not eligible
Recommended regimen for treatment-naïve patients with HCV genotype 1 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 recommended for IFN-eligible persons with HCV genotype 1 infection, regardless of subtype. Rate: Class I, Level A	*Recommended regimen for treatment-naïve patients with HCV genotype 1 who are not eligible to receive IFN.* 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 IFN-ineligible patients with HCV genotype 1 infection, regadless of subtype Rating: Class I, Level B

Eligible	Not eligible
Alternative regimen for treatment-naïve patients with HCV genotype 1 who are eligible to receive IFN. ○ Daily simeprevir (150 mg) for 12 weeks and weight-based RBV (1000 mg [< 75 kg] to 1200 mg [≥ 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	*Alternative regimens for treatment-naïve patients with HCV genotype 1 who are eligible to receive IFN.* ○ Daily sofosbuvir (400 mg) and weight-based RBV (1000 mg [75 kg] to 1200 mg [≥ 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

Eligible	Not eligible
Recommended regimen for HCV genotype 1 PEG / RBV (without an HCV protease inhibitor) non-responder patients: ○ Daily sofobuvir (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	*Recommended regimen for HCV genotype 1 PEG / RBV (with an HCV protease inhibitor) non-responder patients:* ○ Daily sofobuvir (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	<u>Eligbility to receive IFN:</u> ○ 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
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] tto 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 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 currently 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 currently recommended for treatment-naïve genotype 3.

- PEG / RBV for 24 to 48 weeks

  Rating: Class IIb, Lvel 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
Recommended regimen for treatment-naïve patients with HCV genotype 4 who are eligible to receive IFN. ○ Daily sofobuvir (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	*Recommended regimen for treatment-naïve patients with genotype 4 who are not eligible to receive IFN.* ○ 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
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, Lvel A

- Monotherapy with PEG, RBV, or a DAA

  Rating: Class III, Level A

- Telaprevir-, boceprevir-based regimen

  Rating: Class III, Level A

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-eigible 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

Genotype	Recommended	Alternative	Not recommended
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

Genotype	Recommended	Alternative	Not recommended
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	PEG / RBV ± telaprevir or boceprevir
		SOF + RBV x 24 weeks	Monotherapy with PEG, RBV, or a DAA
		SMV x 12 weeks + PEG / RBV x 48 weeks**	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

Genotype	Recommended	Alternative	Not recommended
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 ans 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 preexistant 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

"All life is an experiment. The more experiments you make the better"

Ralph Waldo Emerson

Special considerations: Unique patient populations

- **Renal impairment**

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**

- Give 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

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

Genotype	Recommended	Alternative	NOT Recommended	Allowable anti-retroviral Therapy
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
3	○ SOF + RBV x 24 weeks regardless of treatment history	Treatment naïve and PEG / RBV relapsers: None Treatment experienced (prior PEG RBV non-responders) **IFN eligible:** SOF + PEG / RBV x 12 weeks **IFN ineligibile:** None	PEG / RBV x 24-48 weeks Any regimen with TVR, BOC, or SMV	All except didanosine, 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

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).

- Give the risk of cirrhosis, hepatocellular carcinoma (HCC) and mortality in hepatitis B and hepatitis C virus (HBV/HCV) monoinfected and coinfected 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)

- **HCV and Liver Transplantion**

- Give 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

SO YOU WANT TO BE A HEPATOLOGIST!

- Give 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

- 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 and HCC**

➢ Demography
  - Patient
    - Alcohol drinking (heavy > 50 gm/d)
    - Male gender
    - Larger BMI
  - Older age of HCV onset and diagnosis
  - HCV infection for > 25 years
  - Absence of previous HCV treatment
  - Failure of HCV to respond to IFN (interferon)

➢ Pathology
  - Some degree of hepatic fibrosis
  - Associated iron overload (including hereditary hemochromatosis)

➢ Pathophysiology

- Give the pathophysiology of the development of HCC in HBV infection, even in the absence of cirrhosis.
  - HBV is incorporated into cellular DNA (in 90% of HCC patients)
  - Chromosomal insertion is random
  - 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
    - HCV ~ 2/100 patient years
  - Presence of
    - EV ((esophageal varices)
    - Lab' abnormalities
      - ↓ platelets
      - ↑ AP (alkaline phosphatase)

➢ Risk factors

- Give risk factors for the development of HCC associated with HCV.
  - Male
  - Cirrhosis
  - Genotype HCV Ib
  - Long duration of HCV
  - Older age
  - Hepatitis B co-infection with HBV, HIV
  - Heavy alcohol intake
  - Obesity +/- NASH

Adapted from: Gores GJ. *AGA Institute Post Graduate course book* 2006: pg. 251-2.

HEPATOCELLULAR CANCER (HCC)

➢ Clinical

Auscultating an arterial bruit in the RUQ of a patient with cirrhosis suggests
- HCC.
- ↑ flow in HA (hepatic artery)
- Aneurysms

- 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

➢ Laboratory

SO YOU WANT TO BE A GASTROENTEROLOGIST!

- 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 diagnosticimaging, 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
- If ↑ AFP (serum alpha-fetoprotein) is present before locoregional therapy, the level may be used to follow response.
- If AFP falls, then begins to rise again, repeat diagnostic imaging is indicated.
- The drawback of the following serum AFP concentration is that only some HCCs are associated with an ↑AFP

Size of HCC	Elevation of AFP
- < 2 cm diameter	60%
- 2 cm to 5 cm	72%

- AFP
  - Performance depends on cutoff value: 20 mg/ml, sensitivity 25-65%
  - 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.)

- Give the circumstances when an elevated AFP (alfa fetoprotein) > 200 mg/mL is considered by AASLD guidelines to be diagnostic of HCC.
  - Cirrhosis, mass in the liver (especially when > 2 cm)

➢ Prognosis

Prognostic factors in HCC:

- Patient
  - ECOG classification
  - Presence of symptoms
- Liver function
  - Child-Pugh class
  - Serum bilirubin
  - Albumin levels
  - Presence/absence of portal hypertension

- Pathology
  - Risk of seeding from tumour biopsy ~ 3%
  - Not usually necessary to biopsy liver to diagnose HCC (compatible clinical presentation, plus two characteristically abnormal diagnostic imaging studies)

- Give the pathology of hepatocellular (HCC).

  - Gross
    - Nodules
    - Large circumscribed mass
    - Diffuse infiltration

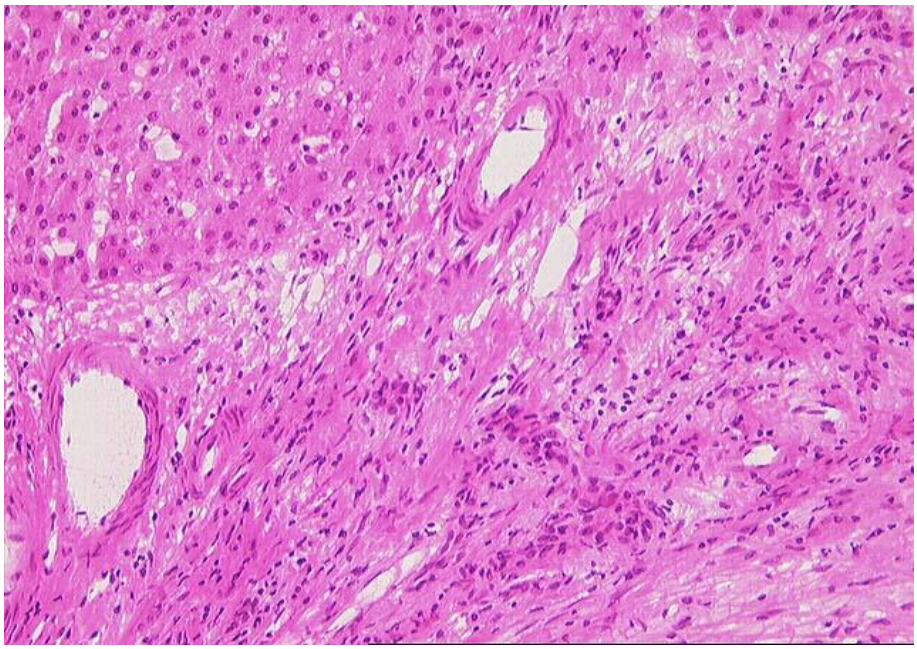
  - Microscopic
    - Well-differentiated
      - Trabecular form (thick trabeculae)
        - Hepatocytes – polygonal
        - Cytoplasm - ↓ eosinophilia
        - Nuclei
          - Large
          - Hyperdramatic
        - Nucleoli – prominent
        - Bile production

      - Acinar (pseudoglandular) form
        - Gland-lie structures arund a bile canaliculus
        - Bile canaliculus contains bile

    - Moderately differentiated
      - Pleomorphic, multinucleated giant cells
      - Cell nests
      - Central ischemic necrosis
      - Little bile connective tissue

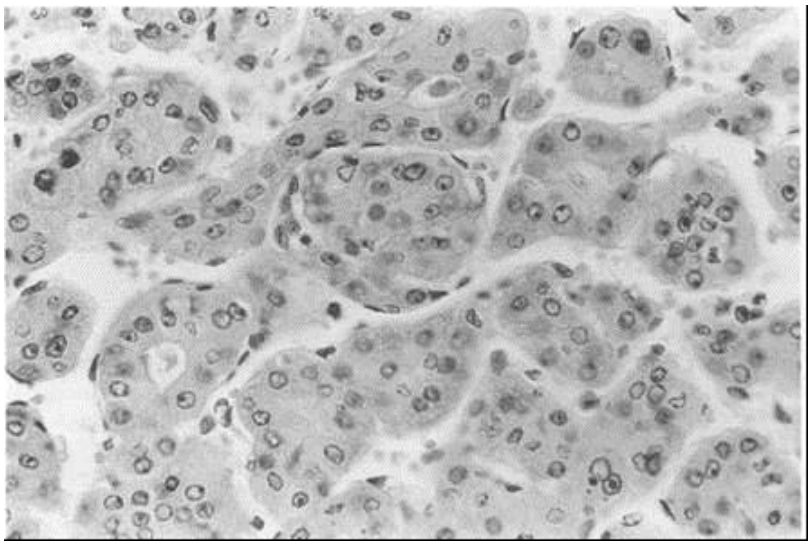
    - Differentiated
      - Pleomorphic cells and nuclei
      - Bizz are giant cells
      - Globular hyaline
      - Mallory hyaline

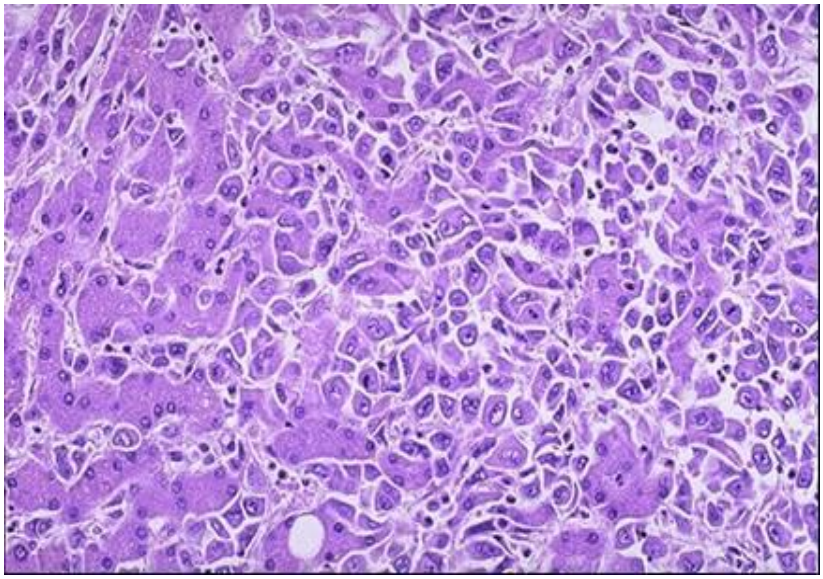
Case: Clinical vignette: A patient with known HIV and HBV from Calgary, AB, presents with worsening ascites and cachexia. You suspect hepatocellular carcinoma (HCC).



- 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 Patho*l 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.





- Give **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)
  - Alpha 1- antitrypsin deficiency
  - Congenital/familial

    - Previously resected HCC
        - 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)
        - M:F 2:1-4:1; increased BMI, androgenic hormones

Adapted from: Hytiroglou P, et al. *Gastroenterol Clin North Am* 2007;36(4):867-87.

- With cirrhosis
    - HCV
    - HCV +ALD + obesity (accelerated)
    - Alcoholic liver disease
    - 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

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.; and Kew MC. *Sleisenger & Fordtran's Gastrointestinal and Liver Disease: Pathophysiology/Diagnosis/Management* 2006: pg.2014; and 2010: pg. 1575.

SO YOU WANT TO BE A HEPATOLOGIST!

The presence of active inflammation increases the risk of HCC in the patient with chronic HCV infection.

- Give the type of T cells as well as 2 adduct inflammatory markers which reflect a poor prognosis in HCV associated HCC
    - CD 68-pos cells
    - 8-OHdG (8-hydroxydeoxyguanosine) DNA adducts
    - 4-HNE (hydroxynonenal) protein adduct

➢ Prognosis / risk stratification / staging

- Give the prognostic factors in HCC.
    - Patient
        - ECOG classification of HCC
        - Presence of symptoms
    - Liver function
        - Child-Pugh class
        - Bilirubin concentration
        - Albumin concentration
        - 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.

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- 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.

- Give 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

- Give the components of the **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.

- Diagnostic imaging
  - Hepatic nodules < 2 cm in diameter on imaging may still contain a focus of HCC.
  - Imaging techniques may show hypervascularization in the arterial phase, followed by washout in the venous phase, suggestive of malignancy.
  - Importance of DI in HCC
    - 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.
    - Hepatic regenerative activity → ↑AFP
    - Risk of seeding from tumour biopsy ~ 3%: this is why liver biopsy avoided if possible, and diagnosis of HCC may be from imaging studies.

- 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
  - Focular 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.

- 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**
  - 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

- Abdominal ultrasound
  - Sensitivity, > 60%, specificity, > 90%

- CT
  - Arterial enhancement (hypervascular, supplied by hepatic artery) and washout, for HCC, sensitivity is 90% and specificityis 95%
  - HCC hallmark on diagnostic imaging
    - Based on the dynamics of the arterial enhancement and delayed venous washout
    - Some features may also occur in cholangiocarcinoma
  - 4 phase hepatic tumour protocol for HCC
  - CT
    - Arterial neovascularization
    - ↓ HA, PV supply
  - Dynamic multiphase (dM) CT
    - Assess HA (hepatic artery) and PV (portal vein)
    - dM CT detects small HCC not found on conventional CT
    - Small HCC's may be iso-dense on conventional CT
  - 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)
    - Enhancement of the capsule in the porto-venous and delayed phase.
  - IOUS (intraoperative [including laparoscopic] ultrasound)
    - 16% of planned partial hepatectomy's may be canceled because of IOUS showing inoperability
    - may help to guide segmental or non-anatomic resections
  - Ideal for patients with good hepatic function (C-P class A)
  - Surgical resection (partial hepatectomy) in carefully selected patients potentially curative (5-year survival rates > 90%)
  - % off newly diagnosed HCC patients eligible for resections ~ 15%
  - Ideal patients
    - 1 tumor
    - Confined to liver (not IIIb, IIIc, Iva, IVb)
    - No hepatic vascular invasion
    - No PHT (portal hypertension)
    - Good hepatic functional reserve (C-P class A)

- "Shades of grey" - some hepatobiliary surgeon's will operate for stages
  - IIIB Invasion of PV (portal vein) or HV (hepatic vein)
  - IIIC Direct invasion of adjacent organs (other than gallbladder)
  - IVA Perforation of visceral peritoneum
  - IVB Nodal* or distant metastases
  - C-P B Child-Pugh stage B
- PVE (portal vein embolization) before partial hepatectomy for HCC (especially right side HCC) may lead to physiological hepatic hypertrophy
- Patients with cirrhosis may have benign lymphadenopathy at the portal hepatis, and in the portacaval space, so diagnostic imaging findings at these times does not necessarily signify HCC
- If the nodes have the same density as the HCC itself, biopsy the nodes to determine if they are involved (IVB), in which case partial hepatectomy might not be performed (please see above, "nodal or distant metastases")
- Fibrolamellar HCC can be resected together with lymph node resection

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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

- MRI
  - T2 hyperintensity
  - 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

- Gad-MR (gadolinium magnetic resonance)
  - The most sensitive and specific imaging technique for the diagnosis of HCC
- Other methods
  - Contrast-enhanced ultrasonography
  - Helical-computed tomography
  - Superparamagnetic iron oxide magnetic resonance (Lesni et al., AJC 2010; 105: 599-609).
- Fibrosis progression in HCC directly plus HBV related to viral load
- 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.

- Importance of size of HCCs
  - Only when factors other than the size of HCC are considered, is the prognosis affected, eg.
    - Operative risks
      - Comorbidities
    - Hepatic reserve C-P stage
    - Vascular invasion
    - Metastases
    - Territorial perforation and seeding
    - Multifocal HCCs
  - With HCC ≥ 10 cm) the overall program survival rate is 27%

- For the patients with these larger (≥ 10 cm) HCC, factors which identify the patient with a poorer outcome from hepatic resection (partial hepatectomy) include
  - Multiple HCCs (↑ T classification)
  - Vascular invasion
  - Severe fibrosis
  - AFP ≥ 1000 ng/mL

➢ Importance of size and function of liver
  - Hepatic volumetry
  - 15 min clearance of ICE-15 (indocyanine green)
  - WHVPG (wedge hepatic venous pressure gradient, to exclude significant portal hypertension)

- 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

- Give 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 T_2, 150-T_1)
  - 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, αAT deficiency

Adapted from: Talwalkar JA, and Gores GJ. *Gastroenterology* 2004;127(5 Suppl 1):S126-32.

- Screening / surveillance
  - In patient with cirrhosis, perform screening abdominal ultrasound and then q 6 mon
  - 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

- 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

- Give the risk of cirrhosis, hepatocellular carcinoma (HCC) and mortality in hepatitis B and hepatitis C virus (HBV/HCV) monoinfected and coinfected 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

[1]Zarski et al, 1998
[2]Shi et al, 2005 Donato et al, 1998
[3]Amin et al, 2006 Di Marco et al, 1999

Printed with permission: Wursthorn, et al. *Best Practice Res Clin Gastroenterol* 2008;22:1063-1079.

"Doing the best at this moment puts you in the best place for the next moment."

Oprah Winfrey

SO YOU WANT TO BE A HEPATOLOGIST!

The AASLD recommends ultrasonic surveillance (US) for selected HBV infected persons every 6 months. This provided superior survival than when US is performed every 12 month. When US is performed at three month screening intervals more small (< 10 mm diameter) lesions are found.

- Give the reason why this 3 month rather than 6 month US screening interval is not recommended.
  - Survival from HCC depends on several factors such as the size of the tumor and not the risk of having an HCC.
  - Focal lesion < 1 cm may not be HCC; by performing US every 3 months, when > 1 cm, perform more sensitive diagnostic imaging for HCC characteristics of ↑ arterial vascularity; and venous phase washout.
  - It is the larger tumor which is more likely to grow even larger, and to spread and worsen prognosis.
  - There is no difference in
    - The quantitative incidence of the development of HCC if focal lesion were detected by US by 3 or 6 months screening intervals
    - Survival, decompensation or liver transplantation

CT scanning and performing serial AFP measurements increased sensitivity for finding HCC, but are **not** recommended for screening.

- Give the reason why:
  - Combining ultrasonography (US) of the liver to detect a focal lesion is associated with an increased rate of false positives, as also is CT screening.
  - If a focal lesion is identified on US, then contrast diagnostic imaging is recommended
    - 4-phase CT scan
    - Dynamic contrast enhanced MRI

CLINICAL ALERT

Although, US screening is recommended for certain groups of patients with chronic liver disease with or without cirrhosis, the benefit for the reduction of mortality from HCC has actually been proven only for HBV.

➢ Causes / associations

- Give 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: Hytiroglou P, et al. *Gastroenterol Clin North Am* 2007;36(4):867-87.

➢ Prevention

- Give steps to reduce the incidence of HCC.
  - Prevent and treat HBV and HCV, including
    - Immunization programs for HBV
    - Safe injection practices
    - Surveillance programs for HCC
  - Change lifestyle
    - Alcohol
    - Smoking
    - Obesity
    - Diabetes
  - Avoid
    - Alpha toxin
    - High intake of red meat/saturated fats
    - Betal nuts
  - Improve quality of drinking water

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

Grandad

➢ Treatment

- Give the **management strategy** of HCC based on CTP class, size and performance status.

○ CTP A, PS-O	– Single HCC < 2cm	– HVPG <10mm Hg and bilirubin < 1.5 mg/dL – Varices/collaterals or HVPG – > 10 mm Hg or bilirubin > 1.5mg/dl	– Surgical resection – Live transplant evaluation – RFA/PEI
○ CTP A-B, PS, 0-2	– Single HCC 2-5 cm	– HVPG <10 mm Hg and bilirubin < 1.5 mg/dL – Varices/collaterals or HVPG – > 10 mm Hg or bilirubin > 1.5mg/dl	– Surgical resection – Liver transplant evaluation – RFA/PEI
	– 2 or 3 HCC masses <3 cm (the largest) – Intermediate stage (multinodular, PS,O) – Advanced stage (portal invasion, metastases)		– Liver transplant evaluation – Radiofrequency ablation – Transarterial chemoembolization – Sorafenib
○ CTP C, PS>2	– Terminal stage		– Symptomatic treatment, palliative care

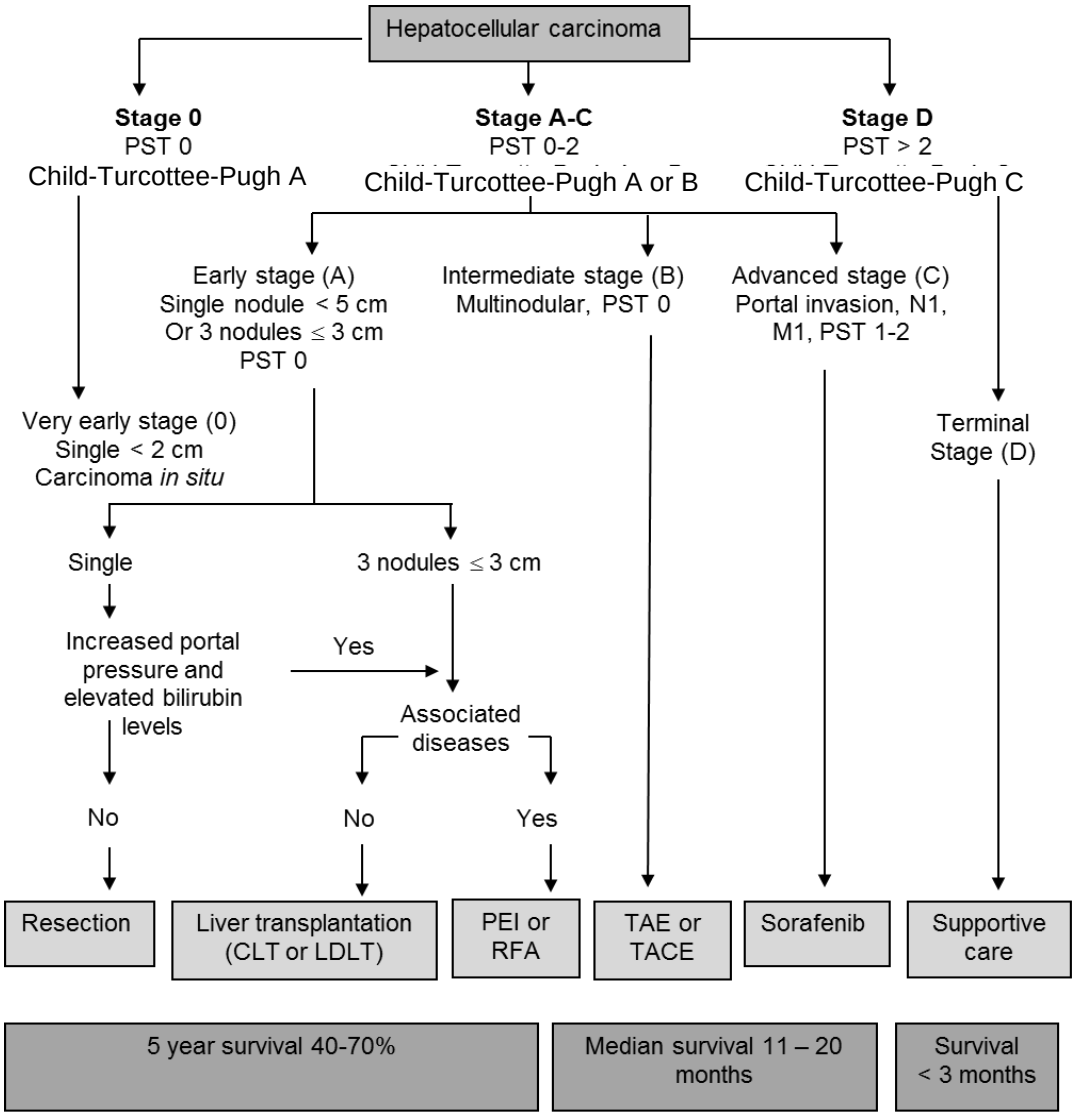
Abbreviations: CTP, Child-Turcotte Pugh; HCC, hepatocellular carcinoma; HVPG, hepatic venous pressure gradient; PEI, percutaneous ethanol injection; PS, performance status; RFA, radiofrequency ablation.

Printed with permission: Garcia Tsao, et al. *The American Journal of Gastroenterology* 2009; 104:1824.

Review the "**menu**" (possible options) of **treatments** for HCC.

- Comprehensive Care
  - Continue appropriate antiviral therapy for HBV, HCV
  - Give appropriate immunizations, eg. HAV, HBV
  - Screening/surveillance for EV (esophageal varices)
- Surgery
  - Resection (partial hepatectomy)
  - Liver transplantation (orthoptic)
  - LDLT (living donor liver transplantation)
- Radiation
  - RFA (radio frequency ablation) +/- neoadjuvant pegylated liposomal doxorubicin or +/- TACE
  - Radioembolization
  - Radiation therapy
    - External beam
    - IMRT (intensity modulated RT)
  - 3D-CRT (three-dimensional confirmal radiation techniques)
  - SBRT (stereotactic body irradiation therapy)
  - PBRT (proton beam radiotherapy)
- Percutaneous
  - Ethanol for acetic acid injection (PEI)
  - Cryoablation
  - PVE (partial vein embolization alone, without chemotherapeutic agent, or with TACE ["double embolization])
  - Laser ablation
  - Microwave ablation
- Drugs
  - TACE (Transarterial chemo embolization into HA [hepatic artery], with or without
    - Lipiodol
    - Procoagulant
    - Drug eluting beads
    - Simultaneous or sequential occlusion of HA (PVE)
  - Systemic chemotherapy
  - Tyrosine kinase inhibitors
  - Interferon - Licartin

- Give the Barcelona Clinic Liver Cancer **(BCLC) algorithm for staging and treating** patients diagnosed as having hepatocellular carcinoma.



