Guideline-Based Management in Hepatology

A. B. R. Thomson

www.giandhepatology.com

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"The Democratization of Knowledge"

Forward

Throughout the history of medicine, and likely even earlier, physicians made decisions as to how to manage their patients based on the best available information. For the younger physician, this information is based largely upon what they are taught. The older physicians reinforced this with the wisdom which comes from experience. In the past, there was only slow development of new knowledge, new understanding of causes and associations, new surgical procedures, new therapies. Now, the half-life of medical knowledge is estimated to be less than five years. Both the junior and senior physician is faced with this mountain of facts, findings and even some fiction. The once-taught knowledge will now not be sufficient even for a few years of competence. We must continue to reinvent ourselves.

Invented was a new term, “CME” continued medical education, or some form of this. The individual physician remained responsible for her/his own information-gathering. Organizations developed- oh how we human primates like to organize ourselves –developed to assist capturing all this data and translating it into usable, reliable and “proven” clinical knowledge.

Also invented was another concept, with its own terms, “levels of evidence”. The austute physician reports a finding to share with colleagues. That one or few patient numbers was expanded to a group. But if your group (read “experience”) differs from mine, then who is correct? Enter the need for statistics, sampling, generalizability, and of cause the placebo. Yet not enough for the placebo to be a matched dummy, it had to be blind, and randomized!

In search of the holy grail, the truth and the realization that there are many truths, based on sampling inclusion / exclusion criteria, age, gender, race and a host of unrecognized factors, even meta-analyses do not always agree. Pity the poor hardworking, compassionate and caring physician, who simply wishes to know. “what is best for the patient sitting in front of me? Medicine gains clinical knowledge from groups, and valiantly tries to apply this to “the one”. How do we travel from evidence, to recommendations, to action?

In our own search for excellence, we read, attend meetings, consult one another, and make use of that mystical beast, “the literature”. The challenge grows to the same level of difficulty as the starting point of trying to translate that mountain of data into useable knowledge. Generally speaking, textbooks offer the suggestions of management and therapeutic

options as the writter's learned opinion, their opinion at the time of writing the text. From writing to publishing and then to reading by the learner, there is a considerable delay. On top of this we need to have considered "the literature", systemic reviews, meta-analyses, the outcome of consensus meeting, and published guidelines. These guidelines may be out of date, or may be timely but apply to patients in one country or ethnic (read "genetically different") group. We must therefore view these texts such as guidelines to be just that, guidelines. Remember the old saying: "Laws (read guidelines) are for the guidance of wise men (read "persons"), and the blind obedience of fools". We we all so wise as to acknowledge the justice of this distinction.

This almost unsurmountable challenge of knowledge generation and wisdom application must now, in this enlightened era, be skillfully interdigitated with so many issues pertaining to the patient and to the physician. We in a multicultural country such as Canada are only too well aware of the importance of the respect for heterogeneity and inclusiveness, and of the importance of these psychosocial, ethnic, religious and other human differences based upon varying value systems. We are helped in creating the ideal well-rounded competent, caring and compassionate (the 3 C's) physician by the Royal College (of Physicians and Surgeons of Canada) and its introduction of the CanMeds roles, which every physician must address beyond the sometimes narrow borders of even the "3 C's" modern physician.

In this text are presented recommendations of the indications for the treatment of disorders in gastroenterology and hepatology, as derived from major guidelines. Subtle differences between topic guidelines are acknowledged, and where no recent guidelines are available, I draw on consensus statements, systemic reviews and meta-analyses. And sometimes even a little bit of common sense which is no longer so common. A number of the pharmaceutical agents which are mentioned may not yet be approved by national authorities or by third party payers. I also strongly recommend the guidelines of the WGO (World Gastroenterology Organization), which address the issue of suggestions in the face of economic disparity and social injustice, and the variability of persons everywhere.

One of the often forgotten aspects of the preparation of management guidelines – often forgotten at least by those who have worked so hard and cleverly to prepare the guidelines – even the best laid plans for the application of

these learned guidelines are useless unless the guidelines are widely distributed and accepted by practicing and not just by “publishing” physicians.