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.

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- 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.

- Give treatment options for the patient with HCC.
    - Staging, MRI – Barcellona 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 mm^3
        - 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: somastostatin, immune modulation, gene therapy, PDT
    - Mixed tyrosine kinase inhibitors (sorafanib)

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.

- 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
- Sorafanib, a mixed kinase inhibitor, prolongs survival in persons with metastatic HCC

- Give a comparison of 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) – Nucleos (t) ide analogues	▪ Antiviral therapy (eradication) ▪ 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.

- 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.

Details of Treatment Options

- **Radiofrequency ablation (RFA)**

➢ Indications

- May be used in C-P class B, or larger tumors confined to the liver
- Most useful to treat
    - HCC < 4 cm
    - HCC recurrent after surgical resection

➢ Procedure

- Each treatment destroys a 3 cm sphere of tumor.
- Frictional heat more than 60°C is generated at the tip of electrode which is placed into the HCC, resulting in necrosis of the tumor.
- 1 application (treatment) is performed at a time
- The zone of coagulation necrosis may be increased from 3 cm to 3.4x larger by giving pegylated liposomal doxorubicin 20 mg IV once 24 hr before RFA treatment.
- TACE may be given as neoadjuvant therapy to RFA.
- Route for RFA for HCC
    - ≤ 3 cm – percutaneous
    - > 3 cm - laparoscopic or laparotomy route for larger tumors

➢ Contraindications

- HCC in the dome of the liver
- HCC in the inferior edge of the liver, especially if the inferior edge HCC is close to the stomach, duodenum or transverse colon.

- Response rates (complete necrosis) of HCC
  - Size
    - < 3 cm — 80% to 90%
    - 3 cm to 5 cm — 50% to 70%
  - Perivascular
    - Yes — 47%
    - No — 88%

- Outcome
  - Local recurrence rates 3% to 6%
  - 3 yr and 5 yr survival rates
    - 1 tumor < 5 cm, 70% to 91%
    - ≤ 3 tumors each ≤ 3 cm, 48% to 77%
    - ≤ 2 cm, 91%
    - 2.1 cm to 5 cm, 74%
    - > 5 cm, 59%
  - Comparative outcomes
    - RFA is superior to PEI for
      - ↑ survival
      - ↑ cancer-free survival
      - ↓ local recurrence
    - Resection is superior to PEI
      - ↑ survival
      - ↑ cancer-free survival
      - ↓ local recurrence
    - Resection is superior to RFA (especially for tumors > 3 cm)
      - ↑ 3 yr overall survival, OR 0.56
      - ↓ local recurrence

Abbreviations: PEI, percutaneous ethanol injection; RFA, radiofrequency ablation

  - Adverse outcomes
    - Major morbidity* — 2.2% to 11%
    - Mortality rate — 0.3% to 0.8%

*the complication is often PVT (portal vein thrombosis), which occurs especially in cirrhotics

SO YOU WANT TO BE A HEPATOLOGIST!

- In the context of partial hepatectomy for HCC, give the explanation for what is the “pringle maneuver”.
    - The usual principal for clamping the blood vessels at the time of hepatic resection is to achieve total vascular occlusion (PV [portal vein], HA [hepatic artery], and IVC [inferior vena cava, both supra- and infradiaphragmatic portions]).
    - In the contrast to total vascular occlusion, the Pringle maneuver achieves intermittent occlusion by way of clamping just the hepatoduodenal ligament.

CLINICAL TIP

The post ablation syndrome” has been described after hepatic chemoembolization for HCC, and less often after RFA.

- Give the features of the **post-ablation syndrome**.
    - General
        - Fever
        - Malaise
    - GI
        - Nausea
        - RUQ pain
    - Lab’
        - ↑ ALT / ↑ AST

- **Percutaneous Ethanol Injection (PEI)**

➢ Indication

- Cirrhotic patient (low hepatic reserve) with HCCs < 5 cm (high risk of HCC recurrence: e.g. For tumor ≤ 3 cm, recurrence rate is 38%)
- Non-resectable patient not suitable for RFA because of location of HCC eg.
    - Next to the gallbladder
    - Adjacent to hepatic hilum
    - Close to blood vessel

- Outpatient
- Inpatient (general anaesthesia)
  - Multiple injections over 30 min
- The HCC patients who will do best from TACE are those with
  - Large HCC
  - Non-surgical candidate
  - Child-Pugh class A or B cirrhosis
  - no extrahepatic spread
  - no vascular invasion
  - Neoadjuvant therapy (before hepatic resection)
  - "Bridging" for orthoptic liver transplantation (LT) (allows "down staging"of HCC in 25%, making patient suitable for LT by the Milan criteria.

SO YOU WANT TO BE A HEPATOLOGIST!

TACE is useful for HCC which is not resectable, or where there are multifocal HCCs not suitable for other locoregional therapies, all for "bridging" therapy while awaiting LT.

- Give the role of TACE as neoadjuvant therapy before partial hepatectomy.
  - None! TACE given before resection for HCC actually increases mortality!

- Procedure
  - Injections of 95% pure alcohol
  - Results in
    - Thrombosis in microvasculature of HCC
    - Tissue ischemia
    - Coagulation necrosis around area of injection
    - Fibrous reaction
- Contraindications
  - HCC in the dome of liver
  - Extrahepatic disease
  - HCC volume > 30% of liver volume

- Patient
  - PVT (portal vein thrombosis)
  - C-P class C
  - PT > 40% of normal
  - Platelets 40, 000 µL

➢ Outcomes

- Complete response depends on HCC size

Size, cm	Complete response	Local recurrence
< 2	100%	
< 3	70% to 80%	10% to 33%
> 3	50% to 60%	44% to 50%

- Survival rates (SR) with PEI

Description of HCC	5-yr survival rates
– Size	
▪ < 3 cm	40% to 54%
▪ 3 cm to 5 cm	32% to 37%
▪ 1 HCC < 2cm	54%
▪ 2 cm to 5 cm	39%
– Child-Pugh Class A	
▪ C-P A	51%
▪ C-P B	0%

➢ Complications

- Give major complications of PEI.
  - Liver
    - Failure
    - Bleeding (intraperitoneal)
    - PVT (portal vein thrombosis)
    - Infarction
  - Bile duct
    - Necrosis
    - Fistula
  - General
    - Hypotension
    - Renal failure

- Comparisons
  - Size of HCC ≤ 2 cm, RFA = PEI
  - RFA superior to PEI > 2 cm
    - Overall survival – OR 1.92
    - Cancer-free survival – OR 2.72
    - Local recurrence – OR 0.29
  - PEI similar to surgical resection (partial hepatomy [PH]
    - For 1 small HCC, PEI=PH
    - For 1 HCC < 4 cm, PEI < PH
    - For 1 HCC ≤ 5 cm, PEI=PH
  - PEI plus TACE

Outcome	PEI +TACE	PEI
Residual HCC		
- 1 yr	3.7%	34.1%
- 3 yr	19.3%	39.3%
Survival rate		
- 1 yr	100%	91%
- 3 yr	81%	66%
- 5 yr	40%	38%
Complications of PEI		
- Mortality	0%	
- Morbidity	2.2%	

Abbreviations: PEI, percutaneous ethanol injection;TACE, transarterial chemoembolization

- **Transarterial chemoembolization (TACE)**

- Indications
  - Often used for
    - Large unresectable HCC (nonsurgical candidate), and not suitable for local ablation (i.e. advanced disease), e.g. HCC > 10 cm or multifocal tumors not suited for other locoregional Rx.

- Procedure
  - The HA is catheterized, the blood vessels feeding the HCC are identified, and the chemotherapy is infused into the second- or third-order branches of the right or left hepatic artery (selective and super selective branches, respectively).

- Injection of chemotherapeutic agent with or without lipiodol or a procoagulant agent, or beads, or simultaneous or sequential occlusion of HA (PVE, portal vein embolization) into the HA (the hepatic artery, the major blood supply for the HCC).
- The HA supplies blood to the HCC whereas the PV (portal vein) supplies the rest of the liver.
- There is no evidence of a benefit using the lipiodol or gelatine vs. PVA (polyvinyl alcohol.
- TACE may be followed by PVE (" double embolization"), and when given prior to resection (neoadjuvant therapy) may be beneficial, especially when the right side of the liver is involved, and the resection will be a right hepatectomy.

- **TACE plus sorafenib**
  - HCV associated HCC, C-P score A
  - If there is complete response to TACE, the TACE may be followed by sorafenib 400 mg po bid or placebo
  - TACE-sorafenib is associated with ↓ intrahepatic recurrence of HCC in 6 months: 22% vs. 77%

- **TACE with doxorubicin** (drug-eluting beads)
  - Promising initial non-placebo controlled studies in C-P class A or B cirrhosis
  - 6 month response:
    - CR plus PR (complete plus partial response), 58%
    - Stable disease, 39%
    - Progression, 1%
  - There is no consensus as to which chemotherapeutic agent to use, e.g. Doxorubicin
    - TACE may be combined with sorafenib
    - TACE may be used with drug imbeaded beads
  - TACE may be repeated on multiple occasions, unless extent of ischemic hepatic damage puts patient at risk of liver failure.

- TACE, or bland embolization must not be done if there is already impaired hepatic function or if there is a risk of the blood supply to the remainder of the liver being compromised;
  - PVT (portal vein thrombosis)
  - HE (hepatic encephalopathy)
  - Biliary obstruction
  - Child-Pugh C cirrhosis
- It is possible to make cautious use of TACE or HA embolization under the following conditions:
  - PHT / decompensation
    - Ascites
    - EVB (esophageal variceal bleeding) in recent past
    - Thrombocytopenia
    - Macroscopic vascular invasion
  - Comorbidities
    - Cardiac failure
    - Renal failure
  - HCC > 50% of the liver
  - Lab serum abnormalities
    - ↑ Bilirubin > 2 mg/dL
    - ↑ LDH > 425 U/L
    - ↑ ALT > 100 U/L

➢ Complications

- Give serious complications of TACE.
  - Liver failure (~7.5%)
    - From ischemic necrosis, which may produce or worsen liver failure
  - Upper GI bleeding (3% to 5%)
    - From TACE entering gastroduodenal arteries (right or left gastric artery)
  - Biliary tree (2%)
    - Strictures
    - Dilation
    - Cholecystitis
  - Kidney (2%)
    - Renal failure
  - Lung
    - Interstitial pneumonia (80% mortality rate)
    - Pulmonary embolus from lipiodol
  - Brain
    - CVA from lipiodol embolus
  - Mortality from TACE 2% to 3%

Abbreviation: CVA, cerebrovascular accident

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.

- Give the likely explanation for development of hepatic decompensation after TACE.

    - 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.

- **Cryoablation**

➢ Procedure

- Percutaneous insertion of cryoprobe into HCCs with circulation of argon gas or liquid nitrogen.
- Alternating freezing and thawing of HCC causes necrosis and an ice ball.

➢ Outcome

- Cryoablation has largely been replaced by RFA, because of lower HCC recurrence rates (2% vs. 14%), and lower complication rates (3% vs. 41%).

- **Laser ablation**

➢ Procedure

- Percutaneous ultrasound guided laser ablation of HCC

➢ Outcome

- Outcomes for 1 HCC ≤ 4 cm, ≤ 3 HCC ≤ 3 cm each
    - Complete initial response 78%
    - Median disease-free survival 26 month
    - Cumulater survival rates
        - 3-year 61%
        - 5-year 61% to 24%
    - Mortality rate from treatment < 1%

Clinical interest: laser ablation of HCC destroys the tumor, but laser ablation may also be used for a tumor thrombus causing PVT (portal vein occlusion due to portal vein thrombosis).

- **Microwave ablation (MWA)**

➢ Procedure
  - Implanted electrode can be used for multiple applications to deliver high frequency energy to HCC

➢ Outcome
  - Complete response rates 89% to 95%
  - Survival rates
    - 3-year 51% to 81%
    - 5-year 52%

➢ Comparison
  - MWA equivalent to RFA (HCC < 4 cm)

Outcome	MWA	RFA
– Complete response rate	89%	96%
– 2-year local recurrence	24%	12%

- **Portal Vein Embolization (PVE)**

➢ Procedure
  - Two types of PVE
    - TIPE
      - Transileocolic portal embolization
    - PTPE
      - Percutaneous transhepatic portal embolization
  - May be performed by itself or with TACE.
  - May lead to physiological hypertrophy of the remaining liver (10% ↑ hepatic volume).
  - May be a bridge to partial hepatectomy.

- Outcome

Benefit	With PVE	Without PVE
90-day mortality rate	0%	18%
Major complications	10%	36%
Liver volume (median standardized future live remnant volume)*		
– Pre	23%	NA
– Post	34%	NA

* predicts post-resection mortality in cirrhotics

Abbreviations: NA, not applicable / not available; PVE, portal vein embolization

- **External Beam Radiation Therapy (RT)**

- Procedure
  - External beam RT
  - Improvements with delivery of radiation beam by
    - IMRT (intensity modulated RT)
    - 3D-CRT (3 dimensional conformal radiation techniques)
    - May be used with TACE open PV obstruction caused by a tumor thrombus
    - Stereotactic body (SB) RT (SBRT)
    - May deliver up to 100 Gy of radiation
    - Multiple targeted treatments of hepatic as well as extracranial HCC
    - Promising early results

- Outcome
  - High rate of tumor recurrence

- **Radioembolization**

- Procedure
  - 90 Y (yttrium) - class microspheres or lipiodol labelled with 131 I (iodine-131) injected into HA.

- Indications
  - Advanced disease, but life expectancy > 3 months
  - PVT (portal vein thrombosis)
  - Bridging/down staging for partial hepatectomy, or liver transplant
- Contraindication
  - Pre-treatment 99 mTc scan remonstrating risk of lung or intestinal potential from radiation damage
  - Limited hepatic reserve, including previous mediation
- Outcomes
  - Probably similar to TACE: median TTP (time to [tumor] progression), 7.9 months
- Complications
  - Post embolization syndrome (20% to 55%)
  - Hepatic failure (up to 4%)

- **Systemic Cytotoxic Chemotherapy**

- Procedure
  - May have benefit for patients with advanced unresectable HCC not suitable for locoregional therapy, and without C-P class C cirrhosis.
  - There is a wide range of chemotherapeutic agents studied:
    - Doxorubicin, with or without tamoxifen
    - 5-FU (5-fluorouracil), with or without leucovorin
    - Gemcitabine, with or without cisplatin or pegylated liposomal doxorubicin.

CLINICAL CAUTION

- Beware the use of chemotherapy in HCC
  - No benefit as adjuvant (post partial hepatectomy) therapy in terms of in patients with biopsy proven cirrhosis who have had an hepatic resection for HCC, adjuvant chemotherapy actually ↑ mortality

SO YOU WANT TO BE A HEPATOLOGIST!

Systemic cytotoxic chemotherapy is not often been used for the treatment of HCC, because the tumor may respond poorly, especially if the patient has cirrhosis

Give 3 molecular or biochemical factors which contribute to the refractory nature of HCC towards systemic chemotherapy.

- The related chemotherapy refractory nature of HCC may be related to its
  - High expression of
    - P-glycoprotein
    - Glutathione-S-transferase
    - HSPs (heat shock proteins)
  - p53 mutations

- Outcomes
  - Possible combinations
    - Aggressive therapy for young, health HCC patients
      - Doxorubicin, cisplatin and IFN α
      - Doxorubicin, cisplatin and 5-FU
    - For older or frail HCC patients
      - Capecitabine
    - Sick or jaundice HCC patients
      - 5-FU plus leucovorin

- Thoughtful considerations
  - Treatment decisions about your individual patient must be made on the basis of what is best for that individual.
  - The availability of funding for a diagnostic procedure or treatment may however be by public or private providers, which limit approved management.
  - "Cost-effectiveness analysis suggests that surveillance for HCC patients who are hepatitis B carriers is cost effective once the annual incidence of HCC exceeds 0.2%". (Sherman M, UpToDate, 2012).
  - The quoted risk for location HBV carriers to develop HCC is less than 0.2% per year. As such, some might argue that HCC surveillance not be offered to these persons.

Pharmaceuticals

- **Tyrosine kinase inhibitors (TKI)**
  - Sorafenib
    - Multi-target TKI
    - Useful for advanced HCC
    - For not yet proven adjuvant therapy of HCC
    - TKI inhibits Raf kinase and VEGFR (vascular endothelial growth factor receptor)
    - 400 mg po bid
    - Prolongs survival by about 2 months to 3 months in persons with advanced HCC, although those with HCV associated HCC may enjoy a slight better response
    - Less effective in C-P class C than A or B
- **Interferon (IFN)**
  - IFN α given IM after hepatic resection for HBV-associated HCC was beneficial adjuvant therapy, as compared with partial hepatectomy and no IFN α.
    - 2-year mortality rate RR 0.65
    - HCC recurrence RR 0.86
  - MicroRNAs (miRNAs) modify the post transcriptional expression of genes
  - HBV infected HCC patients with ↓ miRNA-26 responded to adjuvant IFN.
- **Biologicals**
  - Licartin is a 131-I-radio labeled murine monoclonal antibody.
  - Targets HAb18G/CD147 on HCC.
  - For HCC positive for HAb18G/CD147 on HCC (immunohistochemistry) of liver biopsy, this biological improves outcomes.

Outcome	Licartin	No Licartin
HCC recurrence	27%	57%
1-year survival	83%	62%

Surgery for HCC

- **Resection**
  - No cirrhosis
    - Couinaud anatomical segments
    - Remove up to 66% of functional hepatic parenchyma
    - Use laparoscopic and IOUS (intraoperative ultrasound) to identify which inflow portal and outflow hepatic veins to ligate at the time of resection
  - Cirrhosis
    - Anatomic or wedge resection
    - May removes no more than 25% of functional hepatic parenchyma
    - PVE may be used preoperatively to cause hypertrophy of hepatic parenchyma and thus ↑ functional hepatic parenchyma
  - Anterior “no touch” technique
    - ↓ hospital mortality (10% to 1.7%)
    - ↑ median overall survival on 23 months to 68 months
  - Centrally located tumors (segments IV, V, VII)
    - Extended right hemihepatectomy, or left hemihepatectomy
    - Central hepatectomy (mesohepatectomy)
  - Minimally invasive surgery
    - Similar 3’ and five year survival rates, as compared to open surgery
    - Shorter operative time and blood loss

Abbreviation: PVE, portal vein embolization

➢ Early (perioperative) mortality

- Give factors which increase early (perioperative) mortality rate from hepatic resection for HCC.
  - Presence of cirrhosis

	30-day postoperative mortality rate
- No cirrhosis	0.8% to 7%
- Cirrhosis	14% to 24%

- ↑ risk from liver failure with
  - Cirrhosis
  - Intraoperative blood loss > 1500 mL
  - Postoperative infection
  - Failure to perform hepatic volumetric assessment to determine when PVE would be beneficial
- Ferequency of complication
  - Perioperative bleeding, < 10% of complications
  - Bile leak, 8%
  - Pleural effusion, 7%

➢ Post resection surveillance for recurrent HCC

- Ultrasonographic imaging every 3 months to 6 months for two years, then annually
- Serum AFP; if initially increased, then repeat every 3 months or two years, then every 6 months

➢ Spontaneous HCC rupture

- 10% of HCC rupture spontaneously
- 38% 30 day mortality
- ↓ outcomes from hepatic resection

Outcomes	Rupture-neg	Rupture-pos
– Median survival, month	49	26
– Extrahepatic recurrence, %	26	46

➢ Late mortality

- Give factors which predict lower late post-resection mortality.
  - TNM stage

	TNM stage	5-yr survival rate
Stage I	(T1)	55%
Stage II	(T2)	37%
Stage III	(T3a, T3b, T4)	16%

- HCC prevalence area

Prevalence area	5- year survival rates
– Low	27% - 49%
– High	11%

- C-P class
  - Mortality rates tend to be higher when hepatic resection is for HCC < 5 cm in a C-P class A patient, as compared with HCC > 8 cm in C-P class B or C.
- PVE plus major hepatectomy

  PVE ↑ five-year overall survival as well as DFS (disease-free survival)
- Portal oriented resection
- Negative resection margin of +/- 1 cm
- No vascular involvement
- No cirrhosis vs. cirrhosis lowers survival from 81% to 35%, respectively
- Inactive HBV infection (if HCC related to HBV)
  - HCC risk areas frequently have HCC associated with HBV infection
- If recurrence occur intrahepatic recurrences have a better prognosis than extrahepatic HCC recurrences.

- Liver transplantation (LT; cadaveric liver; aka deceased donor liver transplantation {DDLT])
  - Ideal for patients with poorer hepatic reserve function eg. Cirrhosis (i.e. patients who would not be a candidate for resection)
    - In carefully selected patients, 3-4 year survival rates of 75% to 85%
  - Ideal patient
    - Early-stage HCC eg.
    - 1 HCC ≤ 5 cm diameter, or
    - ≥ 3 HCC, largest of which is ≤ 3 cm
    - No gross vascular invasion
    - No nodal or distant metastases
    - Adequate hepatic reserve
  - Allocation of donor liver
    - Based on MELD score, modified for HCC based on Milan or UCSF criteria (tumor size, number) ALTSG modification of the TNM staging system (stage II), and ones on the LT waiting list.
  - While waiting for LT (Orthoptic liver transplantation), use bridging therapy with TACE or RFA for “down-sizing” of HCC to meet criteria for LT.

- Immunosuppression (IM) for Liver Transplantation for HCC
  - Necessary to ↓ risk of graft rejection
  - IM may ↑ reactivation of HBV, HCV / HSV
  - Maintain lowest possible levels of IM (eg. serum cyclosporin, ≤ 190 ng/mL)
  - Sirolimus may be superior to tacrolimus or cyclosporin used for LT for HCC:
    - Fewer post-LT recurrence of HCC
    - ↑ post-LT recurrence
      - HR, 0.53
      - OR (5-yr), 2.47
    - ↓ HCC recurrence
      - OR, 0.42

- LDLT (living donor liver transplantation)
  - LDLT compares favourable with DDLT (deceased donor liver transplantation) in terms of
    - 5-yr. HCC recurrence (12% vs. 14%), and
    - Overall survival (70% and 71%, respectively)

CLINICAL CURIOSITY

The HCC patient who has TACE or RFA as a "bridge" to LT while being a wait-listed patient, and who has a complete response for at least 60% HCC tumor necrosis from the adjuvants, locoregional therapy has a better outcome once the liver transplant has been performed.

  - Depending upon patient selection, outcomes may be as good as hepatic resection or locoregional treatments, especially when HCC is associated with limited hepatic reserve, i.e. cirrhosis, and when there is only one tumor < 5 cm.

HCC treatments	Survival rates	
	3 year	5 year
– Orthoptic liver transplantation	72%	68%
– Hepatic resection	64%	44%
– PEI (percutaneous ethanol infusion)	54%	36%
– TACE	32%	22%

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Depending upon the country, the Milan or the UCSF (University of California, San Francisco) criteria are used for LT (liver transplantation) for HCC.

- Give the Milan and the UCSF criteria for liver transplantation for HCC.

Tumor	Milan	UCSF
○ 1 tumor	≤ 5 cm	≤ 6 cm
○ ≤ 3 tumors	None > 3 cm	Total tumor diameter ≤ 8 cm
○ No macrovascular involvement		
○ No extrahepatic metastasis (lymph nodes, abdominal organs, lungs, bones)		
○ Note: in the original Mazzaferro studies which established the Milan criteria, HCV- associated HCC was a predictor of poor prognosis.		

Assessing response of locoregional therapy of HCC

- Diagnostic imaging
  - Assessment is derived from measurements made from dynamic CT or MRI, usually performed one month after the locoregional therapy.
  - The objective of locoregional therapy of HCC is to cause necrosis of the tumor.
  - Numerous outcome measures are used to assess the benefit of therapy,
    - Overall survival
    - Disease-free survival
    - Rate of tumor recurrence
  - For locoregional therapies, the unidimensional RECIST criteria or the bidirectional WHO criteria may be used to assess the extent of HCC necrosis.
  - Using this diagnostic imaging approach, several terms are used to describe response:

– CR (complete response)	▪ No uptake of contrast into the tumor ▪ This complete response is thought to signify complete necrosis of HCC
– PR (partial response)	▪ A > 50% decrease in uptake of contrast, as determined by comparing pre- and post- treatment enhancement
– PD (progressive disease	▪ A 25% increase size of ≥ 1 measurable HCC, or ▪ A new HCC lesion

FIBROLAMELLAR HCC

- Histopathology
  - Hepatocytes
    - Large
    - Eosinophilic
  - Cytoplasm
    - Large mitochondria
    - Hyaline bodies
  - Fibrous stroma
    - Forming trabeculae or nodules
  - Stain for cytokerain 19 to determine if the HCC is the even more aggressive progenitor cell variety arising from stems cells near the canals of Hering

- Give the non-pathological characteristics which differentiate FLM (fibrolamellae HCC) from HCC.
  - Younger persons
  - Not associated with
    - Cirrhosis
    - HBV, HCV
  - No AFP secreted
  - Better prognosis

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

Apoorve Dubey

OTHER HEPATOTROPIC VIRUSES

- **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-RVA-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

"Let's change the interactions between alerting, orienting and executive functions, and control in a standard curing paradigm."

…..Grandad

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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 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%)

- 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)**

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

- Laboratory

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

- Give 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

- Histopathology

- 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.

- Give 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

➢ Clinical

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

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- Give the 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-High-Curtis is perihepatitis, usually caused by salpingo-oophoritis from

- Chlamydia trachomatis
- Gonococcus

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- 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
  - Anchovy 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

- Clinical (acute)
  - General
    - Fever
    - Rigors
    - Bleeding
  - Clinical
    - Eyes
      - Conjunctivitis
      - Jaundice
    - Heart
      - Temperature-pulse dissociation
    - Lung
      - Cough, no sputum
    - MSK
      - Myalgias
    - Kidney
      - $\downarrow Na^+$, $\downarrow K^+$
      - Renal insufficiency
    - Hematology
      - lymphadenopathy
    - Liver
      - ALF (rare)
  - Laboratory
    - ↑AST, ↑ bilirubin

Amebic Liver Disease

- Clinical
  - 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 attention (dark)
    - Enhancing rim of hepatic tissue

- Give 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

- Treatment

- Give 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

Echinococcal ("hydratid") Cyst of the Liver

- Demography
  - Sheepherder (also think of fasciolosis)
- Cinical
  - 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

Liver Parasites

- Give the likely hepatic parasitic infection for 15 of the following "**buzzwords**" or associations for liver parasites.

Association	Associated Condition (s)
o Abscess filled with "anchovy paste"	Amebiasis
o Anaphylaxis after cystic rupture	Echinococcosis
o Biliary ductal fibrosis	Clonorchiasis
o Contaminated freshwater plants	Fascioliasis
o Cyst filled with "hydrated sand"	Echinococcosis
o Cyst surrounded by "daughter cysts"	Echinococcosis
o Epilepsy	Schistosomiasis
o Gallstones	Clonorchiasis
o Hepatic abscess with elevation of right hemidiaphragm with adhesion obliterating the costophrenic angle	Amebiasis
o Liver cysts with eggshell calcifications	Echinococcosis
o Portal hypertension without stigmata of chronic liver disease	Schistosomiasis
o Portal vein granulomas and fibrosis	Schistosomiasis
o Reduviid bug (aka "kissing bug")	American trypanosomiasis (aka Chagas disease)
o Sandfly	Leishmaniasis (kakal-azar)
o Serum sickness (aka Katayama fever)	Schistosomiasis
o Sheepherder	Fascioliasis, echinococccosis
o Smooth, round cyst with internal septations	Echinococcosis
o Solitary hepatic cyst of right lobe	Echinococcosis, amebiasis
o Strong male predominance	Amebiasis
o Enlarging cyst	Fascioliasis
o Tortuous tract in liver on CT	
o Transverse myelitis	Schistosomiasis
o Tsetse fly	African trypanosomiasis (aka sleeping sickness)
o Undercooked fish	Clonorchiasis

Printed with permission: Spiegel BM, Karsan AA. Acing the hepatology questions on the GI board exam. Slack Incorporated 2012, Table 44-1, page 145-146.

Liver Flukes

CBD obstruction with Fascoild hepatica or gigantica treatment nitazoxanide 500 mg bid for 7 days (80% cure rate)

- Echinococcosis
  - Sheepherder
  - Cyst
    - Single
    - Right lobe of liver
    - Smooth
    - Round
    - Internal septatione
    - Calcifications
    - Cyst contains “hydrated sand”
    - “daughter cysts”
  - Anaphylaxis if cyst ruptures
- Fascioliasis
  - Sheepherder
  - Eating contaminated fresh water plants
  - CT scan – “tortous tracks”
- Schistosomiasis
  - Granulomas and fibrosis of portal vein (pre-sinusoidal portal hypertension)
  - CNS / PNS
    - Epilepsy
    - Transverse myelitis
  - Common in Egypt (peri Mile river)

"There is no achievement without goals."

Robert J. McKaine

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

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"Be aware of the big picture in the patients' life, not just blinkers on the obvious medical problem."

Dr. Joel Huurwitz

IRON OVERLOAD SYNDROMES

➢ Classification

- 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
      Hepcidin (HAMP), or
      HJV (hemojuvelin)
    - TFR2 (tranferin receptor 2)
      Hemojuvelin BMP (bone morphogenetic protein) binding to its receptor on the hepatocyte surface.
      Loss-of-function mutation or gain-of-function
    - 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
    - Parenteral iron overload
    - African iron overload
    - Multiple red blood cell transfusions
    - Long-term hemodialysis

- Chronic liver disease
  - Hepatitis C
  - Hepatitis B
  - Alcoholic liver disease (ALD)
  - Nonalcoholic fatty liver disease (NAFLD / NASH)
  - Porphyria cutanea tarda (PCT)

SO YOU WANT TO BE A GASTROENTEROLOGIST!

- 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

- Chronic inflammatory

SO YOU WANT TO BE A GASTROENTEROLOGIST!

- Give the mechanism of Fe overload which occur 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

- 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.

Hereditary Hemochromatosis (HH)

➢ Pathophysiology

- 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

- Give the role of **hepcidin** in iron homeostasis.
  - Binds to ferroportin on BLM (basolateral membrane) of duodenocyte and on macrophages, and causes the ferroportin to be internalized and inactive, with ↓ exit of iron from enterocyte, as well as ↓ iron exit from macrophages.
  - Inverse correlation between hepcidin level and iron deficiency: iron deficiency → ↓ hepcidin →
  - ↑ ferroportin in BLM causes ↑ Fe transfer out of enterocyte, and overall ↑ iron absorption
  - ↑ HJV - ↓ hepcidin - ↑ iron absorption
  - ↑ hepcidin - ↑ ferroportin internalization - ↓ Fe transport across enterocyte BLM
  - BMP binding to its receptor on the hepatocyte increases SMAD protein-dependent activation of hepatocyte expression

- Give the speculated mechanism of HFE in sensing of BIS (body iron stores).
  - HFE may bind to TFR1 and TFR2
  - The HFE-TFR1 complex on the surface of the hepatocyte senses TS (transferrin saturation)
  - When TS↑, diferric transferrin displaces HFE from the HFE-TFR1 complex
  - HFE now binds to TFR2
  - HFE-TFR2 complex causes the hepatocyte to sense ↓ TS (and ↓ BIS), so expression of hepcidin falls, and iron absorption increases

- Give the changes in iron binding, sensing and transport proteins in HFE and non-HFE HH.
  - Mutations of HFE, HJV, hepcidin, TFR2, ↑ ROS, ↑ IL-6, HFE – TFR2 complex → ↓ hepcidin expression → ↑ active ferroportin (and ↑ AMT1) → ↑ Fe absorption → ↑ BIS (body iron stores).
  - As BIS increase → ↑ BMP binding to hepatocyte receptors → ↑ SMAD protein-dependent increased expression of hepcidin → ↑ inactive ferroportin → ↓ iron absorption
  - 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

- Give the speculated 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
  - Activate stellate cells lead to hepatic fibrosis

➢ Genetics

- 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, transferring 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 transferring 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 transferring 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 transferring 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

- 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 cirrhosis / 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 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)

➢ Laboratory
  - 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 transferring saturation levels. There is no enrichment of HFE mutations in persons with alcoholic liver disease and elevated iron studies.

➢ Diagnostic imaging

- 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

➢ Histopathology

- 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

- 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

➢ Special tests

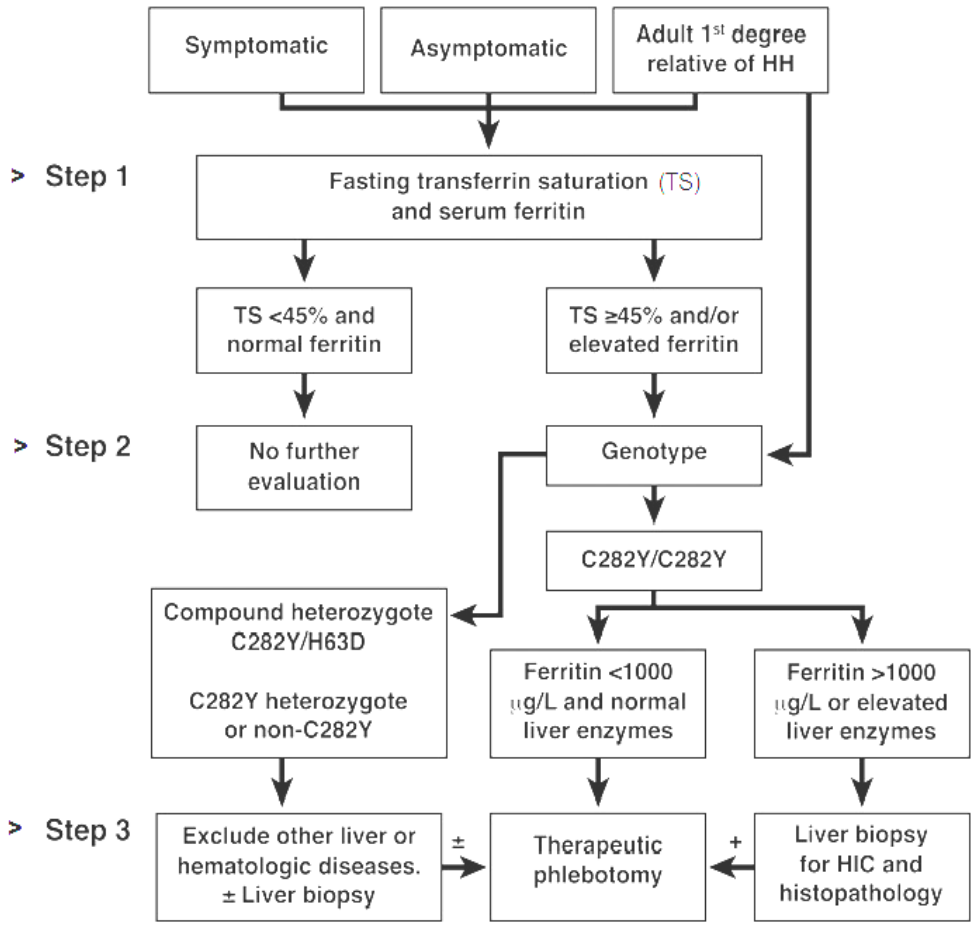
A liver biopsy is performed in a C282Y / C282Y homozygote because of ↑ transaminases or serum ferritin > 1000 ng/mL:

- 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
  - HII (hepatic iron index) = HIC / age of patient (years)
    - > 1.9, HH
    - < 1.9, likely secondary iron overload

- 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

➢ Diagnosis

- 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.

➢ Prognosis

- Give the clues that the patient with HH (hereditary hemochromatosis) does not have cirrhosis.
  - < 40 years
  - No hepatomegaly
  - Ferritin < 1000 mg/mL
  - AST normal

➢ Treatment

- 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.
- Phlebotomy
  - 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%
  - 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.
  - One phlebotomy (removal of 500 mL blood) weekly or biweekly
  - Check hematocrit/hemoglobin prior to each phlebotomy. Allow hematocrit/hemoglobin to fall by no more than 20% of prior level
  - Check serum ferritin concentration every 10-12 phlebotomies
  - Stop frequent phlebotomy when serum ferritin reaches 50-100 µg/L
  - Continue phlebotomy at intervals to keep serum ferritin between 50 and 100 µg/L
- Liver transplantation corrects the defect in HFE (inHH, 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%
- Avoid vitamin C supplements

- Liver transplantation corrects the defect in HH, but the 5 year survival rate is less than in non-HFE Fe-overload, o non-FE overload liver patients 5 year survival rate
  - Normal iron stores, 75%
  - Non-HFE Fe overload, 63%
  - HFE, Fe overload, 34%
- Sceening
  - Although HCC risk is increased in HH even without the presence of cirrhosis, there are no accepted guidelines for HCC screening.
- Treatment of secondary iron overload due to dyserythropoiesis
  - Deferoxamine (Desferal) at a dose of 20-40 mg/kg body weight per day
  - Deferasirox (Exjade) given orally
  - Consider follow-up liver biopsy to ascertain adequacy of iron removal
  - Avoid vitamin C supplements

Please see: Swan MG. Chapter 58. In: Therapeutic Choices. Grey J, Ed. 6th Edition, Canadian Pharmacists Association: Ottawa, ON, 2011, Table 6: Hereditary Hemochromatosis, page 779.

- 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
  - May reverse fibrosis
  - 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 idex (HII)

  - Eliminate of risk of HH-related HCC if iron removal is achieved before development of cirrhosis
  - ↓ portal hypertension in patients wih 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.

SO YOU WANT TO BE A HEPATOLOGIST!

- Give the effect of phlebotomy on the following complications of HH.
  - Development of HCC
  - Regression of cirrhosis
  - Arthropathy
  - Hypogonadism
  - Answer: 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

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 +/+).

- Give 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 genotypes

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

- 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	– Desforoximine
Hepatitis B infection	– Antiviral therapy
Hepatitis C infection	– Antiviral therapy
Non-alcoholic steatohepatitis	– Weight reduction

Source: Adams P. Gastroenterology 2011; 1142-1143

WILSON DISEASE

- 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.

- Clinical
  - High index of suspicion
    - Young persons with ALF
    - Kayser-Fleischer rings (in 50%)
    - Serum bilirubin > 20 mg/dL (↑ total + ↑ - unconjugated bilirubin due to Coambs negative hemolytic anemia)
    - ↓ serum ceruloplasmin (in 85%; 15% ceruloplasmin is normal, and ceruloplasmin is reduced in half of patients with ALF not due to Wilson disease)
    - ↑ serum non-ceruloplasmin-bound plasma and urinary copper concentrations
    - ↓ serum alkaline phosphatase (AP) or uric acid concentrations
    - ↑ bilirubin (mg/dL) / AP (IU/L) > 2.0
  - Clinical course varies from asymptomatic ↑ ALT / bilirubin, to acute liver failure (ALF), , to chronic hepatitis, and cirrhosis

- Give **clinical features** that suggest the diagnosis of WD.
  - Hepatic asymptomatic hepatomegaly
    - Acute liver failure
    - Acute hepatitis
    - Chronic hepatitis
    - Autoimmune-like hepatitis
    - Isolated splenomegaly
    - Persistently elevated serum aminotransferase activity (AST, ALT)
    - Fatty liver
    - Cirrhosis: compensated or decompensated

- Neuropsychiatric symptoms
  - Depression
  - Neurotic impulsive behavior
  - Personality changes
  - Psychosis
- Neurological
  - Basal ganglia involvement
    - Disorder of gait
    - Rigidity
  - Movement disorders (tremor, involuntary movements)
  - Drooling, dysarthria
  - Rigid dystonia
  - Pseudobulbar palsy
  - Dysautonomia
  - Migraine headaches
  - Insomnia
  - Seizures
- 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.

➢ Treatment

Clinical Cautions

- **No** penicillamine during pregnancy, or ↓↓↓ dose during pregnancy (FDA D)
- Do not stop penicillinamine too rapid in WD (→ ALF)

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 ofa person with NAFLD, always ask yourself-could this be WD?

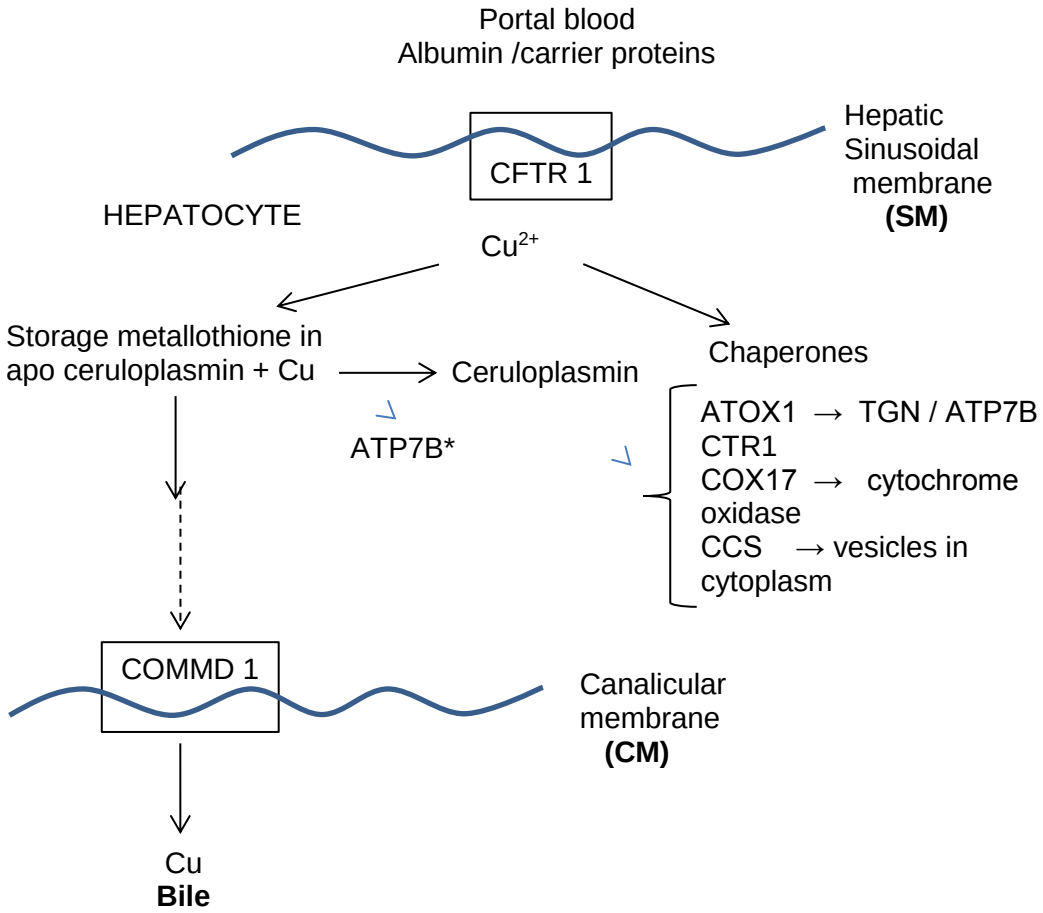
➢ Pathophysiology

- 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 (α2-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.



➢ Histopathology

- Give the histopathological changes in the liver in WD.
    - Lysosomal deposits of Cu-metallothionon (orcein stains), especially in Kupffer cells
    - Inflammation, including interstitial hepatitis
    - Mallory bodies
    - Patchy involvement of cystic dilation of mitochondrial cristae

➢ Laboratory

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.

- Give 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 ("free") copper
  - ↑ copper in the urine (reflects ↑ non-ceruloplasmin-bound copper)
  - ↑ liver copper (> 250 µg per g dry weight of liver)

- Give the false-negative and false-positive outine tests for **diagnosis** of WD.

Test	Typical finding	False negative	False positive
○ Serum cerulo-plasmin	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
○ 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 µmol/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: J Hepatol. 2012;56(3):671-85, Table 4.

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

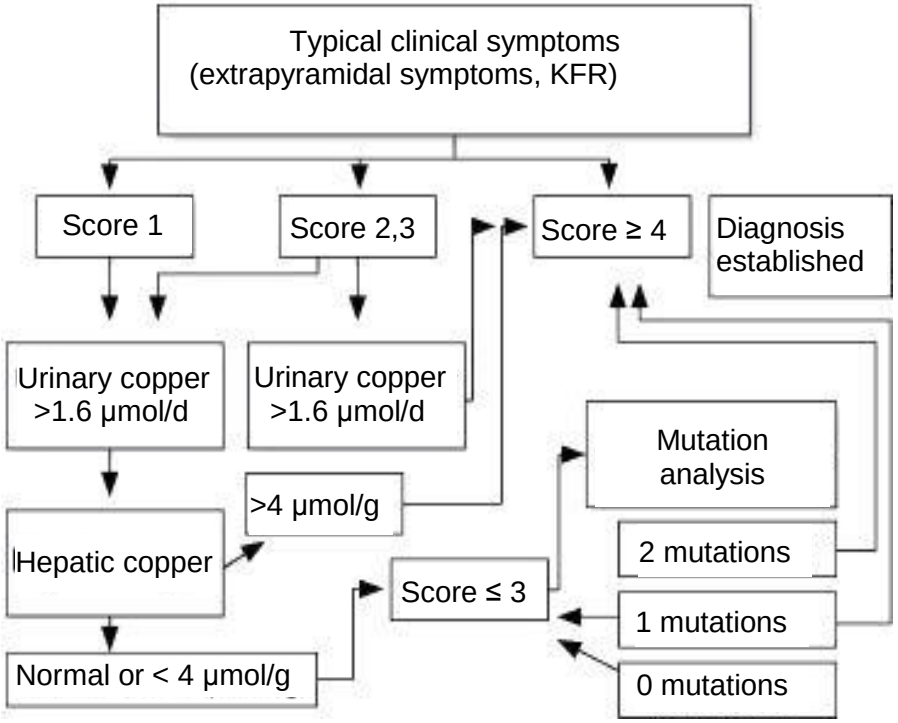
- Diagnosis
  - The gold standard for diagnosis of WD
    - Hepatic copper > 250 µg / g dry tissue – Yes
    - ↓ serum ceruloplasmin
    - Free copper, ↑ urine copper – No (seen in heterozygotes, and other chronic cholestatic conditions)

Another MCQ Alert

You had understood that in Wilson disease (WD) the serum copper concentration was reduced, but you have seen in a review of a self-test MCQ (multiple choice question) an option of choosing increased serum copper as a correct answer. Give how this is possible.

- The copper in the serum is sually 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

- 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



Printed with permission: European Association for Study of Liver. EASL Clinical Practice Guidelines: Wilson disease. J Hepatol. 2012;56(3):671-85, Figure 1.

"When we are no longer able to change a situation,
we are challenged to change ourselves."

Viktor Frankl

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.

Typical clinical symptoms and signs		Other tests	
○ KF rings		Liver copper (in the absence)	
- Present	2	- > 5x ULN (>4 µmol/g)	2
- Absent	0	- 0.8-4 µmol/kg	1
		- Normal (< 0.8 µmol/g)	-1
○ Neurologic symptoms**		- Rhodamine-positive granules	1
- Severe	2	Urinary copper (in the absence)	
- Mild	1	- Normal	0
- Absent	0	- 1.2x ULN	1
		- > 2x ULN	2
○ Serum ceruloplasmin		- Normal but > 5x ULN	3
- Normal (> 2 g/L)	0		
- 0.1- 0.2 g/L	1		
- < 0.1 g/L	2		
○ Coombs-negative hemolytic anemia		Mutation analysis detection	
		- On both chromosomes	4
- Present	1	- On 1 chromosome	1
- Absent	0	- No mutations	0

Total Score	Interpretation
≥ 4 or more	Diagnosis established
3	Diagnosis possible, more tests needed
≤ 2 or less	Diagnosis very unlikely

Printed with permission: European Association for Study of Liver. EASL Clinical Practice Guidelines: Wilson's disease. J Hepatol. 2012;56(3):671-85, Table 5; developed at the 8th International Meeting on Wilson disease.

➢ Treatment

Drug	Mode of Action	Neurological Deterioration during initial treatment	Side Effects	Comments
Penicillamine	General chelator → cupruria	~ 15% during initial treatment	• Fever, rash, proteinuria, lupus-like reaction	↓ dose before surgery (to promote wound-healing)
				During pregnancy
			• Aplastic anemia	
			• Leukopenia	
			• Thrombocytopenia	Maximum dose 20 mg/kg/day; reduce by 25% when clinically stable
			• Nephrotic syndrome	
			• Degenerative changes in skin	
			• Elastosis perforans serpingosa	
			• Serous retinitis	
			• Hepatotoxicity	
Trientine	General chelator → cupruria	~ 15%	• Gastritis	↓ dose before surgery During pregnancy Maximum dose 20 mg/kg/day; reduce by 25% when clinically stable
			• Gastritis• Aplastic anemia rare• Sideroblastic anemia	
			• Sideroblastic anemia	
Zinc	Metallothionein inducer ↓ copper absorption	Rare	• Gastritis; biochemical pancreatitis	No dosage reduction for surgery or pregnancy
			• Zinc accumulation	Usual dose in adults: 50 mg elemental Zn three times daily; *minimum* dose in adults: 50 mg elemental Zn twice daily
			• Possible changes in immune function	
Tetrathio-Molybdate	Chelator ↓ copper absorption	Rare	• Anemia; neutropenia	Experimental in the United States and Canada
			• Hepatotoxicity	

Permission granted: Roberts EA, et al. Hepatology. 2008 ;47(6):2089-111.

- **Penicillamine** (D-penicillamine)
- Give the mechanism of action of penicillamine in WD.
  - Penicillamine contains a free sulfhydral group
  - The sulfhydryl groups of penicillamine binds the excess tissue copper
  - The penicillamine-bound copper is excreted in the urine.

  - Monthly monitoring of CBC, RBC or WBC casts, > 10 RBC per HPF
  - Full therapeutic effect seen in 4 to 6 months
  - Remove accumulated tissue copper (Cu)
    - D-penicillamine chelator of copper (free sulfhydryl group)
    - Take 1 hr before or 2 hr after meal: food ↓ absorption by 50%
    - Binds Cu and excretes it into the urine
    - AEs in 30% → trientine
    - Begin D-penicillamine 250 mg po per day, increasing by 250 mg q 4 to 7 days until maximum of 750 mg bid
    - Over first 4 to 6 months, urinary copper excretion should be 2000 µg per day (32 µmol)
  - May reverse fibrosis / cirrhosis
  - Penicillamine inactivates pyridoxine, leading to pyridoxal phosphate deficiency: when on Penicillamine, also take supplement of pyridoxine 2 mg po per day
  - If there are neurological symptoms, use cotherapy of Penicillamine plus oral zinc
  - Maintain reduced tissue copper levels (prevent reaccumulation)
    - When clinically stable
    - Lab'-stable LEs and LTs
      - Non-ceruloplasmin-bound serum copper < 15 mg/dL (150 mg/L)
      - 24-hr urinary copper 200 µg to 500 µg (3 µm to 8 µm / per day
      - Dose reduction 750 mg bid →750 mg to 1000 mg po per day, in 2 divided doses
    - Lower dose of chelators
    - Indications for dose reduction from initial to maintenance doses of chelators
    - Maintain urinary copper excretion at ~ 500 mcg (8 µ mol) per day

Clinical Curiosity

- When beginning chelation therapy in persons with WD, paradoxically there may develop.
  - New neurological abnormalities (10% - 20%), or neurological deterioration during initial phase of treatment
  - Hepatic decompensation
  - Do not stop treatment with a chelator: even a few days of stopping therapy may precipitate
    - Acute liver failure
    - New neurological abnormalities
    - Severe hemolysis
    - Maternal fatality if stopped in pregnancy

Another Clinical Curiosity

- With the use of penicillamine in WD, there is an expected decrease in the previous elevated ALT/ billirubin.
  - For unknown reasons, about 1/3 of children on Penicillamine who are compliant in taking doses sufficient to achieve desired outcome of ↑ urinary copper excretion, will still have ↑ ALT.
  - In an adult, the lack of falling ALT or lack of achieving target concentrations of urine copper is usually caused by non-compliance to the medications

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

Alberto Agraso and Mony Dojeiji

- Give 15 **adverse effects** of the copper chelator Penicillamine.

Penicillamine early reaction (sensitivity), 1 wk to 3 wk

○ Hypersensitivity reaction	- Fever - Rash - Lymphadenopathy - Neutropenia - Thrombocytopenia
○ Skin	- Rash - Pemphigoid lesions - Lichen planis
○ Lung	- Good pasture syndrome
○ Hematology	- Lymadenopathy - Neutropenia - Thrombocytopenia - Aplastic anemia - Hemolysis
○ Kidney	- Proteinuria (stop Penicillamine for > 2 g protein per day in urine (2 + dipstick), or ↓ glomerular filtration rate) - Nephrotic syndrome - Cresenteric glomerulonephritis - Renal tubular acidosis
○ GI / Liver	- Hepatoxicity - Loss of taste - Anorexia - Nausea / vomiting
○ MSK	- Polymyositis - Lupus-like syndrome - Myasthenia gravis
○ Nutrition	- Pyridoxil phosphate deficiency

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.

➢ Special consideration

- Give special considerations for treatment of Wilson disease.

❖ **Pregnancy**

- Trimesters 1 and 2 - penicillamine or trientine, 750 mg to 1000 mg per day
- 3rd trimester – Penicillamine 500 mg per day
- Because penicillamine is FDA class D, switch to zinc po
- Lactation
  - Increase back to prepregnancy doses

❖ **Preoperatively**

- Reduce dose of penicillamine by half, and continue into the post-operative period before re-establishing the presurgery dose (this may obviate the possibility of Penicillamine decreasing wound healing)

❖ **Acute liver failure** (ALF) in WD

- Use modified King's prognostic scoring system to determine if / when LT (liver transplantation) should be performed
  - Components of King's College prognostic scoring system for ALF in WD is based on
    - Serum bilirubin
    - ALT
    - INR
    - WBC
  - Performance characteristics
    - Sensitivity 93%
    - Specificity 98%
    - PPV 88%

  *Dhawan A, et al. Liver Transpl 200; 11: 441.

- Must assess for possible liver transplantation (LT), since ALF from WD is **fatal without LT.**
  - Liver transplant (LT) is curative for WD
  - Fresh frozen plasma replacement
    - Rapidly remove excess copper

Trientine

- Penicillamine early sensitivity reaction switch> trientine 20 mg/kg per day in 2 or 3 divided doses per day, maximum of 1500 mg per day
- Family **screening** of siblings of index WD patient
- Trientine, 20 mg / kg per day in 2 or 3 divided doses per day, maximum of 1500 mg per day

Zinc acetate

- Competitive inhibition of copper absorption
  - 50 mg po tid
  - More effective for neurological than for hepatic disease

Low copper diet (optional)

- Organ
  - Liver
  - Kidney
- Exotic
  - Shellfish
  - Mushroom
  - Unprocessed wheat
- Legumes
  - Beans
  - Peas
- Luxury
  - Chocolate
  - Cocoa, dried fruits
- "Eat exotic organs with chocolate and beans"

- 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.

- 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
    - FDA class D
  - 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.

A1- TRYPSIN (A 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 (emphysemia) and liver (cirrhosis)

- Pathophysiology

- 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

- Histopathology
  - ↓ bile ducts
  - Intracellular cholestasis
  - Inflammation
  - Steatosis
  - PAS (periodic acid-Schiff) – positive, diastase-resistant globular inclusions of polymers of α1-ATZ protein in periportal hepatocytes and Kupffer cells
  - IHC (immunohistochemistry)
    - Staining with monoclonal antibody to α1-ATZ confirms α1-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 α1-AT
    - Children, 83%
    - Adults, 90%

Curiosity!

- "Liver transplantation with grafts from donors with unrecognized α1-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).

"Life is like a bicycle.

To keep balanced, you must keep moving."

Albert Einstein

AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE (ADPKD)

➢ Pathophysiology

The patient with ADPKD (autosomal dominant polycystic kidney disease) develops esophageal varice but no ascites. There are no signs of portal hypertension /cirrhosis.

- Give the 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

- Give a cause of WD 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.

➢ Clinical

- 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)

- 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
    - 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.
  - Secondary
    - Cardiopulmonary disease
      - Centrilobular necrosis
    - Drug hepatotoxicity
      - Cirrhosis
  - Specific and / or secondary
    - Muscocele
    - 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).

SICKLE CELL DISEASE

- Give 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 choledochalithiasis
        - Acute cholecystitis and cholangitis
        - Ischemic cholangiopathy

Printed with permission: Ahmed S, et al. *Best Practice & Research Clinical Gastroenterology* 2005;19(2): 299.

MITOCHONDRIAL CYTOPATHIES

- 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.

- Give 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.

- Give the dietary therapy of **hereditary liver diseases** (in addition to always avoiding alcohol).

Disorder	Dietary intervention
o Hemochromatosis	– Avoidance of excess dietary iron, selection of foods containing phytates or tannins to reduce iron absorption (together with appropriate phlebotomy treatment)
o Wilson disease	– Low-copper diet, zinc supplementation (together with chelating agent); green tea
o Cystic fibrosis	– High-fat diet, pancreatic enzyme supplements, fat-soluble vitamin supplements, medium chain triglycerides (MCT)
o Hereditary fructose intolerance	– Low fructose, low sucrose diet
o Galactosemia	– Galactose-free diet
o Tyrosinemia	– Low phenylaline and tyrosine diet
o Glycogen storage disease	– Continuous glucose feeding
o Cerebrotendinous xanthomatosis	– Deoxycholic acid supplementation

Adapted from: Thapa BR. *Indian J Pediatr*. 1999; 66(1 Suppl): S110-9.

DRUG- INDUCED LIVER INJURY (DILI)

- Demography
  - Most common drugs causing DILI
    - Acetaminophen
    - Antibiotics
      - Amoxicillin-clavulanate

- Hepatic drug

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 f 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 1 reactions are catalyzed by microsomal drug oxidase, the key component of when 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.

- Give 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
Antiandrogens	Chronic viral hepatitis B, C
Antiretrovirals (e.g. zalcitabine, saquinavir)	Hepatitis B, C
Ibuprofen (NSAIDs)	Hepatitis C
Methimazole	Chronic hepatitis B
Methotrexate	Alcoholic liver disease, NAFLD
Oral contraceptives	Women with liver tumours, or history of jaundice of pregnancy
Rifampin	Primary biliary cirrhosis
Vitamin A (high doses)	Alcoholic liver disease

Adapted from: Gupta NK, and Lewis JH. *Aliment Pharmacol Ther* 2008; 28(9): 1021-41.

- Give 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_i^{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 then susceptibility 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

- In the context of DILI, give the meaning of the Hy 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 cute 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: Clinics 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".

➢ Histopathology

- Give histopathological changes of the spectrum of DILI.
  - Asymptomatic liver disease
  - Acute hepatitis
    - The ALT / AST or serum bilirubin may be increased Hy's law: when aminotransferases and serum bilirubin are increased, prognosis is poor (mortality rate ~ 10% zonal or nonzonal necrosis mortality rate ~ 5%
  - Acute / chronic steatosis ↓ beta-oxidation → microvesicular steatosis (acute) → macrovesicular (fat droplet occupies > ½ of cytoplasm) steatosis (chronic) histologically resembles NAFLD, NASH and ALD (alcoholic liver disease)
    - Examples of causative drugs
      - Ibuprofen
      - Sulindac

- Acute liver failure (ALF) aka fulminant hepatic failure
  - Mortality rate ~ 50%, especially if serum bilirubin > 3 x ULN
- Chronic hepatitis
  - Occurs in 5% to 10% of adverse drug reactions
  - More common with cholestatic or cholestatis plus hepatocellular liver injury
  - Autoimmune-like chronic hepatitis (AIH)
    - Female > males
    - Positive ANA, anti-smooth muscle antibody
    - ↑ globulins in serum
  - Histopathologically identical to type 1 autoimmune hepatitis
    - Examples of causative drugs
      - Phenytoin
      - Diclofenac
  - Viral hepaititis-like
    - Serology negative
    - Histopathology similar to chronic viral hepatitis
    - Examples of causative drugs
      - Aspirin
      - Isoniazid
- Chronic granulomatous hepatitis
  - Non-caveating granulomas examples of causative drugs
    - Mesalamine
    - Sulfonamides
    - Periportal hepatitis
    - Hepatocellular injury or cholestasis
    - Not associated with bile ducts
- Phospholipidosis
  - Phospholipids fill lysosomes, which make hepatocytes appear “foamy” (foamy hepatocytes)
  - Examples of causative drugs
    - Amiodarone
    - Chlorpromazine

- Cholestasis with / without hepatitis
  - Pure cholestasis
    - Bile plugs in zone 3
    - Minimal hepatocellular inflammation
    - Examples of causative drugs
      - OCA (oral contraceptive agents)
      - Anabolic steroids
  - Cholestatic cholestasis
    - Cholestasis surrounded by inflammation
    - Proliferation of bile ducts
    - ↑ ALT / AST, ↑ AP, ↑ GGT
    - Symptoms of hypersensitivity
    - Typical causative drugs
      - NSAIDs
      - Erythromycin
  - PBC-like
    - Histopathologically similar to PBC
    - Serologically AMA-negative
    - Typical causative drugs
      - Amitriptyline
      - Erythromycin
    - Ductopenic cholestasis
    - Examples of causative drugs
      - Amoxicillin
      - Clindamycin
  - Scleosing cholangitis
    - Diagnostic imaging (ERCP, MRCP) and histopathology similar to PBS (primary biliary sclerosis)
- Fibrosis / cirrhosis
- Vascular disease endothelial damage → thrombosis
  - NC, HV, PV thrombosis
  - SOS (sinusoidal obstruction syndrome; aka veno-occlusive disease)
  - Sinusoidal dilation
  - Cavernous hemangioma
  - NRH (nodular regenerative hypertension
  - Peliosis hepatitis

- Hepatic vein (HV) thrombosis
  - B-CS (Budd-Chiari syndrome)
  - Associated with
    - Coagulation disorders
    - Myeloproliferative disorders
    - Use of OCA (oral contraceptive agent)
- Autoimmune hepatitis
- Steatohepatitis with / without fibrosis
- Tumor
  - FNH
  - Hepatic adenoma
  - HCC
  - Cavernous hemangioma

➢ Risk factors

- Give 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, methrotrexate
  - 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

- Give 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	– 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 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.

Risk factors	Importance	Implications for Prevention
○ Other diseases	– 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
○ 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 **m**ethylene**d**ioxy**m**eth**a**mphetamine.

- Give 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 tthan to memorize this list. In the patient with liver disease, look up this list, or look up the dugs to be used

Adapted from: Gupta NK, and Lewis JH. *Aliment Pharmacol Ther* 2008; 28(9): 1021-41.

- Give 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.

- Give hepatobiliary complications of the **use of oral contraceptive agents** (OCAs).

  - Gallstones
    - Cholestasis
    - Unmasking PBC, and other cholestatic diseases
  - Liver
    - Unmasking porphyria
    - Tumours
      - Hepatic adenomas (causative)
      - ↑ size of FNH (focal nodular hyperplasia)
      - Hepatocellular carcinoma (rare)
    - ↑ risk of NASH
    - Vascular
      - Budd-Chiari syndrome (hepatic obstruction)
      - Peliosis hepatic (sinusoidal dilation)

- Treatment
  - Supportive care
  - NAC for acetaminophen toxicity
  - 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.

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

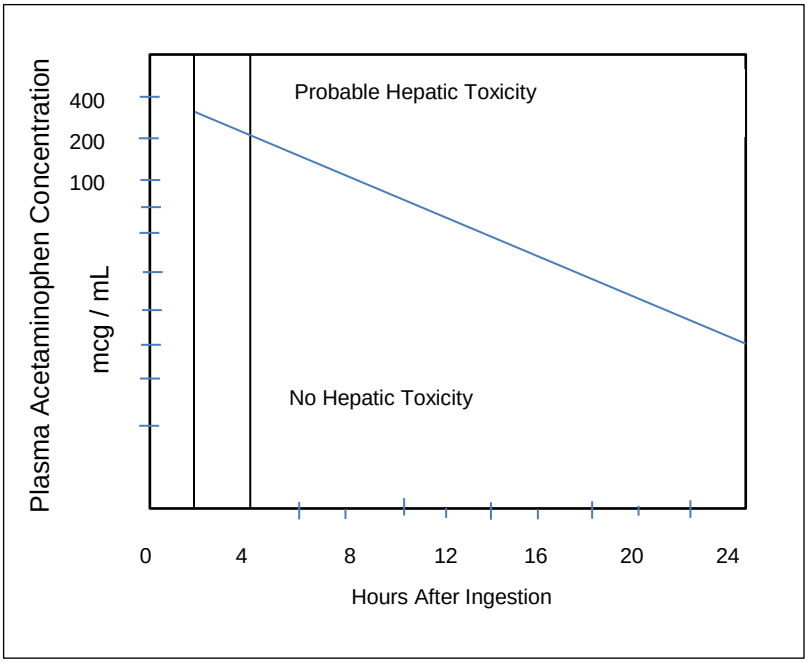
  - Glucocorticosteroids, only for DRESS syndrome:
    - Drug rash
    - Eosinophilia
    - Systemic symptoms
  - NAC, at doses suggested for acetaminophen toxicity

- 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 acetominophen

Acetaminophen Overdose

- Give 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.

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.

SO YOU WANT TO BE A HEPATOLOGIST!

- 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 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 hr
    - Dose 2. 50 mg/kg NAC in 500 ml D5W over 4 hours.
    - Dose 3. 125 mg/kg NAC in 1000 ml D5W over 19 hr
    - Dose 4. 150 mg/kg NAC in 1000 ml D5W over 24 hr
    - Dose 5. 150 mg/kg NAC in 1000 ml D5W over 24 hr

- 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.

- 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.

VASCULAR DISEASES

- Classification

- Classify and give examples of 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)

Printed with permission: Kamath PS. *Mayo Clinic Gastroenterology and Hepatology Board Review* 2008: pg. 337.

Portal Colopathy

- Definition
  - 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 / associations
  - 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.

- Causes / associations

- Give 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
    - MOIVC (membranous obstruction of the inferior vena cava)
  - NA/Europe
    - Thrombosis of hepatic veins, from thrombogenic states, e.g. myeloproliferative disorders (JAK_2 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
  - 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 peformed, it might show a "spider web" appearance suggestive of BCS (BCS → ↓ HV flow → ↑ accessary HV flow → spider appearance on venography).
  - Curiosity: a very large candate lobe may compress the IVC (inferior vena cava) and further ↓ HV outflow.

- Give the acute and chronic **pathological changes** of Budd-Chiari Syndrome.
  - Acute centrilobular, portal sinusoids
    - Congestion
    - Sinusoidal distention
    - Hemorrhage
    - Necrosis
    - Little inflammation
    - Wide subendothelium
  - Chronic
    - Patchy, asymmetrical involvement
    - Perivenular sclerosis
    - Hepatocellular necrosis
    - Regenerative nodules
    - Cirrhosis

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
      - Portosystemic shunt surgery (PSS)
        - PV becomes the hepatic outflow tract
        - No IVC stenosis
        - IVC pressure < 20 mm Hg
        - Embolectomy (selected cases)
        - Liver transplant

- Give what must be excluded in the patient with Budd-Chiari Syndrome before considering LT.

  - Associated hepatic malignancy
  - Other contraindications for LT

"Success is not final, failure is not fatal:
It is the courage to continue that counts."

Winston Churchill

- Give the **treatment** options and indications for the use of 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, jepaticencephalopathy; IVC, inferior vena cava; TIPS, transjugular intrahepatic portasystemic shunt

Printed with permission: Kamath PS. *Mayo Clinic Gastroenterology and Hepatology Board Review* 2008: pg. 344.

Portal Vein Thrombosis (PVT)

➢ Causes / associations

- Give 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

- Give the **clinical features and treatment** of hepatic artery stenosis, hepatic artery and thrombosis, as well as portal vein stenosis or thrombosis.

Time of occurrence	Leading symptoms	Treatment
❖ 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
○ Late	– Slight increase in LFTs – Portal hypertension – Ascites – Variceal bleeding	▪ Endoscopic treatment Rt-PA lysis therapy ▪ Elective retransplantation
❖ 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
❖ 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.

Obstruction in Splenic or Vein, and Portal Vein (PV)

- 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 sphenectomy.

- Give the circumstance whe splenectomy would not be curative for SVT.
  - A SVT combined with a portal vein thrombosis (PVT) would not be cured by splenectomy.

- Give the progression over time of obstruction of PV.
  - Thrombus
    ↓
  - Constriction
  - Compression (invasion)
    ↓

Collagenous formation

↓

Cavernous transformation of venous channels

↓

Portal cavernoma

Hepatic Artery Aneurysm (HAA)

➢ Pathophysiology

- 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

➢ Laboratory

- Give laboratory measurements which suggest ischemic hepatitis.
    - ↑↑↑ AST (> 1,000 IU)
    - ↑↑ 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

➢ Pathology

- 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.

- 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 artherosclerosis 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

- 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 medusa suggests ↑.blood flow in the abdominal wall veins, arising from recanalization of the umbilical vein, producing the C-B (Cruveilhier – Baumgarten) murmur.

Patient with ascites despite salt restriction plus complaince in taking appropriate diuretics loses the ascites when a hepatic bruit develops.

- 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).

- 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%

"Goals in writing are dreams with deadlines."

Brian Tracy

Sinusoidal Obstruction Syndrome (SOS, aka Veno-occlusive disease)

- Definition
  - Diffuse, ideopathic endothelial injury causing non-thrombotic obstruction of central hepatic venules and hepatic sinusoids, leading to dilation of sinusoids and hepatic congestion.

- Causes / associations
  - 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 infection
  - Hereditary hemochromatosis (HH)
  - Pre-existing chronic liver diseases
  - Recent bacterial / viral infections

- Clinical
  - Resembles BCS
  - Painful hepatomegaly
  - Develops 10-20 days after BMT

- 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)

Disease	Timing	Diagnosis
○ Cholestasis and 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
○ 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

Disease	Timing	Diagnosis
○ Idiopathic hyper-ammonemia	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.

- Laboratory
  - Conjugated hyperbilirubinemia > 2 mg/dL
  - Thrombocytopenia

➢ Diagnostic imaging

- 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

➢ 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 from 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)

ACUTE LIVER FAILURE (ALF)

- Definitions
  - "….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".
  - The rapid development of hepatocellular dysfunction (coagulopathy, mental status changes [encephalopathy]) and often jaundice) in a patient without prior liver disease" (an illness of < 26 wk duration).
  - The time interval between the onset of illness and the development of ALF is < 8 wks, although some authors suggest a range of different time intervals:
    - Hyperacute ≤ 1 week
    - Acute 1 to 4 weeks
    - Subacute 4 to 24 weeks

Note: subgroups based on the duration of the illness have no prognostic significance, and the use of these terms is no longer wide-spread

- Demography
  - < 1 / 10^5 per year
  - 1-year survival ~ 2/3
  - 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

- 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

- In America the commonest causes of ALF are as follows:
  - Acetaminophen overdose, 46%
  - Indeterminate, 14%
  - Drug-related (other than acetaminophen), 11%
  - HBV, 7%
  - Other causes, 7% (e.g. malignant infiltration, pregnancy (pre-eclampsia)
  - Autoimmune, 5%
  - Ischemic, 4%
  - HDV, 3%
  - Wilson disease, 2%

- 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

➢ Prognosis
  - 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.)

➢ Causes / associations

- Give a **classification** of the causes of acute hepatic failure (ALF).
  - 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 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 if portal vein at surgery)
  - Infiltration
  - Leukemia, lymphoma, metastatic carcinoma

- Pregnancy
  - Eclampsia
  - Preeclampsia
  - HELLP
  - AFLP (acute fatty liver of pregnancy)
  - HEV
- Syncythial 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.

➢ Clinical

- Give the pathogenesis of the major complications of acute liver failure.

Complication	Pathogenesis
CNS (↑ ICP "coning)	
– Encephalopathy	▪ Cerebral edema
CVS (↓ BP)	
– Hypotension	▪ Hypovolemia ▪ ↓ vascular resistance
Respiratory	
– Respiratory failure	▪ ARDS (DAD)
Kidney	
– Renal failure (acute kidney injury [AKI])	▪ Hypovolemia ▪ Hepatorenal syndrome (HRS) ▪ Acute tubular necrosis (ATN) ▪ NSAID damage
Pancreas	
– Pancreatitis	▪ Unknown
GI	
– Gastrointestinal hemorrhage	▪ Stress ulceration ▪ Esophageal varices (PHT)
– Hypoglycemia	▪ ↓ hepatic glucose synthesis
– Infections	▪ ↓ immune function ▪ Invasive procedures

Complication	Pathogenesis
– Coagulopathy	▪ ↓ clotting factor synthesis ▪ Thrombocytopenia ▪ Fibrinolysis

Abbreviations: ARDS, Acute respiratory distress syndrome; BP, systemic blood pressure; CT, computed tomography; DAD, diffuse alveolar damage; ICP, intracranial pressure; NSAIDs, nonsteroidal anti-inflammatory drugs; PHT, portal hypertension.

Adapted form: *Sleisenger and Fordtran's Gastrointestinal and Liver Disease: Pathophysiology/ Diagnosis/ Management*. Ninth edition, 2010, Table 93-4: pg. 1561.

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Major complications of ALF include HE, coagulopathy, jaundice, GI bleeding, and hypoglycemia.

- Give 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
  - Dissememinated intravascular coagular (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)

➢ 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)

- Blood work
    - Alpha-fetoprotein (AFP)
    - ALT, AST, AP, GGT
    - Albumin, INR, bilirubin
    - 1° /2° electrolytes
    - Type and screen blood for possible transfusion
    - 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

- Give 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 ↑ PO_4^- to help the liver regenerate).
  - ↓ factor V

- Give the cause of ALF in which there is a marked increase in both ALT and LDH.
  - Acute ischemic injury of the liver

  - 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.

➢ 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

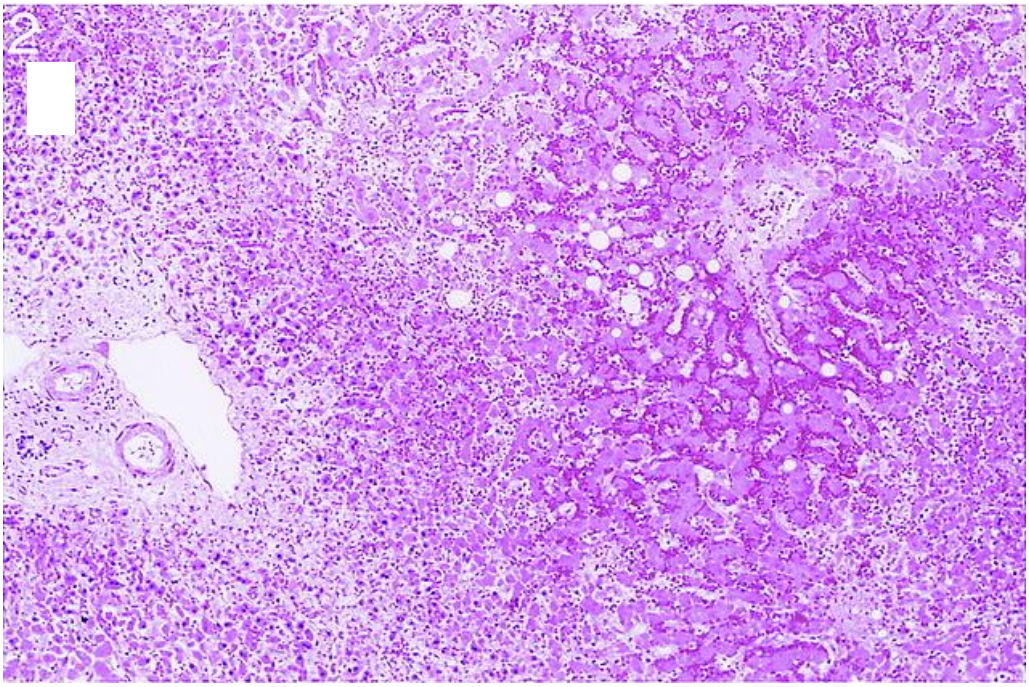
Adapted from: Gill RQ, and Sterling RK. *J Clin Gastroenterol* 2001;33:191-8.

➢ Histopathology

Case: 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.

➢ Differential

- The diagnosis of ALF is based on clinical findings, and must be differentiated from conditions with similar clinical findings:

- Give the 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 hepatic conditions in which pre-existing cirrhosis may be often unrecognized.
  - HBV, vertically-acquired
  - WD (Wilson disease)
  - AIH (autoimmune hepatitis)

➢ Risk stratification

- 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.

- Give the **performance characteristics** of 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.

- 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)

- Treatment
  - 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.)

- Give the treatment of ALF.
  - Specific therapy of underlying cause (please see later section)
  - ICU admission
  - Assessment for possible liver transplantation
  - Infection
    - Treat associated infection detected from periodic surveillance cultures
  - Encephalopathy
    - Grade I / II
      - Lactulose po/pr
    - Grade III / IV
      - Intubation
      - Elevation load of bed 30^{o}
      - ICP monitoring (debatable): maintain ICP < 20 mm Hg
      - Monitor clinically
      - Cushing triad for ↑ ICP
        - ↓ PR
        - ↑ SBP
        - Irregular respiration
      - Suspect cerebral edema
        - ↑ serum NH_3 > 150 µm
        - HE III / IV
        - Need for vasopressors to maintain MAP
      - Hyperventilation for $PaCO_2$ of 25-30 mm Hg
      - Hypothermia to core 33-34^{o}C
      - Hypertonic saline (→ serum Na^+ of 145-15 mmol/L)
      - Mannitol, IV bolus 0.5-1.0 g /kg BW, repeat 1 to 2 times as long as serum osmolarity < 320 mOsm/L
      - Treat seizures with phenytoin (short-acting refractory seizures)
      - **No** use for glucocorticosteroids
  - Coagulopathy
    - Vitamin K
    - FFP for bleeding
    - Platelets for bleeding or for invasive procedures
    - R factor VII for invasive procedures

- PPI for prophylaxis of stress ulceration
- Acute renal failure
  - Continuous hemodialysis (rather than intermittent hemodialysis)
  - Metabolic homeostasis
- Acute adrenal insufficiency
  - About 2/3 of patients with ALF have adrenal insufficiency, so the patient may either be given a treat of IV steroids, or adrenal insufficiency may be formally tested with a cosyntropin stimulation test.
- Hypotension
  - Volume replacement
  - Pressors / vasoppressin
- Nutritional support
- Liver transplant
  - May be needed in the patient with ALF secondary to EHS (exertional heat shock), or other causes of ALF, where non-responsive to medical care

Abbreviations: ICP, intracranial pressure; CCC, cerebral perfusion pressure (=MAP-ICP); MAP, mean arterial pressure; ARR, acute renal pressure; HE, hepatic encephalopathy

- Give treatment for the specific 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
  - Budd-Chiari syndrome
    - Anticoagulation
    - Thrombolysis
  - Alcoholic hepatitis (Maddrey score > 32)
  - Autoimmune hepatitis
    - Corticosteroids

- HBV
  - Nucleoside or nucleotide analogues
- DILI plus DRESS syndrome
  - Glucocorticosteroids, NAC

- Liver Transplantation
- The **King's College risk stratification criteria** for liver transplantation in acute liver failure (ALF)
  - Acetaminophen
    - INR > 6.5 (PT > 100 sec), serum creatinine > 3.4 mg/dl, stage 3 or 4 hepatic encephalopathy
    - Arterial lactate > 3.5, 4 hours after resuscitation
    - pH < 7.30 or arterial lactate > 3.0 12 hours after resuscitation; or
  - Non-acetaminophen
    - INR > 6.5 (PT > 100 sec); or
    - Any 3 of the following:
    - INR > 3.5 (PT > 50 sec)
    - Age < 10 or > 40 years
    - Bilirubin > 17.5 mg/dl
    - Duration of jaundice > 7 days

"Motivation is what gets you started,
Habit is what keeps you going."
Jim Rohn

PORTAL HYPERTENSION (PHT) AND CIRRHOSIS

Portal Hypertension (PHT)

- Definition
  - Hepatic sinusoidal pressure ≥ 6 mm Hg
- Physiology
  - After a meal, portal blood flow increases, with no ↑ 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
- Pathophysiology

- Give the pathogenesis of portal hypertension hyperdynamic circulation – systemic and splanchnic (extrahepatic) vasodilation.
  - Basic factors
    - ↑ systemic sympathetic activity
    - ↑ resistance
    - ↑ flow hyperdynamic circulatory state
    - ↑ collaterals (↑ angiogenesis)
    - ↓ fenestration
    - Ohm's law

      $\Delta P = F \times R$

      F, flow

      ΔP, change in pressure

      R, resistance

- Portal flow and resistance increase
  - Mechanical factors
  - Regenerative nodules
  - Fibrotic bands
  - Defenestration and capillarization of sinusoids
  - Swelling of hepatocytes and kupffer cells
  - Vascular factors
  - Intrahepatic vasoconstriction, and ↓ response to vasodilations

- Hepatic vasoconstriction (splanchnic vascular bed → ↑ increased intrahepatic resistance
  - Hepatic vasoconstriction
  - Law of poiseuille $R = 8 \eta L / \P r^4$
  - Resistance (R) is affected by the length and radius (r) of the vessel, and by the viscosity of the blood
  - Early
    - ↑ nitric oxide (NO)
    - ↑ sheer 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 ↑ sheer stress, ↑ cytokines, and ↑ phosphorylation of eNOS, leading to vasodilation in splanchnic and systemic vascular beds (note below that there is ↓ intrahepatic NO, ↓ intrahepatic vasodilation, ↑ intrahepatic vasoconstriction)
  - Late (cirrhosis)
    - ↓ production of NO
    - ↓ activation of eNOS protein in endothelial cells
    - ↑ 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)

- Give components of each of the vasodilating and vasoconstricting systems involved in the **disturbed hemodynamics** in cirrhosis.

➢ Vasodilator systems

- Adenosine
- Adrenomedullin
- Arterial natriuretic peptide (ANP)
- Bradykinin
- Brain natriuretic peptide (BNP)
- Calcitonin gene-related peptide (CGRP)
- Carbon monoxide (CO)
- Endocannabinoids
- Endothelin-3 (ET-3)
- Endotoxin
- Enkephalins
- Glucagon
- Histamine
- Hydrogen sulphide
- Interleukins
- Natriuretic peptide of type C (CNP)
- Nitric oxide (NO)
- Prostacyclin (PGI_2)
- Substance P
- Tumour necrosis factor-α (TNF-α)
- Vasoactive intestinal polypeptide (VIP)

➢ Vasoconstrictor systems

- Adrenaline and noradrenaline
- Angiotensin II
- Endothelin-1 (ET-1)
- Neuropeptide Y
- Renin-angiotensin-aldosterone system (RAAS)/
- Sympathetic nervous system (SNS)
- Vasopressin (ADH)

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- The **vasodilation in splanchnic and systemic** (peripheral) vascular beds leads to
  - ↑ cardiac output
  - ↓ mean arterial pressure
  - ↑ systemic blood flowing into splanchnic circulation
  - The overall effect is ↓ intrahepatic NO and ↓ intrahepatic vasodilation (effect on endothelial cells as well as possibly on HSCs)
  - ↓ intrahepatic vasodilation results in ↑ intrahepatic vasoconstriction
  - ↑ intrahepatic vasoconstriction leads to ↑↑ intrahepatic resistance (law of Poiseuille)

- Giving nitric oxide (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.
    - In cirrhosis, there is ↑ intestinal endotoxin (LPS) → ↑ TGF-β, ↑ ET-1, with binding to ET-A receptors on HSC, and intrahepatic vasoconstriction

Abbreviations: HSC, hepatic stellate cell; LPS, lipopolysaccharide; eNOS, endothelial NO synthase

    - ↑ sympathetic activity (norepinephrine)
        - Will also act as an intrahepatic vasoconstrictor, as also will
        - Angiotension
        - Leukotrienes
        - Thromboxane
    - Hyperdynamic circulation

- Give the pathophysiological components producing the hyperdynamic circulation and cardiovascular dysfunction in persons with cirrhosis.
    - Peripheral and splanchnic arterial vasodilatation
        - Baroreceptor-induced increase in heart rate
    - Autonomic dysfunction
        - Increased sympathetic nervous activity
        - Vagal impairment
    - Alterations in cardiac preload
        - Increased portosystemic shunting
        - Increased blood volume
        - Effects of posture
        - Decreased blood viscosity
    - Alterations in oxygen exchange
        - Anemia
        - Hypoxemia
        - Hepatopulmonary syndrome
        - Portopulmonary hypertension

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- Collateral Circulation
  - As the portal pressure increases
    - There is ↑ flow of blood into the portal vein-systemic collateral circulation increase
    - The direction of blood flow reverses
    - Blood flows abnormally from the portal circulation into the venous component of the systemic system.

- 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 the portal vein.

- Give the circumstance when splenectomy would not be curative for SVT.
  - A SVT combined with a portal vein thrombosis (PVT) would not be cured by splenectomy.

- Give sites of communication of the portal to thesystemic 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
Gastroespohageal 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.

➢ Causes / associations

- Give a **classification** of the causes of portal hypertension based on the site of increased resistance to portal blood flow.
    - Prehepatic
    - Intrahepatic
        - Presinusoidal
        - Sinusoidal
        - Post-sinusoidal
    - Posthepatic

- 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.

- Give 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

- Conditions
  - Gastric antral vascular ectasia / gastric vascular ectasia (GAVE / GVE)
  - Portal hypertensive gastropathy (PHG)
  - Gastric varices +/- esophageal varices
  - Portal hypertensive polyps

- 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.

- Differential

- Compare and contrast portal hypertensive gastropathy (PHG) and gastric antral vascular ectasia (GAVE).

	PHG	GAVE
Distribution	Proximal stomach	Distal stomach
Mosaic pattern (snake skin)	Present	Absent
Red signs	Present	Present
Biopsy		
– Thrombi	-	+++
– Spindle cell proliferation	+	++
– Fibrohyalinosis	+	+++

	PHG	GAVE
○ Treatment	Non-specific beta-blockers TIPS LT	Argon laser Banding Cryotherapy Antrectomy

* Note: In portal hypertension, gastric vascular ectasia may occur at sites other than the antrum

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 if 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 potency 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% - 2.6%) 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, heptorenal syndrome; LVP, large volume paracentesis; PHG, portal hypertensive gastropathy

- Give **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

- Give **complications** of the TIPS (transjugular intrahepatic portosystemic shunt) procedure.
  - Technical complications
    - Neck puncture
    - Indequate 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])
- Cardiopulmonary system (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.

Idiopathic Portal Hypertension (IPH) and Hepatoportal Sclerosis (HPS)

- IPH and HPS are associated with ↑PP (portal pressure) and no obstruction of the extrahepatic portion of the PV (portal vein).

- 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 as the result of the development of shunts between the hepatic artery (HA), hepatic vein (HV), or portal vein (PV).

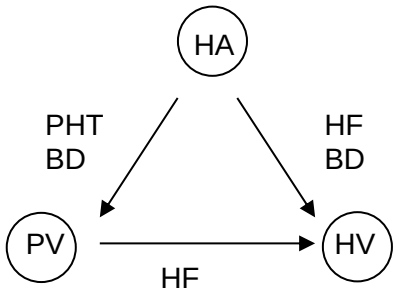
- Give the diagnostic criteria for HHT / OWRD.

The diagnostic criteria for HHT / OWRD include

- Positive family history
- Epistaxis
- Telangiectasias
- AV fistulas (lung, liver)

Intrahepatic Shunts

- 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.

Cirrhosis

➢ Pathophysiology

- Give 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)
        - Angioporetin 1, 2

Adapted from: Jiao J, et al. *Curr Opin Gastroenterol* 2009;25(3):223-9.

➢ Causes / associations

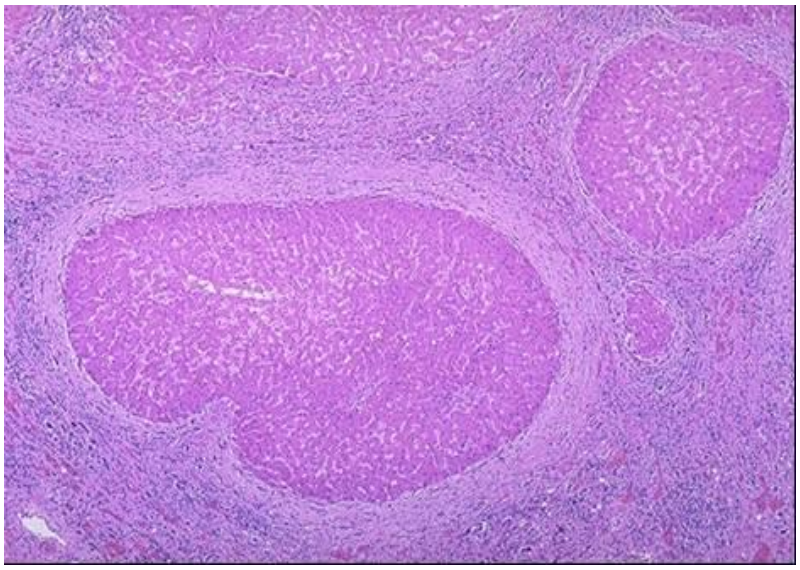
- Classify and give causes of cirrhosis.
    - Viral hepatitis
        - HBV, HCV, HDV
    - Metabolic
        - NASH
        - Hemochromatosis
        - Wilson disease
        - 1-antitrypsin deficiency
        - Galactosemia
        - Tyrosinemia
        - Autoimmune
        - Sclerosing cholangitis
        - Primary biliary cirrhosis
        - Autoimmune Hepatitis

- Drugs/toxins
  - Alcohol
- Congestive
  - Cardiac failure
  - Budd-Chiari Syndrome
- Cystic fibrosis

➢ Histopathology

Case: Clinical vignette: A 58-year-old man from P.E.I. with known alcoholic liver disease presents with resent 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.



➢ Clinical

- Give hepatic/extrahepatic signs of **cirrhosis** on hepatic DI (diagnostic imaging), CT and/or MR.

    - Hepatic
        - Nodularity
        - ↑ periportal space
        - Posterior notch
        - ↑ caudate and lateral segment
        - ↑ candate-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.

- Give 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.

- Give 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

- Give 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

- Give the mechanism(s) of action of drugs used to treat portal hypertension (PHT).

❖ ↓ Portal Blood Flow → ↓ PP (Portal Pressure)

- Octreotide
  - ↓ glucagon
    - ↑ splanchnic vasoconstriction
    - ↓ portal and azygous blood flow
    - ↓ postprandial splanchnic blood blow
  - ↓ 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

- Nitrates
  - Venodilation from ↓ Ca_i^{2+} in smooth muscle in venous wall
- Under study
  - A1-adrenergic antagonists
  - ARBs (angiotensin II receptor type I blockers)
  - Nitrates

Coagulopathy

- Give 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 dysfibrogenemia
    - Altered production of activators / inhibitors of fibrolysis
    - Endotoximemia-associated activation of coagulation cascade
    - ↓ clearance of fibrinolytic proteins
    - ↑ D-dimer
    - ↑ fibrinogen degradation products
    - ↑ clot lysis time

A Practice Curiosity

In cirrhosis, the increase in INR predicts a bad prognosis, but the risk of spontaneous bleeding is not increased by ↑ INR (of course ↑ 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”!

ASCITES

- Definition
  - Free fluid (> 25 mL) in the peritoneal cavity
- 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
    - $Na^+ < 10$ mmol/L
- Pathogenesis

- Give the current theory of the **pathogenesis** of ascites.
  - PHT → ↑ NO → vasodilation →↓ effective arterial BP
    → ↑ vasoconstrictors
    → ↑ vasopressin
    → ↑ renal-aldosterone
    → ↑ sympathetic nervous system (SNS) activity
    → ↑ Na+ -retaining hormones

→ ↑ renal vasoconstriction → ↓ renal function → ↑ retention of Na^+ / H_2O → 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).

- 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 (↑ 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 ↓ 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

- Give an approach to distinguish between hepatic and cardiac causes of ascites:

Sample	Cirrhotic	Cardiac
➢ Ascitic fluid		
o Protein	↓	↑
➢ Blood		
o Hematocrit < 32	Yes (in 32%)	No
o PbNP median concentration (pg/mL)	166	6100

Abbreviation: pbNP, pro-brain-type naturetic peptide

➢ Tips about Ascites

- o If ascitic fluid contains ↑ lymphocytes (not PMNs), suspect
  - Tuberculous peritonitis
  - HCC / hepatic metastases
  - Pancreatitis
- o When malignancy causes the ascitic fluid, it is due to
  - Peritoneal carcinomatosis (commonest causes)
  - Hepatic metastases
  - HCC (hepatocellular cancer)
- o Cytology of ascitic fluid is ~ 100% sensitive to detect peritoneal carcinomatosis, but the sensitivity to detect $1^o/2^o$ liver tumor is low.
  - Increased neutrophils, or fat (chylous ascites) makes ascitic fluid cloudy
- o Ascitic fluid becomes creamy coloured (chylous) when the concentration of triglyceride in ascites > 200 mg/dL.
- o Chylous ascites occurs with cirrhosis, rupture of the intra-abdominal lymphatics (e.g. malignancy surgery – retroperitoneal, radical pelvic)
- o Dark brown (not pink or red) ascitic fluid (bilirubin concentration in ascitic fluid > 6 mg/dL) suggests perforation of
  - Biliary tree
  - Duodenum / jejunum

- In NA (North America, ie. Canada and USA [ascitic]), 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).
- In HIV / AIDs, TB and coccidiodomycosis occur, and look the same on laparoscopy.
- In a patient with chronic renal failure on hemodialysis, look hard for causes of ascites before diagnosing idiopathic (nephrogenous) ascites.
- ↑ 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

- Give indications for **diagnostic paracentesis.**
  - Ascites, new onset
  - SBP, suspected
  - Admission to hospital
  - GI bleeding
  - Shock
  - Fever
  - HE (hepatic encephalopathy)
  - Systemic infection / sepsis
  - Non-specific GI symptoms
  - Worsening liver function
  - Worsening renal function
  - Practical suggestion
    - In cirrhotic ascites, have the mindset to perform a diagnostic paracentesis (DP), unless there is a good reason not to do so!

CLINICAL TRICKS!

- How can you predict if a patient with ascites will need diuretics to mobilize their ascites?
- Na^+ is lost from the body through renal excretion as well as from non-renal sources (e.g. sweating).
- If you are on an 88 mEq per day salt diet, to remain in Na^+ balance, you will excrete 88 mEq per day, (determined on a 24-hr urine collection)
- So, if a patient is on a 2 gm salt diet, she/he will excrete 88 mEq Na^+ in the urine each day.
- If the daily urinary Na^+ excretion is ≥ 88 mEq/day, the patient may mobilize their ascites by diet alone.

CLINICAL SCENARIO

A cirrhotic patient on furosemide plus addiction develops painful gynecomastia, but his healthcare plan does not provide for switching the spironolactone to amiloride.

- Give the other therapy that can be used so that the patient continues to enjoy the K^+ retaining effects while still taking the K^+-depleting furosemide.
  - Tamoxifen is useful to treat painful gynecomastia, even if the causative agent, the spironolactone, is continued.

➢ Prognosis

- 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.

➢ Treatment

- Clinical Tips
  - Avoid drugs which may worsen ascites, or other liver complications.
    - NSAIDs
      - Inhibition of prostaglandin synthesis is associated with
        - Renal vasoconstriction
        - Worsening of renal function lowering of response to diuretics
    - ACEIs/ARBs (angiotensin converting enzyme inhibitors/angiotensin II receptor blockers)
    - Beta-blockers
    - Aminoglycosides
    - Amphotericin
    - ACE-inhibitors (ACE-I) / ARBs
    - Angiotensin II antagonists
    - α1 adrenergic receptor blockers
    - β blockers
    - Cautious use of contrast media for diagnostic imaging

  - The treatment of ascites is not an emergency, but likely represents decompensation from previously compensated liver disease.
  - Understand the treatment objectives
    - Patient may look and feel better with treatment of ascites
    - ↓ abdominal discomfort
    - ↓ dyspsnea
    - ↓ risk of SBP (spontaneous bacterial peritonitis), from ↑ opsonic activity in ascitic fluid
    - ↓ plasma volume
    - ↓ portal pressure
    - ↓ risk of EVB (esophageal variceal bleeding)
    - Slowly remove ascitic fluid to prevent redevelopment of HRS (hepatorenal syndrome)
      - No peripheral edema, ~ 500 mL/day, or 0.5 kg body weight
      - With edema, faster removal possible
      - Some authorities suggest more aggressive therapeutic paracentesis, ie. large volume paracentesis, (LVR) with albumin infusion

- Treat the underlying
  - Liver disease
  - Complication

- Salt restricton, 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 ($\uparrow Na^+$, $\uparrow$ or $\downarrow K^+$)

- Give 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 prerequition 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).

- 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 diureses
  - TIPS will modulize 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
- The peritoneal surface absorbs only up to 500 mL/day of ascitic fluid.
- Excessive use of diuretics above this physiological level of ascitic fluid mobilization of 500 mL/day
  - Does not ↑ removal of ascitic fluid
  - Causes depletion of fluid from intravascular spaces.
  - Causes contraction alkalosis and prerenal azotemia.
  - Spot urine Na^+ < 10 mmol/L
- Undertake vaccinations
  - 1^o / 2^o prevention of bleeding from esophageal / gastric varices
- Consider diagnostic paracentesis to rule out spontaneous bacterial peritonitis (SBP)

CLINICAL CAUTION

- BB (beta blockers, including non-specific BB [NSBB])
  - May ↑ resistance to diuretics
  - May ↑ mortality from diuretic-resistant ascites
- Beta-blockers are relatively contraindicated in cirrhotics with ascites.
- But, did you know - Initiation of the beta-blocker nadolol in cirrhosis patients with high risk varices can delay or prevent the first occurrence of clinically evident ascites seen in patients who have ≥ 10% ↓ in baseline HVPG pressure.

Clinical Gem

- 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.

Diuretics

- Give the laboratory guidance for diuretic therapy in cirrhotic patients with ascites.
  - Spot urine sample Na^+ > 10 mmol / L
  - 24-hr urine culture Na^+ > 78 mEq / day while on 2 g / d salt diet
  - Urine Na^+ / urine K^+ >1

- Give the reason why diuretic use should **not** be overaggressive.
  - Start with furosemide 40 mg plus aldactone 100 mg po 8 am, slowly increasing to maximum of 160/400 per day, depending upon response and creatinine.
    - Regular monitoring of serum electrolytes, and daily intake of Na+
    - Consider obtaining daily weight of patient
    - Urinary electrolytes if response to diuretics stalls
  - IV albumin may be effective to assist diuresis
  - Stopping rules
    - Hypokalemia < 3 mmol / L d/c furosemide
    - Hyperkalemia > 6 mmol / L d/c aldactone
    - In the presence of ascites requiring therapeutic paracentesis, stop diuretics if Na^+_u > mmol/day
    - Cr > 180
    - Hyponatremia < 120 mmol / L, d/c diuretics, consider fluid restriction (~ 2 L/ day)
    - Development of hepatic encephalopathy, reassess need for diuretics
    - Development of SBP, consider stopping diuretics

- For grade 3 ascites (large or gross ascites with marked abdominal distention), LVP (large volume paracentesis) is recommended, with albumin 8 g/L of ascites removal
  - Continue non-added salt diet plus lowest possible doses of diuretics to prevent re-accumulation of the ascites
  - Stop diuretics if Na^+_u > 30 mmol / day

SO YOU WANT TO BE A HEPATOLOGIST!

Some patients with cirrhosis have diabetes and associated proteinuric chronic renal disease, so that it might seem reasonable to treat with angiotensin inhibition. Alternatively, the cirrhotic patient may have unassociated systemic hypertension (cirrhosis itself is associated with systemic hypertension).

- Give the reason why ACEIs/ARBs should be avoided in the patient with cirrhosis +/- ascites.
  - In cirrhosis
    - Systemic hypertension is associated with ↑ renin-angiotensin system activity
    - Renal perfusion and glomerular filtration may already be reduced
  - Giving ACEIs/ARBs may dramatically further lower systemic blood pressure and worsen already impaired renal function.

➢ Vaptans
  - IV canivaptin
  - PO tolvaptin 15 mg po od, slowly titrated to 60 mg / day, with slow increase of serum Na^+ < 8 mmol / L (to avoid the osmotic demyelination syndrome)

Trivia
  - The laparoscopic appearance suggestive of peritoneal TB
    - "millet-seed"
    - "violin-string"

- Give examples of **non-diuretic treatments** for ascites.

o Peritoneal carcinomatous from ovarian cancer	– Surgical debulking
o Tuberculous ascites	– Appropriate antituberculous therapy
o Chlamydia ascites	– Tetracycline
o Lupus	– Glucocorticosteroids
o Nephrogenous ascites	– Hemodialysis
o Alcoholic cirrhosis	– Stop drinking alcohol
o NASH	– Weight loss
	– Treatment of metabolic syndrome
	– Vitamin E (possibly)
o AIH	– Corticosteroids / immune suppression
o Portal hypertension	– Low salt / fluid restriction
o HBV	– Interferon, or oral nucleoside
o HCV	– Interferon plus ribavirin plus third agent
o Preoperative	– Change IV from normal saline
o Paracentesis	– Continue regular paracentesis, including LVP
o TIPS	– Doppler ultrasound to exclude possible vascular obstruction (eg. Budd-Chiari syndrome)
	– Consider inserting new stent

Abbreviation: LVP, large volume paracentesis

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

Og Mandino

SO YOU WANT TO BE A HEPATOLOGIST!

- Give **precautions** to consider when using vaptans.
  - Restriction of water intake is often used to treat hypervolumic hyponatremia, but this is not recommended when the cirrhotic with ascites and hypervolemic hyponatremias is treated with tolvaptin.
  - Do not use IV saline
  - Do not use drugs that either inhibit or induce CYP 3A enzymes in the liver.
  - Do not use vaptans if the patient has a reduced level of consciousness, such as from hepatic encephalopathy.

- Give the **reason for these restrictions** when using tolvaptin for hypervolemic hyponatremia.
  - Daily changes of serum Na^+ concentration of > 8 to 10 mmol / L per day may cause osmotic demyelination syndrome.
  - Rapid changes in serum Na^+ with IV saline are to be avoided, and the saline may only make the associated ascites worse.
  - Drugs that inhibit CYP 3A4 (ketoconazole, clarithromycin, grapefruit juice) will increase the blood concentration of vaptans, whereas inducers of CYP 3A (such as rifampin, barbiturates, phenytoin) will decrease the blood concentration of vaptans, and therefore their effectiveness.

Refractory Ascites

- 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)

- Terms
  - 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.

- Prognosis
  - 1 year mortality rate for ascites refractory to medical care ~ 68%

➢ Treatment

- Give a treatment strategy for refractory ascites.
  - Total paracentesis, plus albumin infusion
    - 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
  - 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
  - Coated stent
    - 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

- Give the pros and cons of **albumin infusion** being given in conjunction with a therapeutic paracentesis.
  - Pros
    - Prevents post-paracentesis ↑ renin concentration and development of paracentesis-induuced circulation dysfunction
    - Risk of hepatorenal syndrome after therapeutic paracentesis > 5 L ascites
  - Con
    - No benefit on survival rate
    - ↓ opsonin in ascitic fluid
    - Considerable cost
    - Increasing serum albumin concecntration leads to
      - ↑ breakdown of albumin
      - ↓ synthesis of albumin

Abbreviations: TIPS, transjugular intrahepatic portosystemic shunt

Printed with permission: Garcia Tsao, et al. *Am J Gastroenterol* 2009; 104:1816.

SO YOU WANT TO BE A HEPATOLOGIST!

- 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

- Give 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.

- Give types of tumors which commonly metastasize to the peritoneum.
  - Adenocarcinoma - GI
    - Stomach
    - Colon
    - Pancreas
  - Lymphoma - Non-GI
    - Ovary
    - Lung
  - Sarcoma

➢ Pathophysiology

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- Give 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

➢ Clinical

SO YOU WANT TO BE A GASTROENTEROLOGIST!

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

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 monomibrobial non-neutrocytic bacterial (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
  - An ascitic fluid count of ≥ 250 PMN /mm^3 makes the diagnosis of spontaneous bacterial peritonitis (SBP), and empiric antibiotic treatment must be started immediately, with adjustment of antibiotic when culture results come back – "do not wait for the cultures"
  - The causative organisms of SBP are E. Coli, Klebsiella, and eg., less frequently Streptococcus and Staphylococcus.

- Types

- Give the types of SBP.

	PMN / mm^3 (> 250 neutrophils)	Ascitic culture	Rx
Primary			
– Classical SBP	+	+	+
– Culture-negative neutrocytic ascites (CNNA)	+	-	+
– Monomicrobial nonneutrocytic bacterial (MNB) ascites	-	+	-
Secondary ascites (bacteriascites)			
– Nonneutrocytic* polymicrobial	-	+	+

*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; 1º, primary; 2º, secondary

- Diagnosing secondary bacterial peritonitis (2º 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**.

- 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,

- Give the exception.
  - With ascites associated with rupture of the gallbladder, the ascitic fluid amylase concentration will be normal.

Bacterial peritonitis may be caused by perforation of the bowel, causing secondary bacterial peritonitis.

- False positive neutrocytes in ascitic fluid
  - An ascitic fluid neutrocyte count > 250 mm^3 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 / mm^3 (Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier, Philadelphia, 2010, page 1523).

- Give 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, substrate 1 PMN in order to achieve a corrected count to diagnosis neutrolytic ascites.
  - Caution: if a blood contamination tap has set 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.

CLINICAL ALERT

- 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
  - To the development of renal failure
- Persons at risk of developing SBP include
  - Those with a previous episode of SBP
  - SBP occurring with variceal hemorrhage
  - Low protein ascites
  - Use of proton pump inhibitors
- Once SBP has occurred, the one year mortality rate is 50-70%

CLINICAL TIP

For treatment purposes, consider mono-microbial non-neutrocytic bacterial (MNB) and culture-negative neutrocytic ascites (CNNA) and as spontaneous bacterial peritonitis (SBP, aka neutrocytic, culture positive monomicrobial ascites)

- Pathophysiology
  - 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 esophagealvarices 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 hepaticencephalopathy

- 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)
  - If there is ascites, tap it to exclude treatment SBP, rather than assuming these symptoms / signs are just from the alcoholic liver disease (acute alcoholic hepatitis).

SO YOU WANT TO BE A GASTROENTEROLOGIST!

A patient with paracentesis-proven ascites who is in another hospital has persistent ascitic fluid PMN > 250 cell / mm^3 on second tap after 4 days of IV cefotaxime

- Give questions that you need to ask to help you determine if the patient is at increased risk of cefotaxime-resistance, or the need to alter their diagnosis, and for the cefotaxime to be replaced by levofloxacin.
    - Cefotaxime resistance in SBP is more likely if the patient has
        - Renal dysfunction
        - High MELD score
        - A urinary catheter
        - A central line
        - Acquired the SBP while in hospital (nosocomially acquired, representing 41% of cefotaxime-resistant cases
        - Frequent contact with healthcare workers increases the risk of cefotaxime resistance (21%)
        - Previous quinolone prophylaxis, e.g. previous SBP, or EVB (esophageal variceal bleeding)

- Criteria for diagnosis
    - Cirrhosis with ascites
    - Serum creatinine >1.5 mg/dl (133 mol/L)
    - Absence of shock
    - 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
    - volume expansion with albumin at 1 g/kg/day up to a maximum of 100 g/day
    - No current or recent treatment with nephrotoxic drugs
    - Absence of parenchymal renal disease as defined by proteinuria <0.5 g/day, no microhaematuria (<50 red cells/high powered field), and normal renal ultrasonography

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 8.

Please see: Swan MG. Chapter 58. In: Therapeutic Choices. Grey J, Ed. 6th Edition, Canadian Pharmacists Association: Ottawa, ON, 2011, Table 1: Ascites, page 773.

- Laboratory
  - The median colony count of bacteria in the ascitic fluid in SBP is only 1 organism per mL
  - When ascitic fluid contains 10^4 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).

- Treatment

- **SBP and CNNA (Culture-negative neutrocytic ascites)**

- 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.

MCQ TRICK

- SBP is considered to be “primary, and includes “classical SBP” CNNA and MNB
- MNB is not treated
- Strictly speaking, in a question such as the above, while secondary non-neutrocytic polymicrobial ascites is of course treated, it would not be included in the answer because it is not truly SBP.

- 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*
- 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 rena dysfunction persists
  - Avoid aminoglycosides
- 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
  - Please see below

* 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.

- 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 ≥ 68 µmol / L) and renal failure (serum creatinine ≥ 88 µmol / 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 diagnostic paracentesis, and if
    - Neutrophils > 250 / mm^3, treat as for classical SBP or CNNA
    - Neutrophils < 250 / 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)

➢ Prevention

- Indications for prophylaxis
  - 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.

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.

Interesting Clinical Treatment Challenges Following SBP

Ascitic fluid neutrophils ≥ 250 / mm^3	Ascitic fluid culture	Treatment for SBP
Yes	Yes	Yes
Yes	No	Yes
No	Yes	Repeat diagnostic paracentesis, and if Neutrophils > 250 / mm^3, treat Neutrophils < 250 / mm^3, follow patient

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.

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 gran-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 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)

- Definitions
  - 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).
  - Hyponatremia may preceed the development of HRS (type I HRS)
  - Other important definitions
    - Most cirrhotics with renal dysfunction do not have HRS (only 15-20% have HRS)
    - is associated with intense vasoconstriction, which may cause the HRS to progress to acute tubular arterial necrosis (ATN)
    - No parenchymal renal disease, as defined by
      - Proteinuria < 500 mg/day
      - No microhematuria (< 50 red cells/high powered field), and
      - Normal renal ultrasonography (no obstruction; < 1.5 mg/dL)
    - No hypovolemia, as defined by no sustained improvement of renal function (creatinine decreasing to <133 mol/L) following at least
      - 48 hr of diuretic withdrawal (if on diuretics), and
      - Correction of hypovolemia with adequate volume expansion with intravenous albumin
    - No nephrotoxic drug e.g.
      - Diuretics
      - Aminoglycoside
    - Contrast for diagnostic imaging
  - Suspicion of HRS
    - 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%
  - HRS reduces 3 year survival from liver transplant to 60% versus ~75% when there is no HRS

Printed with permission: EASL clinical practice guidelines. *J Hepatol*. 2010;53(3):397-417.

➢ Types

- Give 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)

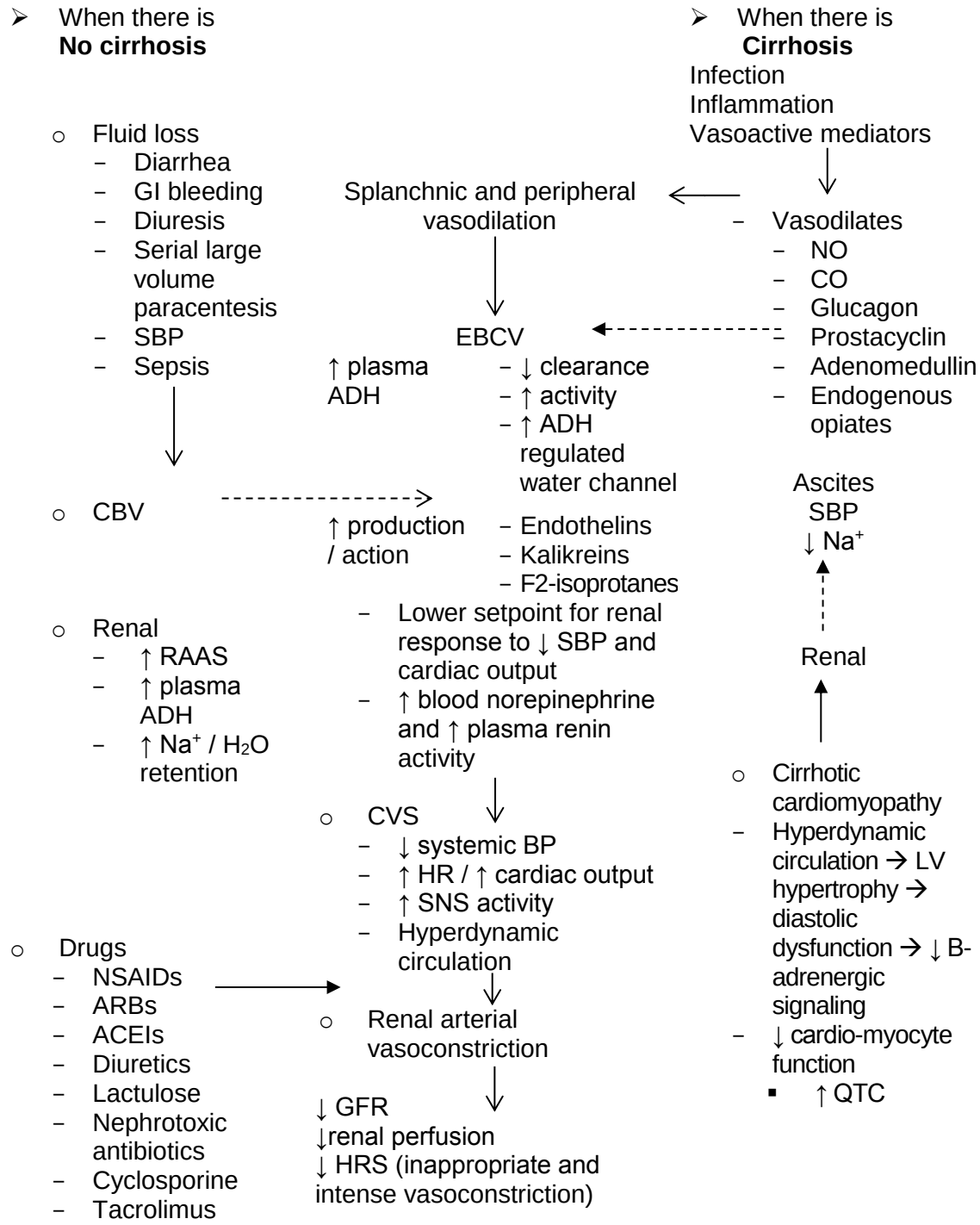
Abbreviations: ALF, acute liver failure; ATN, acute tubular necrosis; MAP, mean arterial pressure; SBP, spontaneous bacterial peritonitis; SBP, systolic blood pressure

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

- Give the pathophysiology of renal arterial vasoconstriction.



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-antgiotensin-aldosterone system; SBP, systemic blood pressure

➢ Diagnosis

- 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 ↑ 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)

CLINICAL TIP

- Change in the serum creatinine (Cr) concentration may be a better indicator of the diagnosis of HRS than an integrated baseline Cr.
  - The urinary Cr may be lower in the malnourished cirrhotic, so that an abnormal creatinine concentration (<1.5 mg/dL [> 133 µmol/L) may be present, despite a ↓ CrC (creatinine clearance) < 20 mL/min.

- 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.

- Give the laboratory variables used to differentiate between prerenal azotemia (PRA), hepatorenal syndrome (HRS), and acute renal failure (ARF).

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: Osmp, osmolality of plasma; Osmu, osmolality of urine

- Longterm criteria
  - Cirrhosis, plus ascitic fluid total protein < 1.5 g/dL, plus Child-Pugh score > 9, plus serum bilirubin > 3 mg/dL (> 51.3 µmol / L), or
  - Serum creatinine > 1.2 mg / dL 100 µmol / L, or
  - Blood urea (nitrogen > 20 mg / dL, or
  - Serum Na^+ < 130 mEq / L

CLINICAL DELEMMA:

- Does HRS cause acute tubular necrosis (ATN)?
- The intense renal vasoconstriction of HRS may cause renal ischemic and could possibly cause ATN.
- Rather than entering this debate, look for other precipitants of ATN, e.g.
  - Bleeding
  - Sepsis
  - Drugs:
    - Diuretics in excess
    - Aminoglycosides
    - Contrast material for diagnostic imaging, e.g. CT contrast
    - ACE inhibitor / ARBs
- In every patient with possible HRS / ATN, give a fluid challenge
  - If serum Cr does not fall, then presume a diagnosis of HRS, and treat according.
- If the patient is on diuretics and may have diuretic-associated azotemia, stop the diuretics before considering the diagnosis of HRS.

Abbreviations: ACE, angiotensin converting enzymes; ARB, angiotensin receptor blocker

- Prevention of HRS
  - Severe alcoholic hepatitis – pentoxifylline
  - Severe cirrhosis – Norfloxacin ↓ risk of HRS
  - Treat / prevent spontaneous bacterial peritonitis (SBP)
    - Albumin infusion day1, 2
      - 1.5 g/kg
    - Day 3
      - 1.0 g/kg albumin
    - Norfloxacin (NOR)
      - 400 mg per day

- Drugs to avoid
  - NSAIDs
  - ACE inhibitors / ARBs
  - Antibiotics
  - Diagnostic imaging (CT) contrast
- Combined kidney-liver transplantation
  - HRS, non-response to vasopressors, prolonged renal support > 12 weeks

Abbreviations: ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; IV, 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.

- Treatment
  - Consider HRS in a patient with cirrhosis and ascites and
    - Creatinine level of >1.5 mg/dL
    - NSAIDs, diuretics, other nephrotoxic drugs
  - Where possible, treat the underlying liver disease
  - Exclude prerenal and renal causes of ↑ serum creatinine, including bacterial infection (most common and important trigger for HRS).

- Pharmacotherapy
  - Stop nephrotoxic drugs
    - 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 µmol / 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 date for the efficacy of norepinephrine (NOR) or midodrine, plus octreotide plus albumin.
    - Octreotide 100 µg to 200 µg SC tid, plus

Outcome	NOR	Placebo
↓ risk of HRS 1-yr	28%	41%
↑ survival 3-month	94%	62%
1-year	60%	48%

  - Alternative (bridging therapy)

Vasoconstrictors plus albumin for ≥ 7 days	Octreotide plus	100-200 mcg SC tid	Goal : ↑ MAP by 15 mmHg
	Midodrine, or	5-15 mg po tid	
	Terlipressin[a]	0.5 – 2.0 mg IV every 4-6 h	
		50-100 g IV qd	

  - 35-50% of type I HRS responds to vasoconstrictors (midodrine, terlipressin, norepinephrine)

Abbreviation: MAP, mean arterial pressure

- Note: There are other drugs which have been successfully used to prevent SBP, and not necessarily been studied yet to prevent HRS, such as
  - Ciprofloxacin 500 mg po od, or TMX (trimethoprim-sulfamethoxazole, 1 double-strength tab po od, or
  - Ceftriaxone 1 gm IV per day (please see below, prevention of SBP).

- 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

"Rewarding anticipation activates a reward network: that is the success of the not-so-common random acts of kindness."

Grandad

HEPATIC ENCEPHALOPATHY (HE; aka PSE, PORTOSYSTEMIC ENCEPHALOPATHY)

- Demography
  - HE occurs in ½ to ¾ of cirrhotics
  - Effects of HE non-transplanted mortality rate > 50% in 3 year

- Pathophysiology

- Give an outline of 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

	glutaminase (deamination)	
glutamine	→	glutamate + NH_3
	←	glutamine synthetase (amination)

    - 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
    - NH_3 → urea, periportal hepatocytes → glutamine, perivenous hepatocytes
    - In presence of hyponatremia, myoinositol falls, with less compensation for ↑ intracellular glutamine
  - Skeletal muscle
    - Normally responsible for uptake of 50% of NH_3
    - In cirrhosis, atrophy of skeletal muscles → ↓ muscle synthesis of glutamine
  - Kidney
    - ↑ 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
  - ↑ brain blood flow
  - ↑ blood brain barrier permeability → ↑ brain NH_3 and glutamate → astrocyte swelling
- In presence of hypokalemia and metabolic alkalosis, $NH_4 \rightarrow NH_3$, which crosses BBB
- Plasma NH_3 > 150 µmol is associated with brain herniation
- Abnormal form and function of astrocytes, with reduced glutamine synthetase and peripheral type benzodiazepine receptors (PTBR)
  - ↑ mitochondrial permeability → ↑ astrocyte swelling → ↑ brain edema
- ↑ NH_3 activates N-methyl-D-aspartate-nitric oxide-C-guanylate cyclase (NMDA-NO-C6MP) signal transduction pathway → impairment of
  - Memory
  - Learning
  - Sleep

- Brain
  - ↑ BB permeability → ↑ NH_3 uptake
  - ↑ NH_3 taken uptake into
    - Cerebellum
    - Basal ganglia
    - ↑ brain edema
    - ↑ swelling of astrocytes - ↑ neurosteroids → ↑ activity of GABA-benzodiazepine system
    - ↑ benzodiazepine system
    - ↑ production of glutamine by astrocytes

Neurotransmitter system	Findings in HE
○ ↑ GABA, ↑ serotonin	– ↑ serotonin turnover, synaptic defect
○ ↑ endogenous BZs	– Neuro-inhibition
○ Glutamate (neuro-excitation)	– ↓ receptors → ↓ uptake of glutamate – ↓ glutamatergic neurotransmitter function
○ Dopamine/Noradrenaline (motor/cognitive)	– ↓false neurotransmitters

Abbreviations: BZ, benzodiazepine; GABA-γ-aminobutyric acid

➢ Histopathology

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

- Give the clinical neurological deficits in MHE.
  - Affect/ emotion
  - Behaviour
  - Cognition/ memory/ attention
  - Note: Language and verbal skills are relatively spared in HE
- Give important areas of assessment of the patient with possible MHE.
  - Exclude other causes of metabolic encephalopathy
  - Exclude possible precipitating factors of HE
  - 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)

- 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-orperate with the physical examination will have tremor and asterixis. Patients with stage 3 or 4 may not be able to corporate for the clinical testing for these signs.

- Give (upper motor neuron) signs in stage 3 or 4 HE which can be demonstrated without the patient's co-orporation.
    - Hyperreflexia
    - Clonus
    - Hyperigidity
    - 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 cerebal edema complicating worsening encephalopathy" (Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier 2010, page 1601).

➢ Laboratory

The finding of an elevated serum ammonia concentration is not specific for the diagnosis of hepatic encephalopathy.

- Give 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 NH3 ≥ 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 → ↓ 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.

"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

- Treatment

Diagnosis of hepatic encephalopathy

Rule out other causes of encephalopathy

- Drugs
  - Sensitivity to CNS drugs
  - Drug intoxication
- CNS
  - Prior seizure or stroke (postictal confusion)
  - Delirium tremens
  - Wernicke-Korsakoff syndrome
  - Intracerebral hemorrhage
  - CNS sepsis
  - Cerebral edema and/or intracranial hypertension*
- Lung
  - Hypoxia
  - Hypercapnia
  - Acidosis
- Kidney
  - Gross electrolyte changes
  - Uremia
- Endocrine
  - Hypoglycemia*
  - Pancreatic encephalopathy

Identify precipitating cause of hepatic encephalopathy

- Gastrointestinal hemorrhage
- Constipation / dietary protein overload
- Poor compliance with lactulose therapy
- Recent anesthesia
- Bowel obstruction or ileus
- Liver
  - Prior portal decompression procedure (eg. TIPS)*
  - Superimposed hepatic injury*
  - Development of hepatocellular carcinoma
- Dehydration
- Hypokalemia / alkalosis
- Uremia
- CNS
  - CNS active drugs
  - Sepsis

Initiate empiric treatment for hepatic encephalopathy

- Lactulose, oral dose of 1-30 ml twice daily
- Rifaximin, oral dose of 550 mg twice daily
- Neomycin, oral dose of 500 mg four times daily (use high doses with caution)
- Metronidazole, oral dose of 250 mg four times daily
- Vancomycin, oral dose of 250 mg four times daily
- Sodium benzoate, oral dose 5 g twice daily (not approved for use in the USA)
- Flumazenil, intravenous injection of 1-3 mg (potentially effective, but very short duration of action)

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), lacitol beta-galactosidosorbitol (traps NH_3)
  - Enters colon, broken down by colonic bacteria to lactic acid and acetic acid, with acidification of stool pH < 5

$$NH_3 \xrightarrow{pH < 5} NH_4^+ \text{ (non-absorbable)}$$

- 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 → ↓ NH_3

- Antibiotics (pre-, pro- and synbiotics)
  - ↑ lactobacillus spp., ↓ urease-containing bacteria → ↓ NH_3 production
  - ↑ bacterial NH_3 utilization
  - ↓ pro-inflammatory response
  - ↓ gut permeability
  - ↓ bacterial translocation

- L-ornithine-L-aspartate (LOLA)
  - Activate the urea cycle → ↑ NH_3 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 (proprionate, butyrate, violerate)

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 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. ↑ severity of HE score
    - ↑ agitation
  - Titrate sedation to point where patient's speech is slurred.

➢ Prognosis

- Give the survival rate and etiological factors for the 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 microbiotica
  - This ↓ microbiotica → ↓ 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

Minimal Hepatic Encephalopathy (MHE)

- Give reasons to diagnose and treat MHE.
  - ↑ cognitive function
  - ↑ driving performance
  - ↑ performance in workplace
  - ↑ quality of life
  - ↑ sleep
  - ↑ survival
  - ↓ development of overt clinically evident HE

Adapted from: Ortiz M, et al. *J Hepatol* 2005;42 Suppl(1):S45-53.

- Give management options for MHE.
  - Reverse any precipitants (eg. drugs)
  - Cathartics: Lactulose
  - Antibiotics: Flagyl, vanesmycin, ampicillin, rifampin
  - Probiotics

Adapted from: Holstege A, et al. *Best Practice & Research Clinical Gastroenterology* 2007; 21(3): pg. 541.

PULMONARY COMPLICATIONS OF CHRONIC LIVER DISEASE

➢ Causes / associations

- Give potential causes of **increasing dyspnea** in a patient with chronic liver disease.
  - Heart
    - Cardiac failure (including cirrhotic cardiomyotomy, and tricuspid valve incompetence)
  - Lung
    - Pulmonary hypertension (portopulmonary hypertension syndrome, PPH)
    - Pleural/pericardial effusions
    - Atelectasis secondary to ascites
    - Pulmonary embolus
    - Aspiration pneumonia
    - Pulmonary infection
    - Pulmonary fibrosis (methotrexate)
    - Interstitial lung disease
  - Metabolic
    - Acidosis
    - Severe anemia
  - Liver disease
    - Liver disease – associated with lung disease
      - Cystic fibrosis
      - α_1 – antitrypin deficiency
      - Pulmonary fibrosis from use of methotrexate
    - Pulmonary complications of chronic liver disease
      - Spontaneous bacterial hydrothorax
      - Hepatopulmonary syndrome (HPS)

Adapted from: Kim YK, et al. *Radiographics* 2009;29(3):825-37.

➢ Diagnosis

- 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)
  - Pleural tap
- Ascites
  - 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.

Spontaneous Bacterial Hydrothorax (SBH)

- SBH may develop in cirrhotic pleural effusion (hydrothorax) with / without ascites.

➢ Laboratory

- Give characteristics of pleural fluid in hepatic hydrothorax.
  - Cell count <250 polymorphonuclear cells mm^3 (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.

➢ Treatment

- Perform DP (diagnostic paracentesis) of hydrothorax
- If hydrothorax fluid
  - > 250 / mm^3 neutrophils, plus positive culture → treat> 500 / mm^3 but negative culture (in the absence of pneumonia)

HEPATOPULMONARY SYNDROME (HPS)

- Definition
  - Intra-pulmonary vasodilation and shunting occurring in the presence of chronic liver disease or pulmonary hypertension, resulting in acute or alveolar-arterial O_2 gradient > 15 mmHg (> 20 mmHg for persons > 64 years)
  - ↑ Aa PO_2 (age-corrected alveolar-arterial oxygen) gradient (< 64 years, 15 mm Hg; > 64 years, 20 mm Hg) arising from intrapulmonary vasodilation
  - Diagnostic approach if PO_2 from pulse oximeter is < 96, then there is likely moderate severe HRS (Pa O_2 < 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: $AaPO_2$, alveolar-arterial O_2 pressure gradient for oxygen; PaO_2, 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

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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 nitric oxide (NO) and carbon monoxide (CO) in cirrhosis complicated by hepatorenal syndrome.
  - NO
    - ↑ production / release of endothelin – 1 → ↑ endothelin – B receptors in pulmonary microvasculature → ↑ eNos (endothelin-1-mediated endothelial NO synthase → ↑ NO
    - ↑ bacterial translocation in gut → ↑ TNF-α → ↑ macrophages adhering to pulmonary vessels → ↑ iNos (inducible NO synthase) → ↑ NO
  - CO
    - The ↑ adherence of macrophages to pulmoandy vessels ↑ the production of CO through heme oxygenase-1

➢ Clinical

- Give the clinical changes which suggest that the patient with cirrhosis has developed HPS (hepatopulmonary syndrome).
  - Presence of cirrhosis plus
    - Platypnea (↑ 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 PaO_2 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

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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.
  - Platypnia – Dyspnea, which is
    - ↑ when upright
    - ↓ when supine
  - Orthodeoxia – Hypoxia / hypoxemia, which is
    - ↑ when upright

- Laboratory
  - ↑ $AaPO_2$ and ↓ PaO_2
  - Orthodeoxia (↑ hypoxemia on sitting up)
  - Lung perfusion showing brain uptake > 40% (↑ 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

- Special tests
  - Pulmonary function testing (PFT)
    - ↓ diffusion capacity on pulmonary function testing (PFT)

- 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
  - ↑ 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 PaO_2 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
  - O_2, 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 ↑ PA (pulmonary artery) pressure due to
    - Volume overload and ↑ cardiac output (from ↓ systemic vascular resistance and hyperdynamic circulation)

- ↑ pulmonary vascular resistance in PPH →
  - ↓ NO plus ↑ endothelin-1 → PA vasoconstriction
  - Obliteration of pulmonary arterioles may occur from intimal proliferation, adventitial fibrosis, and thrombosis of pulmonary vasculature
  - ↑MPAP > 25 mm Hg
  - ↑ PVR > 240 dynes /s / cm^{-5}
  - ↓ PCWP < 15 mm Hg
- ↑ mPAP (mean pulmonary arterial pressure)
  - > 25 mm Hg, at rest
  - > 30 mm Hg, with exercise
- ↑ PVR (pulmonary vascular resistance) > 240 dynes / sec / cm^{-5}
- The presence of
  - PHT (pulmonary hypertension)
  - Portosystemic shunts
  - Hemodynamic abnormalities in portal vein
- 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

- Fatigue, SOBOE, orthopnea, hemoptysis, palpitations
- Hypoxemia and cyanosis are absent
- PPH is more common in persons with cirrhosis and refractory ascites, and in 12% of persons evaluated for liver transplantation

Abbreviation: SOBOE, shotness of breath on exertion

➢ Differential

- 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 (platypnea) – Cyanosis – Finger clubbing – Spider angiomas	▪ Chest pain ▪ SOB on lying down ▪ No cyanosis ▪ RV heave ▪ Pronounced P2 component
○ 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
○ 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
○ ^{99m}TcMAA shunting index (“bubble study”)	–Normal/low PVR	▪ <6% roatrial opacification ▪ Elevated PVR ▪ Normal mPAOP ▪ Large pulmonary arteries

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
○ 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%	▪ Useful when MPAP > 25 and < 35 mmHg

Abbreviations: ^{99m}TcMAA, technetium-99 m-labelled macroaggregated albumin; CEE, contrast enhanced echocardiography; ECG, electrocardiogram; HPS, hepatopulmponary syndrome; MPAP, mean pulmonary artery pressure; 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
  - Bosentan (anti-endothelin activity) plus sildenafil (a phosphodiesterase – inhibitor) and prostacyclin reduce PA pressure
  - Anticoagulation plus long-term O_2 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 – Chicken-wire fibrosis
PBC	– Florid duct 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 (endoplastic 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

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- Give causes of **ground-glass hepatocytes**.
  - Chronic HBV
  - DILI (drug-induced liver injury)
  - Fibrinogen storage disease
  - Glycogenesis, type IV

PREGNANCY AND THE LIVER

- Demography
  - 1/200 prepancies
    - Hyperemesis gravidarium
    - 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

- Give which liver enzymes/ tests of liver function, indicate which increase, decrease, or remain unchanged in normal pregnancy.
  - Unchanged
    - AST, ALT
    - GGT
    - INR
    - Bilirubin
  - Increased
    - Alkaline phosphatase (↑ 2-400%)
    - Fibrinogen (↑ 50%)
    - α- and ß- 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

- Give 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.

- 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 1st trimester	IUGR, fetal brachycardia, hypoglycemia	-
Cyclosporine	**D**		+
D-penicillamine (teratogenic in humans; used for Wilson disease)	**X**	**Contraindicate**	
Interferon	C	**Not recommended**	+
Lamuvidine	C	Low risk	-
Methotrexate	**X**	**Contraindicated**	
Metronidazole	B		

Drug	FDA class	Risk in pregnancy	Risk with nursing
○ **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.

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- Give medications used in gastroenterology and hepatology which have an FDA (food and drug administration, USA) "X" category of fetal risk.
  - Cyclosporine
  - Methotrexate (IBD)
  - Ribavirin (HCV)
  - Thalidomide

- 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

- 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**

➢ Genetics

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- 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

➢ Pathophysiology
  - 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 phosphoplipids.
  - 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

- Give **changes in bile acid metabolism** which occur during pregnancy, and which increase the risk of choletithiasis.
  - ↑ cholesterol
  - ↑ supersaturation
  - ↑ bile acid pool
  - ↑ cholic acid
  - ↓ chenic acid (chenodeoxycholic acid)
  - ↑ volume of gallbladder (fasting/ fed states)
  - ↓ gallbladder contraction

A trick question

- Give 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

- Give factors associated with increased risk of **recurrent cholestasis** of pregnancy.
  - Further pregnancies
  - Drugs
    - Use of OCAs
    - Use of progesterone during subsequent pregnancy
    - Use of estrogen
  - Cholecystectomy for increased risk of
    - Cholelithiasis
    - Cholecystitis
    - Pancreatitis

Viral hepatitis may flare in pregnancy, and gallstones form in pregnancy, and both these as well as pre-existing gallstones may become symptomatic.

- 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.

"Try not to become a man of success but a man of value."

Albert Einstein

Liver Disorders seen only in Pregnancy

- Give the trimester of onset and treatment of 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

- Give mechanisms for the development of **hyperemesis gravidarium (HG)**, and 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
  - 2^{nd} - 3^{rd} trimester
- Pathophysiology
  - Usual cholestatic effects of estrogen in pregnancy, plus
  - Genetic predisposition
    - ↓ canalicular transporters for bile acids, phospholipids and cholesterol (amino phospholipid flippase), and
    - ↓ FXR (the nuclear regulator of bile acid synthesis)

- Risk factors
  - Previous ICP (50% recurrence)
  - Multiple pregnancies
  - 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 (T_2, T_3)
  - 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
      - Prematurity
      - Still birth
      - Spontaneous preterm labour and delivery,
      - Fetal compromise,
      - Fetal cardiac dysrhythmias
      - Meconium stained amniotic fluid
      - 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

- Give the clinical presentation and outcomes from intrahepatic cholestasis of pregnancy (ICP).

- Second or third trimester (T_2, T_3)
- 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

➢ Histopathology

- Liver biopsy is not necessary, but would show intrahepatic cholestasis, centralobular, with bile plugs in cannaliculi and hepatocytes

➢ Prognosis

- 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

➢ Treatment

- 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.

Printed with permission: European Association for the Study of the Liver. Guidelines: Management of cholestatic liver diseases. J Hepatol 2009; 51(2): 237–67.

- Give 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

- 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.

- Give the mechanisms of action of different types of drugs used for the **treatment of pruritus** in patients with cholestatic liver disease.
  - Decrease degree of cholestasis
    - UDCA (use after 1st trimester [T1])
  - Non-absorbable anion exchange resins
    - Cholestyramine
  - Changes in opioidergic neurotransmission
    - Naloxone
    - Natrexone
  - Hepatic enzyme (CYP452) inducers:
    - Rifampicin
    - Metronidazole
    - Phenobarbital
  - Cannabinoid agonist
  - Serotonin antagonists: ondansetron
  - Changes in threshold to experience nociception
    - Dronabinol
  - Antidepressants (SSRIs)
  - Sedation (antihistamines)
  - IV propofol
  - Gabaergic changes: gabapentin
  - UV light
  - Liver transplantation – removes cause of cholestasis

- Invasive procedures
  - Plasmapheresis
  - MARS (extracorporeal albumin dialysis)
  - Biliary drainage

Adapted from: Kremer AE, et al. *Drugs* 2008;68(15):2163-82.

- **T3 – Third Trimester**

ICP, ALF and HELLP

➢ Differential

Acute fatty liver of pregnancy (AFLP), the HELLP syndrome* and intrahepatic cholestasis of pregnancy (ICP) occur only in pregnant women.

- There may be overlap between AFLP and HELLP
- Occur in third trimester (T3)
- Treated by early ("expeditious") delivery
- Caution: the mother may deteriorate after delivery of baby, and require liver transplantation (LT)

- Give the distinguishing characteristics of ICP, HELLP and AFLD.

	ICP	AFLP	HELLP
➢ Clinical: 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%)

	ICP	AFLP	HELLP
➢ Laboratory			
○ Cholestasis	Marked	Modest and late	Mild or absent
○ ALT	Mild to 10–20-fold ↑	5–15-fold, ↑ variable	Mild to 10–20-fold ↑
○ 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
➢ Diagnostic 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 always be suspected of having this diagnosis, 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 PIGF [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 and Liver DIsease in Pregnancy

- Pathophysiology
  - Mother
    - Both HELLP and AFLP may be associated with maternal defects in the mitrochondrial oxidation of fatty acids arising from deficiency of LCHAD (long-chain 3- hydroxyacyl- CoA dehydrogenase).
  - Fetus
    - ↓ 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

- Give the role of deficiency of the mitochondrial fatty acid oxidation enzyme LCHAD (long-chain 3-hydroxyacyl-coenzyme A dehydrogenase) in AFLP.

  - ↓ 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.

- Clinical
  - Associations
    - Hyperreflexia
    - Peripheral edema
    - DIC (disseminated intravascular coagulation)
    - Abruption 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)

- Histopathology
  - 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
    - Hemolysis (from microangiopathic hemolytic anemia) unconjugated hyperbilirubinemia
      - ↑ LDH
      - ↓ haptoglobulin
    - ↑ 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 ≥ 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, give 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 (AFLP)

- Demography
  - 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 preclamptic 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

BEWARE: after AFLP, microvesicular steatosis may progress, and require liver transplantation!

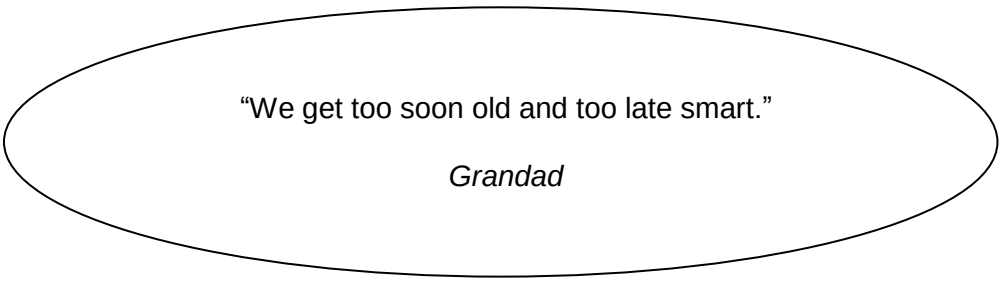
- **Liver Diseases occurring in Pregnancy which are not unique to pregnancy**
- Give the effects of underlying chronic liver disease toliver disease in pregnancy.
  - Rare to become pregnant
  - Prognosis variable
  - ↑ stillbirths
  - ↑ bilirubin → kernicterus

- 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 <u>contraindicated</u> 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
  - **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.

- Were the patient with WD to become pregnant, give the reason why copper-lowering therapy should be continued when D-penicillamine is teratogenetic 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 (T1) 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



JAUNDICE / HYPERBILIRUBINEMIA

➢ Pathophysiology

- 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 rug 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.

- Give 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-glucoronidase
  - Immature liver function
  - Delayed oral feeding

Printed with permission: Machida H. *First Principles of Gastroenterology* 2005: pg. 725.

- 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

- Cholestastic Jaundice (elevated serum alkaline phophatase, 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, telethromycin, 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

- Give 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.

➢ Causes / associations

- Give 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

Congenital Syndromes of Conjugated Hyperbilirubinemia

- Give a comparison of four congenital syndromes of conjugated **hyperbilirubinemia** 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)

- Conjugated hyperbilirubinemias (> 15% of total bilirubin is conjugated)
  - Dubin – Johnson syndrome
    - Defect in MRP_2 gene
  - Rotor syndrome
    - Defect unknown

[1] Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier, Philadelphia, 2010, page 1228.

- Give the variables to differentiate between Gilbert syndrome, Crigler-Najjar (CN) type-1 and -2, Dubin Johnson (DJ) syndrome, and Rotor syndrome (RS).

Variables	Gilbert	CN-T1	CN-T2
❖ Gilbert Crigler – Najjar (CN)			
○ Prevalence	7% of population	Very rare	Uncommon
○ Inheritance (all autosomal)	Dominant	Recessive	Dominant
○ Serum bilirubin concentration	< 100 µmol/L (all conjugated) - ↑ with fasting - ↓ with phenobarbital	> 400 µmol/L (all conjugated) - No response to phenobarbital	<100 µmol/L (about half conjugated) ↓ with phenobarbital
○ Prognosis	Normal	Early death from kernicterus	Usually normal
❖ Dubin Johnson (DJ) and Rotor Syndrome (RS)			
○ Treatment	None needed	Liver graft	Phenobarbital
○ Prevalence	Uncommon	Rare	
○ Inheritance (all autosomal)	Recessive	Recessive	
○ Serum bilirubin concentration (µmol/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	

- Give categories of causes of **conjugated** hyperbilirubinemia in the neonate, and for each give 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.

Lymphoma

- Give 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
  - 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 know 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
  - ↑ left atrial size
  - ↑ myocardial mass
  - ↑ BNP and pro-BNP
  - ↑ 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.

- 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 contractibility
  - 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.

➢ Treatment
  - Left heart failure is rare because of the reduced systemic vascular resistance not afterload reduction
  - Treatment requires preload reduction (O_2 diuretics, sodium restriction)

- Give hepatic conditions associated with cardiac abnormalities, such as arrhythmias and heart failure (HF).
  - HH (hereditary hemochromatosis)
  - Alcoholic cardiomyopathy
  - Cardiac cirrhosis from right-sided heart failure (HF)
  - Drugs, e.g. amiodarone toxicity

HEPATIC TUMORS

➢ Types

- Give the causes / types of hepatic masses / tumors seen on abdominal ultrasound.
- Benign lesions (usually require no further treatment)
  - Cavernous hemangioma
  - Focal fatty liver areas
  - Focal nodular hyperplasia (FNH)
    - 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
- Malignant
  - Cholangiocarcinoma (CA 19.9)
  - Cystadenocarcinoma
  - Epithelioid angiomyolipoma
  - Hemangioendotheliomatosis
  - Liver metastases
  - Lymphomas
  - Mixed epithelial and stromal tumours
  - Mixed hepatocellular-cholangiocarcinoma
  - Primary hepatocellular carcinoma
  - Sarcomas
- Abscesses / cysts
  - 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.

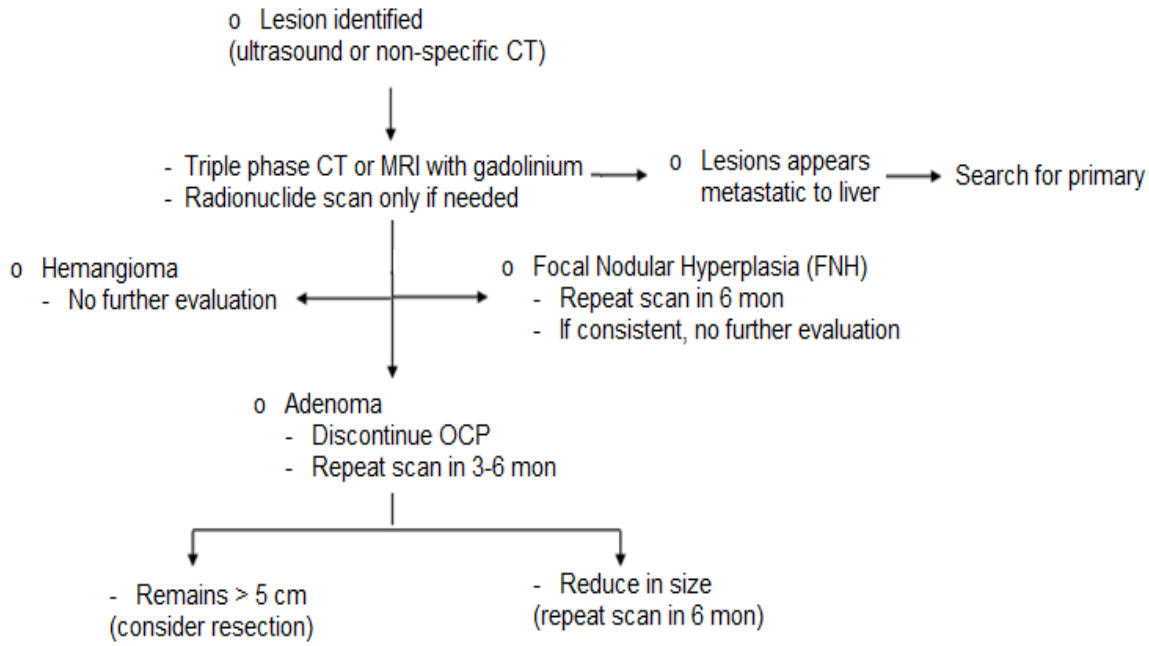
- When a mass is identified in the liver of a person with or without chronic liver disease, a triple phase CT or MRI with gadolinium is performed

- Nuclear scintigraphy with sulphur colloid is taken up by the Kupffer cells
  - ↑ uptake
    - Metastatic lesions (thyroid, breast, lung, pancreas, colon)
    - Hemangioma or cysts
  - ↓ uptake
    - Hepatic adenomas
    - Hepatocellular cancer (HCC)

- Radionucelotide scanning with RBC identifies an hepatic mass as an hemangioma

➢ Diagnosis

- Give an **algorithm** for evaluation of hepatic mass in a patient **without chronic liver disease.**



- Give the diagnostic workup of a liver mass in a patient **with chronic liver disease**.

The sequence of events needed to make the radiological diagnosis depends on the size.

○ Mass <1 cm	- Diagnosis	▪ Low likelihood of being HCC, therefore no specific diagnostic tests ▪ Repeat imaging study every 3 months		
	- Follow up	▪ If no growth in 1-2 years, no HCC; continue screening every 6 months ▪ If growth, treat as HCC		
○ Mass 1-2 cm	- Diagnosis	▪ Two dynamic imaging studies (US, CT scan, or MRI)	- Both with typical vascular pattern - One typical and the other atypical - Both atypical	▪ Treat as HCC ▪ Consider biopsy of mass
	- Follow up after biopsy	▪ Biopsy confirms HCC ▪ Non diagnostic biopsy	- Treat as HCC - Repeat imaging study every 3 months: - If no growth in 1-2 years- no HCC - If growth, treat as HCC	▪ Consider biopsy of mass vs. close follow up
○ Mass >2 cm	- Diagnosis	▪ One dynamic imaging study (US, CT scan, or MRI)	- Typical vascular pattern - Atypical vascular pattern	▪ Treat as HCC
	- Follow up after biopsy	▪ Biopsy confirms HCC ▪ Non diagnostic biopsy	- Treat as HCC - Repeat imaging study every 3 months: - If no growth in 1-2 years- no HCC - If growth, treat as HCC	▪ Biopsy of mass

The contrast enhanced imaging studies of computed tomography (CT) and magnetic resonance imaging (MRI) can use the unique dynamic radiological behaviour of hepatocellular carcinoma (hypervascular on the arterial phase and washout on the delayed venous phase).

Printed with permission: Garcia Tsao, et al. The *American Journal of Gastroenterology* 2009; 104:1822.

Hepatic Cysts

➢ Classification

- 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

➢ Diagnostic imaging

- Give 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
  - Hyperechic lesion with interspersed hypoechoia areas
    - Areas of
      - Necrosis
      - Hemorrhage
      - Fat
  - Vascular
    - Hemangiomas
    - Metastasis from NET (neuroendocrine tumor)

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
  - 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

- Histopathology
  - Common congenital malformation of the liver vasculature, with
  - Ectactic blood vessels with no malignant potential and not affected by oral contraceptive hormones.
  - Because of tortuous vessels and stasis, thrombosis and pain may occur

- Causes / associations
  - 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 / which is suggestive of a cavernous hemangioma.

- Give the findings of diagnostic imaging tests which suggest that a hepatic mass is a cavernous hemangioma.
  - CT or MRI contrast enhanced
    - Centipedal filling of contrast (from the periphery to the center)
    - Well circumscribes
  - RBC nuclear scan with technetium
    - ↑ Uptake of labelled RBC on the venous phage
    - ↑ 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/ 10^6 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

- Causes / associations
  - Estrogen and/or progesterone oral contraceptive agents (OCAs)
  - Anabolic steroids
  - Type I glucagon storage disease

- Pathophysiology
  - HNF 1α inactivation ,through biallelic mutations of the TCF1 gene
  - B-catenin activation
  - Acute inflammation

- Clinical
  - 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

- Histopathology
  - 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

➢ 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

"Be Modest-
There is always a taller mountain."

Grandad

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.

- Pathophysiology
  - Reaction to an arterial malformation

- Histopathology
  - Common congenital malformation of the liver vasculature, with hyperplasia of hepatocytes around the vascular abnormality, leading to a central scan
  - Hyperplastic regenerative nodules separated by fibrosis septae.

- Differential

- 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	10 - 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

- Causes / associations
  - Adenomas
  - Cavernous hemangiomas (20%)

- Epithelial hemangioendothelioma
- HHT (hereditary hemorrhagic telangiectasia)
- Not caused by OCA (oral contraceptive agents), but may enlarge under the influence of OCA
- The telangiectatic subtype of FNH is associated with estrogen use.

➢ Diagnostic Imaging
- Contract-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

- Give the diagnostic imaging features, which help to distinguish between hepatic hemangioma, focal nodular hyperplasia, and adenoma.

	Focal nodular hyperplasia	Hemangioma	Adenoma
• Ultrasound	○ Variable appearance well defined borders	- Hyperechoic well defined borders	- Non diagnostic
• Triple phase CT	○ Pre contrast: Hypo or isodense ○ Homogenous arterial enhancement ○ Hypodense central scar ○ Isodense in delayed imaging	- Pre contrast: hypodense - Centripital globular enhancement - Retained contrast in delayed images	- Pre contrast: Hypo or isodense - Irregular enhancement - Delayed peripheral arterial enhancement during venous phase
• MRI	○ T1: low signal ○ T2: Hyperintense signal with central scar	- T1: well circumscribed low signal - T2: Hyperintense signal	- T1: Low signal intensity with well defined capsule - T2: Heterogenous enhancement

	Focal nodular hyperplasia	Hemangioma	Adenoma
• Gadolinium enhanced MRI	○ Homogenous arterial enhancement ○ Hypodense central scar ○ Contrast accumulates in scar on delayed T1	- Progressive enhancement - Delayed washout on venous phase	- Irregular enhancement with delayed washout
• Radionuclide scan (tagged RBC)	○ Equal or ↑ uptake compared to surrounding liver	- ↑ uptake during venous phase - Delayed emptying	- ↓ uptake compared to surrounding liver

Source: Shiffman ML. *2009 ACG Annual Postgraduate Course*:167-171.

- Give 6 clinical, laboratory and diagnostic imaging **differences** between **FNH and FLHCC** (fibrolamellar hepatocellular cancer).

Feature	FNH	FLHCC
○ 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	+	-

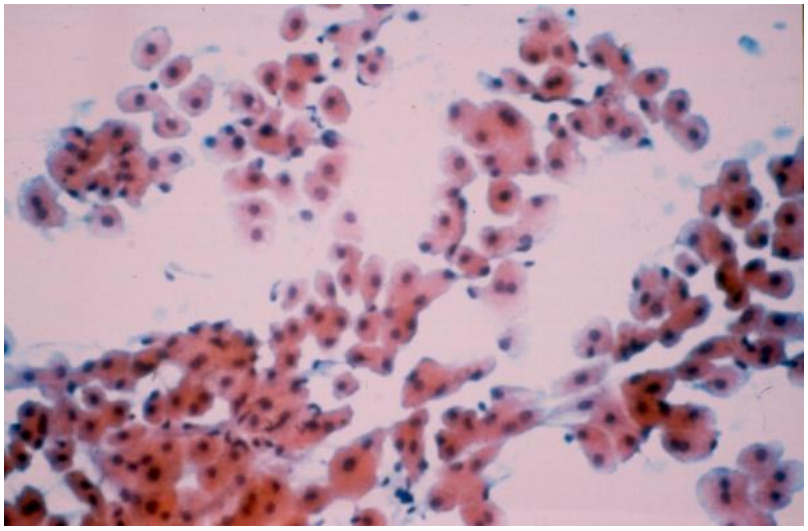
➢ Treatment
  - ○ No malignant potential
  - ○ No treatment needed

Nodular Regenerative Hyperplasia (NRH)

- Definition
  - Regenerative nodules without fibrosis
- Histopathology
  - 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

Case: 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.

- 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
      - Myelopreliferative disorders
      - Lymphoproliferative disorders
    - Drugs
      - Azathioprine
      - Chemotherapeutic agents

- Diagnosis
  - MRI is the best diagnostic imaging test to distinguish HCC from a large cirrhotic nodule

- Treatment
  - Stop offending drug
  - Treat associated hematological disorders

Focal Fatty Liver

- Diagnostic imaging
  - 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
- Clinical associations
  - CNS
    - Berry aneurysms
  - CVS
    - Mitral valve prolapse
  - Biliary tree
    - Biliary microhamartomous
  - Liver
    - Congenital hepatic fibrous
  - Colon
    - Colonic diverticulosis
  - Inguinal hernias
- Diagnostic Imaging
  - MRI
    - T2 – weighted image – bright fluid-filled cysts
- Histopathology
  - May transform to squamous cell carcinoma

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

- Definition
  - Intrauterine malformation of ductal plate

- Pathology
  - 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

"Challenges are what make life interesting and overcoming them is what makes life meaningful."

Joshua J. Marine

CHOLANGIOCARCINOMA

- Demography
  - Prevalence in North America, $1/10^5$
  - Cholangiocarcinoma is the second most common hepatic malignant tumour.

- Causes / associations

- Give 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 sclrosing cholangitis)
    - Caroli disease
    - Choledochal cyst
    - Thorotrast contract dye

- Laboratory

- Give 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%
  - Performance characteristics

	Sensitivity	NPV	Specificity
CA 19-9, biliary obstruction			
▪ Without PSC	53%	72 to 92%	
▪ With PSC	38% to 89%		50% to 98%

- Histopathology
  - 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 Calssification (Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease, 9th Edition. Sauders / 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

- Give the 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)

- 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 of potential recipient

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 $\geq$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 $\geq$10, or $\geq$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 $\leq$5 cm or three or fewer nodules all $\leq$3cm
    - Patient is not a resection candidate

- Status 3
  - Patients with chronic liver disease and a Child-Pugh score $\geq$7

Adapted from: United Network Organ Sharing. *UNOS policy 3.6* June 23, 2009.

- Prognosis (survival rate [SR])
  - 92% 5 yr SR
  - 80% 10 yr SR

- 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.

➢ Indications

- 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 remove 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.

- Give “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.

- Give 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

- Give 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, cytomegalorvirus, Epstein-Barr virus, and human immunodeficiency virus
  - Imaging studies: abdominal ultrasound examination, chest x-ray
- Stage 2
  - 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

- Give complications of liver transplantation (LT).

- Non-pharmacological
  - Surgery-related
    - Failure to wean off ventilator
    - Dehiscence of incision
    - Ileus
    - DVT
    - Atelectasis
    - Non-specific / varied other complications
  - Abdominal bleeding
    - Anastomoses (immediate)
    - Site of implantation (immediate)
  - 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
  - Liver
    - Infections*
    - Jaundice
    - Hepatobiliary complications
    - Acute cellular rejection
    - Biliary obstruction
    - Recurrence of original liver disease
  - CNS
    - Neurological complications*
    - Hearing impairment
    - Depression
    - Neuropathy
    - Seizures

- Endocrine
  - Metabolic syndrome*
  - Hyperuricemia
  - Diabetes
  - Dyslipidemia
  - Obesity
  - Fatigue
  - Sexual dysfunction
- Kidney
  - Chronic renal failure
- CVS
  - Hypertension*
  - Cardiovascular disease
- Vessels
  - Suprahepatic/infrahepatic vena caval obstruction (immediate)
  - Hepatic artery thrombosis (early)
  - Portal vein thrombosis (early)
  - Hepatic artery stenosis (late)
  - Coronary artery disease (dyslipoproteinemia)
  - Cerebrovascular
  - Peripheral vascular
- 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)

- Pharmacological
  - Drug reactions
  - 1° graft failure
  - Rejection
  - Recurrence of disease
  - Death

* risk is approximately 50%

Adapted from: Mueller AR, Platz KP, and Kremer B. *Best Practice & Research Clinical Gastroenterology* 2004;18(5): 882

- Non-GI adverse effects of immune suppression
- Give the most common **adverse effects** of immune-suppressive drugs frequently used after orthotopic liver transplantation.

Adverse effect	Cyclo-sporin	Tacro-limus	Gluco-Corticoids	Azathio-prine	Myco-phenolate Mofetil	mTOR Inhibitors
○ Alopecia	-	+	-	+	+	-
○ Arterial hypertension	+++	++	+++	-	-	+
○ Bone marrow suppression	+	+	-	+++	+++	++
○ Dermatitis	-	+ (rash, pruritus)	+	-	-	++ (oral ulcers, acne)
○ Toxicity Gastrointestinal*	+	+	+	+ pancreatitis	+++ (gastritis and/or diarrhea)	++
○ Hirsutism and/or gingival hyperplasia	+	-	-	-	-	-

Adverse effect	Cyclo Sporin	Tacro-limus	Gluco-Corticoids	Azathio-prine	Myco-phenolate Mofetil	mTOR Inhibitors
○ Hyper-glycemia and diabetes mellitus	-(?)	+	+++	-	-	-
○ Hyper-lipidemia	++	+	++	-	-	+++
○ Impaired wound healing	-	-	+	+	+	++
○ Lymphoma malignancy	++	++	-	?	?	-
○ Myalgia arthralgia	-	-	+	+	-	++
○ Nephro-toxicity	+++ (K+, Mg^{2}+)	+++ (K+, Mg^{2}+)	-	-	-	+ proteinuria
○ Neurotoxicity[a]	++	++	+ psychiatric symptoms	-	+ headache	-
○ Osteoporosis	+	+	+++	-	-	-
○ Pneumonitis	-	-	-	-	-	+

It should be noted that each agent has other specific adverse effects in addition to those listed in the table. [a]Neurotoxicity 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.

"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

- Give the most common complications after liver transplantation.

Group	Approximate risk	Complications
1	50%	○ Fatigue and sexual dysfunction ○ Hypertension ○ Hyperuricemia ○ Metabolic syndrome ○ Neurological disease ○ Serious infections
2	20%-25%	○ Acute cellular rejection ○ Chronic renal failure ○ Diabetes (at 1 yr) ○ Dyslipedemia ○ Obesity
3	10-15%	○ Malignancy

Group 1 – approximate risk of 50%

- **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 anastamosis, 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

- **Hearing impairment**
  - Loss, 52%
  - Tinnitus, 38%
  - Otalgia, 30%
- **Hepatobiliary complications**
  - Biliary leaks and strictures
  - Acute and chronic rejection
- **Hypertension**
  - About 66% develop ↑ SHT (systemic hypertension) post-LT
  - Nocturnal SH may develop from reversed circadian rhythms
  - Aim to have readings ≤ 130/80 mm Hg
  - Treatment
    - Control weight and salt intake
    - Change immunosuppressants (cyclosporin → tacrolimus)
    - Taper steroids
    - Antihypertensive drugs
      - CCBs (calcium channel blockers; block CNI-induced renal vasoconstriction)
      - ACEIs (angiotensin-converting enzyme inhibitors) or
      - ARBs (angiotensin-2 receptor blockers)
    - Caution re ACEIs / ARBs
      - May ↑ K in persons on CNIs (calcineurin inhibitors)
      - Second line, or for renoprotective benefit if microalbubinuria is present

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

Edith Wharton

SO YOU WANT TO BE A HEPATOLOGIST!

The systemic hypertension which develops in about 66% of persons post-LT may be related to a gain of weight, is associated with the development of metabolite syndrome or diabetes. The medications used in the post-LT setting are also involved, especially the CNIs (calcineurin inhibitors) such as Cyc (cyclosporin) or Tac (tacrolimus) and steroids.

- Give the mechanism for the systolic **hypertension** which develops with CNIs in the post-LT setting.
  - Endothelin release → vasoconstriction → ↑ systemic vascular resistance
    → ↑ renal vascular resistance (likely cause basal constriction of the afferent arterioles)
  - Ca^{2+} channels (CCBs) block CNI-associated renal vasoconstriction)
- Give the reason why the second-generation CCBs (calcium channel blockers) such as nicarpidine, amiodipine and felodipine) are considered to be first-line drugs, but first-generation CCB such as nifedipine are not recommended in patients with liver transplantation-associated systemic hypertension.
  - Nifedipine is metabolized by cytochrome P450, and will increase the blood levels of cyclosporin and tacrolimus, and are therefore contraindicated because of the potential adverse effects of these CNIs.
- Give the reason why diuretics such as thiazides are not recommended to treat systemichypertension post-LT.
  - The CNIs may produce dyslipidemia and electrolyte abnormalities (↑ K^+), which may be worsened by the use of that your diuretics such as thiazides.

- **Hyperuricemia and gout**
  - 2-year post-LT
    - Hyperuricemia, 47%
    - Gout, 6%
  - Treatment
    - Acute, colchicine
    - Maintenance, allopurinol (note: may ↑ azathioprine concentration)

- **Infections**
  - Serious infections are
    - A leading cause of death (> 50%) in LT patients
    - Are often in the first 3 months post-LT
    - Fever
      - Urinary or respiratory infection
      - Graft rejection
      - Malignancy
      - Meningitis
    - Headache, fever
    - Arthralgias
      - CMV

- **Neurological complications**
  - Seen in 16% to 80% of post-LT patients
  - 3/4 neurological complications occur within 90 days post-LT (median TTD, 49 days post-LT)

- Give common neurological complications post-LT.
  - Cerebrovascular disease (CVD), 52%
  - Encephalopathy, 19%
  - Infections, 18%
  - Malignancy, 3%
  - Osmotic demyelination syndrome (aka PLS, posterior leukoencephalopathy syndrome, 8%)
  - Seizure, 15%

- **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

Metabolic Syndrome (MS) / Diabetes

- The metabolic syndrome (MS) develops in about half of persons post-LT.
- May be result of the immunosuppressants used to prevent organ rejection.
- Comprised of hypertension, diabetes, obesity (↑ BMI, ↑ waist circumference), and dyslipidemia (↑ LDL-C, ↑ TG)
- Associated with ↑ morbidity and mortality
- Prevalence of new diabetes post-LT
  - 1-yr 27%
  - 3-yr 7%
- Influence of development of diabetes on mortality rate post-LT
  - 1-year no change
  - 10-year ↑
- Treatment
  - Diet
  - Taper steroids
  - Change immunosuppressants (e.g. tacrolimus → cyclosporin)
  - Oral hypoglycemic / insulin
- 1/3 of LT develop obesity post-LT, especially in the first 2 years
  - Treatment
    - Dietary
    - ↓ steroids
    - Change immunosuppressants (e.g. cyclosporin → tacrolimus)
- If bariatric surgery becomes necessary for ↑↑ BMI post-LT
  Endoscopic access to possible post-LT biliary disease becomes difficult
  Immunosuppressive drugs may be poorly or erratically absorbed
  Consider gastric banding, rather than Roux-En-Y

Dyslipidemia

- ↑ cholesterol (LDL-C)
  - Occurs in 16% of 43% of LT patients
  - Slow increase, plateau at 6-month
  - Those with pre-LT hypercholesterolemia have greater risk of ↑ LDL-C post-LT

- ↑ triglyceride
  - 40% to 47% of LT patients
  - Rapid increase in first month, then stable
- Treatment
  - Dietary modification
  - Change in immunosuppressants
    - Steroid withdrawal Cyclo → Tac or Siro
  - Statins which are less interactive with immunosuppressants: prevastatin, fluvastatin
  - Ezetimibe

Chronic Renal Failure

- Incidence of GFR <30 mL/min per 1.73 m^2 post-LT

Time post-LT (years)	Incidence
3	14%
5	18%

- Give pre-and post-LT risk factors for chronic renal failure.
  - Pre-LT (patient)
    - Female gender
    - Older age
    - Diabetes
    - Hypertension
    - HCV infection
    - ↓ GFR (pre-LT)
    - ATN (surgically-associated acute tubular necrosis)
  - Post-LT (drugs)
    - CNI (calcineurin inhibitors)
    - NSAIDS
    - Aminoglycoside antibiotics
    - Trimethoprime-sulfamethoxazole
    - Amphotericin

CLINICAL SUGGESTION: if chronic renal failure develops post-LT, switch from CNIs (cyclosporin or tacrolimus) to MMF or sirolimus

Acute Cellular Rejection (ACR)

- Occurs in ~20% post-LT patients, usually in the first month, and more with DLT (decreased liver transplant) than with LRD (living related donor).
- Early post-LT
  - ↑ALT/↑AP
  - Jaundice, fever → suspect ACR → abnormal RAI (rejection activity index) → liver biopsy or diagnosis
    - Portal tract
    - Inflammation (mixed mononuclear cells)
    - Bile ductules
    - Non-supurative cholangitis
    - Vessels endothelitis

Note: severe ductopenic chronic rejection occurs in 1% of LT patients, especially after repeated episodes of ACR, and retransplantation may be necessary

CLINICAL PEARL: post-LT

- ↑ ALT/AP are neither sensitive nor specific to diagnosis acute cellular rejection (ACR)
- The level of ↑ ALT/AP does not correlate with severity of ACR
- The implication of this is that if you suspect ACR, confirm with a liver biopsy (endothelitis, cholangitis, portal tract inflammation)

- Give the 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.

➢ Histopathology

- 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 settling 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.

- Give the **t**reatment of ACR (acute cellular reaction).
  - Methylprednisolone
    - 1000 mg IV bolus for 1 day, then tapered doses from day 2 to day 7, 200 mg IV od → 20 mg od po
  - 75% respond within 3 days to 5 days
  - For steroid-resistant (non-responsive) ACR
    - Use immune suppressive, i.e. taccrolimus, sirolimus, MMF,ATG, ALG, OKT3, basiliximab
  - When all else fails, retransplantation of liver!

Jaundice

- Biliary tract obstruction
- HAT (hepatic artery thrombosis)
- Graft non-function
- Acute rejection

Cardiovascular (CV) **disease**

- Give factors which contribute to the development of CV disease post-LT.
  - Male gender
  - Hypertension
  - Obesity
  - Diabetes
  - Dyslipidemia
  - Immunosuppressant drugs including steroids, and especially the use of MMF (mycophenolate mofetil)
  - High cumulative risk of cardiovascular (CV) events and CV death post-LT

Years post-LT	Cumulative risk of CV event	% CV deaths
1	5%	42%
3	10%	21%
10	24%	19%

➢ Pathophysiology

- Give the immunopathological steps involved in liver rejection after orthoptic liver transplantation, and the pharmaceutical agents which block these steps.
  - Alloantigenic recognition and T-cell activation
    - The alloantigen is bound to a MHC molecule (major histocompatibility complex)
    - Alloantigen becomes bound to an APC (antigen-presenting cell)
    - The antigen binds to a receptor on the T-cells
    - Ligands on the APC also bind to receptors on the T-cells
    - These T-cell receptors include CD27, CD11a, CD28, CD54 and CD154
    - As a result of this co-stimulation, the T-cell receptor complex is internalized.
    - The internalized t-cell receptor complex binds to immunophilin
  - Clonal expansion (IL-2)
    - IL-2 is secreted from T-cells
    - IL-2 acts in an autocrine manner to bind to the IL-2R (IL-2 receptor) on the surface of hepatocytes
  - IL-2R acts as a transduction signal to stimulate DNA synthesis and proliferation of T and B cells

- Inflammation
  - T-cell proliferation associated with secretion of
    - Cytokines
    - Chemokines
    - Adhesion molecule
- Cytokines, chemokines, adhesion molecules cause recruitment of inflammatory cells
- Cytokines, chemokines, adhesion molecules cause recruitment of inflammatory cells

Steatosis

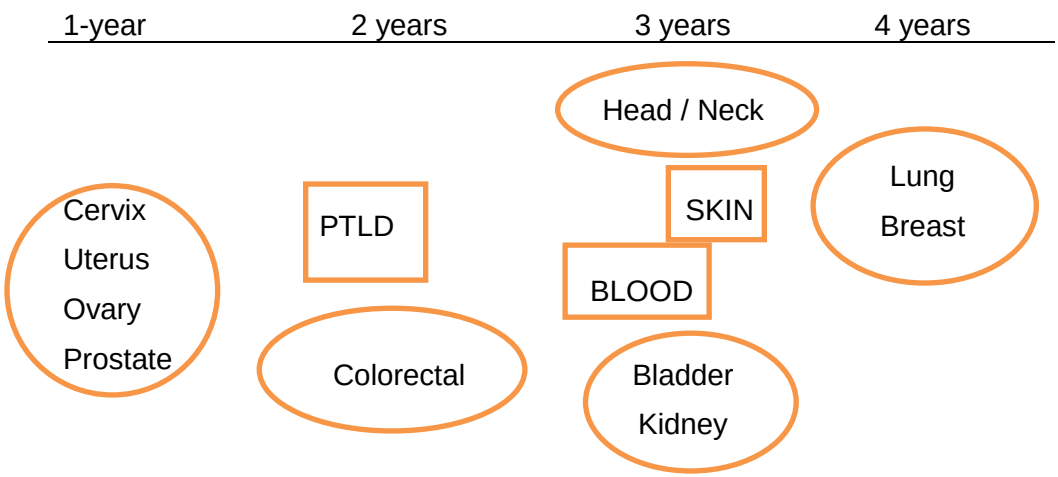
- Give factors which predict the risk for **post-LT steatosis.**
  - Post-LT obesity
  - Diabetes mellitus
  - Hyperlipidemia
  - Arterial hypertension
  - Tacrolimus-based immunosuppression regimen
  - Alcoholic cirrhosis as the primary indication for LT (Dumortier et al., AJG 2010; 105: 613-620).
  - 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.

Malignancy

- Give common tumors after liver transplantation, and their average time-to-develop (TTD).
  - The type of liver disease influences type of post-LT malignancy.
    - ALD
      - (18% in 10 yr) head and neck, as well as esophageal squamous cancer
    - PSC
      - (22% in 10 yr) cholangiocarcinoma
    - HBV
      - HCC

- Overall, the most common post-LT cancers are
  - Skin
    - ~ 2%
    - time to diagnoses (TTD), 36 months to 50 months
  - Blood
    - PTLD (post-transplants lymphoproliferative disorder)
    - ~ 2%
    - TTD, 26 months to 32 months
  - Solid organs
    - Each about 1%
    - Rate increased by age and smoking
- Mean time-to-diagnosis (TTD) post-LT

- Give the mean time-to-diagnosis (TTD) of 10 common tumors post-liver transplantation.



Abbreviation: PTLD, post-transplant lymphoproliferative disorder

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
  - Karposi 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%
- Causes / associations
  - EBV-associated latent infection in B-cells
  - ↑ LDH, ↑ EBV viral load
- Histopathology
  - Extranodal, high grade, poor prognosis
  - B cells originate from recipient, not from donor cells
  - May occur in GI tract (e.g. colon)
- Treatment
  - ↓ 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)
  - Intense surveillance programs
    - Annual
      - CT chest, abdomen
      - PSA, PAP smear
      - Mammogram
      - Skin examination

- Colon
  - Every 2 year for PSC +IBD
  - Every 3-5 years ffor associated family history

Recurrence of original liver disease (all may recur, **except**)

- Congenital
  - Bile duct
    - Atresia
    - Allagille syndrome
  - Cysts
    - Polycystic liver disease
    - Caroli disease
  - Liver
    - Congenital hepatic fibrosis
- Metabolic
  - Wilson disease (WD)
  - Hereditary hemochromatosis (HH)
  - Alpha-1-antitrypsin deficiency (A1AD)
  - DILI (drug is avoided if incriminated)
  - Primary biliary cirrhosis (PBC)

Development of New Liver Disease

- Autoimmune hepatitis (AIH)
- Drug-induced liver injury (DILI)
- Alcoholic liver disease (ALD)
- HAV / HBV /HCV
  - HCV may occur in the severe form of “fibrosing cholestatic hepatitis”, regardless of use of cyclosporin or tacrolimus.
- Primary biliary cirrhosis (PBC)
- Non-alcoholic steatohepatitis (NASH)

- Metabolic syndrome
  - Please see later section on “Immunosuppressive Drugs and Biologics used Post-liver transplantation”.

Recurrence of Liver Disease Leading to Need for Further Liver Transplantation

- Give examples of liver disorders which may recur in the liver **following liver transplant** (recurrence rates in brackets).
  - Inherited
    - Hemochromatosis (late)
  - Infection
    - HBV
    - HCV (more virulent; cholestatic type often fatal)
  - Immune
    - PBC, AIH, PSC (20%)
    - Autoimmune hepatitis (AIH)
  - Infiltration
    - 2° amyloid
    - HCC
  - Metabolic
    - NASH
  - Toxin
    - Alcoholic liver disease (~50%)

Adapted from: Lilly LB, Girgrah N, and Levy G.A. *First Principles of Gastroenterology* 2005: pg. 642.

"The real voyage of discovery consists not in seeking new lands but seeing with new eyes."
Marcel Proust

IMMUNOSUPPRESSIVE DRUGS AND BIOLOGICALS USED POST LIVER TRANSPLANTATION (LT)

To be covered here:

- Cyclosporin
- Tacrolimus
- Corticosteroids
- MMF / MPA
- Biologicals

- Give the relative order of the immunosuppressants in causing the components of the metabolic syndrome ("C-T").
  - Cyclosporin > tacrolimus (calcineurin inhibitors CNIs)
    - Hypertension
    - Obesity (↑ BMI)
    - Dyslipidemia
  - Note
    - 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 recue therapy.

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

Drug class	Hepatic steatosis	Weight gain (↑ BMI)	Systemic hypertension	Dyslipidemia	New onset of DM
Corticosteroids	++	++	+	+	++
CNI	-	+	++	++	++
Antimetabolites	-	-	-	-	-
mToRi	-	-	-	+++	+/-

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

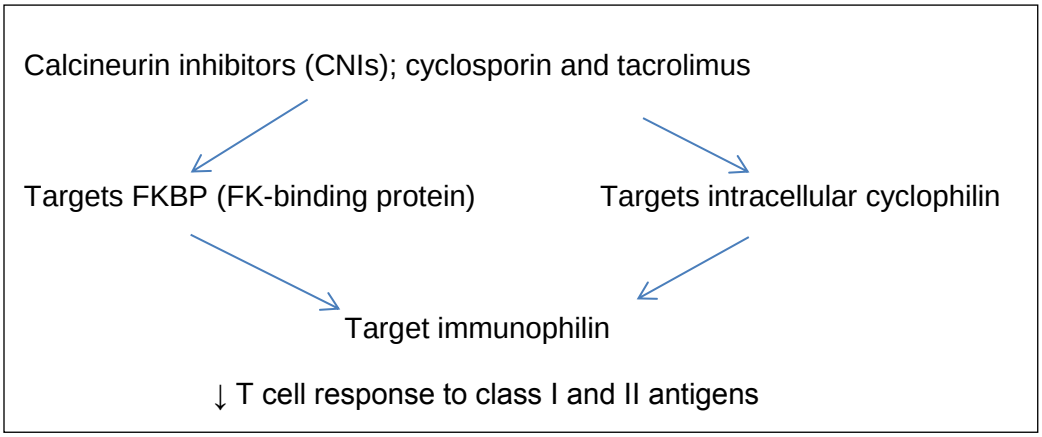
- Give **gastrointestinal complications** of transplant immunosuppression.

  - 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 transplantation
    - Mortality rate ~65%
  - 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.

Cyclosporin (is also spelled with an “e”, cyclosporine)

- A peptide derived from Cylindrocarpon lucidum, (a fungus)
  - Requires bile for intestinal absorption
- The preferred oral formulation is the microemulsified Neoral®
  - Bioavailability only ~ 30%
- Cyclosporin is metabolized by hepatocyte CYP 3A4.
- Metabolites of cyclosporin are not biologically active.
- Cyclosporin is cleared in bile.
- T1/2 is ~ 1 hr
- The trough levels of cyclosporin need to be measured in order to adjust the post-LT IV dose to within a therapeutic window
  - First 3 months 200 ng/mL to 250 ng/mL
  - By 12 months 80 ng/mL to 120 ng/mL
- Dose 2 mg to 4 mg/kg IV per day by continuous infusion.

- Give the mechanism of action of calcineurin inhibitors.



  - Immunophilin stimulates calcineurin
  - Calcineurin removes pyrophosphate from NFAT (nuclear factor of activation of T-cell)
  - NFAT traffics to the nucleus
  - In the nucleus, NFAT drives the transcription of IL-2 in T-cells

- Give factors which lead to the **variability in the blood concentration** of cyclosporin.
  - Gut lumen
    - Fat Malabsorption
    - Bile salt deficiency
  - Liver
    - Polymorphisms in CYP 3A4
  - Foods and drugs
    - Cholestyramine binds cyclosporin in the gut lumen
    - H_2RAs (H2 receptor antagonists), PPIs (proton pump inhibitors), and grapefruit juice after CYP metabolism of cyclosporin

- Give major **adverse effects** of cyclosporin.
  - Drug interactions
  - Kidney
    - Hypertension
      - ↑ K^+
      - ↓ Mg^{2+}
  - Metabolic
    - Gingival hyperplasia
    - Hirsutism
  - Gums / skin
    - Gingival hyperplasia
    - Hirsutism
  - Neurological
    - CNS
      - Seizures
      - Hallucinations
      - Cortical blindness
    - Nerves
      - Polyneuropathy
    - Muscle
      - Myoclonus

CLINICAL TIP:

- Drug interaction
  - Cyclosporin → ↓ HCV replication → ↓ metabolism of CNIs, → ↑ blood levels of CNIs)

Tacrolimus

- A macrolide antibiotic derived from Streptomyces tsukubaensis
- Binds FKBP (FK binding protein)
- Also a calcineurin inhibitor (CNI)
- 100x more potent than cyclosporine
- Metabolized by hepatic CYP 3A4
- Not removed by dialysis
- Adverse effects, comparable to cyclosporine
- Wide oral bioavailability (5% to 67%)

- Oral dose
  - Normal renal function 0.5 mg to 1 mg every 12 hr, increasing dose to achieve blood level of 10 ng/mL to 12 ng/mL for ~ 6 months
  - 6 months to 12 months target tacrolimus blood levels to 6 ng/mL
  - > 12 months 4 ng/mL to 6 ng/mL target tacrolimus concentration to
  - For maintenance of AIH, PBC, PSC, use the higher (6 ng/mL) dose
  - For reduced renal function use

    Lower dose of tacrolimus, or use

    Mycophenolate, or

    Monoclonal antibody

- Special clinical considerations for early post-LT therapy
  - Chronic renal disease
    - Avoid cyclosporin, and use
      - Tacrolimus plus
      - Sirolimus (mTor inhibitor), or
      - MMF plus steroids
      - Hemodialysis as needed
  - Treat associated HCV liver disease

- Give reasons why tacrolimus is the **first line CNI** post-LT, rather than cyclosporin.
  - Patient
    - ↓ Death after LT
  - Liver
    - ↓ Acute hepatic rejection
    - ↓ Steroid-resistant liver rejection
    - ↓ Loss of liver graft
  - CVS
    - ↓ Hypertension
  - Endocrine
    - ↓ Obesity
    - ↓ Dyslipidemia
    - But ↑ diabetes (may lead to ↑ chronic renal failure in the longterm)
  - Kidney
    - Renal insufficiency
  - Cancer
    - ↓ PTLD (post-transplant lymphoproliferative disorder)

Glucocorticosteroids (GCS)

Corticosteroids
- ↓ cell-mediated cytotoxicity
- ↓ antibody binding
- ↓ complement binding
- ↓ T cell synthesis of IL-2, IL-6, IFN-γ (interferon gamma)
- ↑ IL-10

  - GCS and post-LT asscociated HCV
    - Post-LT for HCV-associated cirrhosis, HCV recurs in ~ 99% of donor livers
    - When HCV viral load increases, a flare of hepatitis develops with ↑ ALT.
    - This requires steroid taper, or better yet, don't use steroids in the first place (steroid-free immunosuppression).
    - Everolimus is a synthetic form of sirolimus

Mycophenolate Mofetil (MMF) **and Mycophenolic Acid** (MPA)

- Orally dosed prodrugs derived from the Penicillium fungus.
- Mechanism of action MMF / MPA
  - Short version:
    - ↓ lymphocyte GMP → ↓ DNA synthesis → ↓ proliferative of T and B lymphocytes
  - Long version
    - MMF／ MPA → ↓ IMPDH (inosine monophosphate dehydrogenase)
    - ↓ GMP (guanosine monophosphate)
    - ↓ GTP (guanine triphosphate), or
    - ↓ dGTP (deoxyguanine triphosphate)
    - Proliferation of T and B lymphocytes
- Use
  - Steroid-sparing
  - CNI-sparing
  - For steroid-resistant rejection
  - To reduce risk of renal damage, or neurotoxicity
- Common side effects
  - Bone marrow
    - Suppression
  - GI symptoms
    - Nausea／vomiting
    - Pain
    - Ileus
    - Mouth ulcerations

SO YOU WANT TO BE A HEPATOLOGIST!

MMF and MPA reduce lymphocyte GMP, thereby blocking T-cell proliferation. The side effects of these drugs involve bone marrow suppression and GI symptoms, but there is no nephrotoxicity or neurology. However, the cells of the body require GMP.

- Give the reason why MMF and MA are not as toxic as they should be, since they reduce cellular GMP, and how do they selectively ↓ proliferation of T and B lymphocytes.
  - Most cells of the body have the purine (guanine) salvage pathway
  - Lymphocytes lack the essential enzyme for the guanine salvage pathway, hypoxanthine-guanine phosphoribosyl transferase.
  - Because lymphocytes do not have the guanine salvage pathway, when IMPDH is blocked by MMF／MPA, the lymphocytes cannot maintain adequate lymphocyte levels of GMP, and both the T and B lymphocytes stop proliferating.

Biological (Antibody) **Therapy**

- **Polyclonal antibodies**
  - ATG- antithrombocyte glogulin
  - ALG – antilymphocyte globulin
  - Antibodies against several T-cell antigens: CD2, CD3, CD4, CD8
  - Given IV (central line)
  - Mechanism of action
    - Internalization of antigen complexes into the T-cells
    - ↑ complement in component-mediated T-cell lysis
    - Blocking of killer T-cell activity in graft circulation
  - Adverse effects
    - General
      - Fever, chills (cytokine release syndrome)
    - Skin
      - Rash
    - Blood
      - ↓ RBC
      - ↓ platelets
    - Serum sickness
    - Kidney
      - Nephritis

- **Monoclonal Antibodies**
  - OKT3
    - Monoclonal antibody against CD3-antigen complex on T-cells
    - Mechanism of action similar to polyclonal antibodies
    - 5 mg od for 10 days to 14 days
    - Adverse effects of special concern
      - Recurrence of HCV hepatitis
      - PTLD
        - 3% risk
        - Higher risk if LT for HCV
        - Risk also correlated with use of steroids (HR, 3, 3.6)

Clinical Caution: think twice before using OKT3 in the setting of HCV

- Basiliximab
  - Humanized monoclonal antibody against IL-2R (IL-2 receptor)
  - ↓ T cell proliferation
  - Use
    - CNI-sparing
    - Steroid sparing
  - Reduction of efficacy
    - Monoclonal antibodies develop to IL-2R basiliximab

Treatment Tip

- mTor (mammalian target of rapamycin) bound by sirolimus

"We make a living by what we get, we make a life by what we give."

Winston Churchill

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