One of the major drawbacks to the usual procedure of publishing guidelines is that the very process of publication may impair their wide distribution. In the process of researching this book, the publishers of Canadian, American, British and other European journals containing major guidelines in gastroenterology and hepatology were contacted to obtain permission to publish just the usually only one line statements of recommendation (e.g. “in the patient with new onset dyspepsia, who is over the age of 50, an EGD must be performed to investigate the cause and to exclude the possibility of esophageal or gastric cancer”). Over 95% of the journals required a significant payment for the right to publish each short statement. The authors of the guidelines cannot even give away their guidelines, because they have to sign over the copyright to the journal that usually does not even reimburse them for preparing the document. In fact, some journals go so far as to strongly discouraging even “paraphrasing the guideline statements.

This author recognizes that he is very privileged to be in an institution which provides access to a wide range of medical journals, so that access to these overshore published guidelines is easy. If the physician were a practitioner in the town of North, she / he might subscribe to and read perhaps two or three journals. If the author found her / his colleagues talking about how very useful and practitioner-friendly a particular journal was, they might afford themselves a subscription. But if this author were to practice in less fortunate areas of the world, I could not simply buy one more subscription. So, I would not have the benefit of guidelines, restricted as I would be by costs and controls.

This leaves a good product, a new guideline, sitting idle on the shelf, awaiting effective marketing. I have tried to paraphrase from multiple published guidelines, and included meta-analysis and systemic reviews to be able to make simple and clear suggestions of recommendations. Of course, what you choose to practise will depend both upon your perspective of the relevance of the literature to your patient, their needs and wishes and special circumstances, within the limiting factors of drug availability by approval, and often painful socioeconomic considerations.

This author works to provide current information (see what commercialization has done – I write “current information”, to avoid saying Current Contents ® or Up To Date®!!), against the background of best evidence for indications inclusive and exclusive of modern management.

Through the World Gastroenterology Organization (WGO), the material is made freely available to anyone worldwide who has access to the internet and the www. In this way all physicians will be on a level playing field in terms of what is on the patient's treatment menu of options, the knowledge of indications and available therapies. We physicians are all life-time learners, and may benefit from "free to download" gastroenterology and hepatology books. Other learners, be they medical students, residents or fellow, may also benefit with the alarming exponential rise of the cost of obtain a medical degree. There is becoming a return to the "classification" of physicians – only those from privileged and affluent "upper class" families will become the physicians in the future. This is not right; the search for all rounded physician must always be inclusive of trainees from all walks of life.

This book series represents small steps taken slowly on solid ground, to broaden the reach of medical knowledge. Each one of us has a part we can play to give back as thanks to those who helped us in our professional careers. Each one of us may help in this process of the democratization of knowledge, and of peace through medicine.

The Approach

D	Diagnosis	D	Drugs (now, and for follow up / maintenance)
E	Explain	E	Endoscopic options
C	Consent, informed	S	Surgical options
L	Lifestyle	S	Screening, surveillance, vaccinations (SSV)

The words "management" and "treatment" are often used interchangeably. On an examination, you don't know whether the examiner wishes you to discuss the overall aspects of the management of the patient with the pathological condition, or just the treatment of the condition without consideration of the broader needs of the patient. The suggestion is therefore that unless it is made clear by the question, that such a question be answered broadly by considering nine steps of patient care, called "DECAL DESS".

- Diagnosis – Confirm the diagnosis
- Explanation – Explain to patient in appropriate language and tone the nature of their illness, the treatment

options, the risk and benefits, emphasizing what are their choices; explain implications of diagnosis for screening needs of the family.

- Consent
  - Establish a management plan with the patient's consent and "buy-in", as well as where possible or appropriate, their family support, complementary and alternative medicine together with informed consent
- Associations
  - Treat underlying causes or associations
- Life style considerations
  - Life style changes
    - Diet
    - Exercise
    - Weight
    - Smoking
    - Sleeping
    - Hobbies and fun interests
    - Psychological and religion needs
    - Social interactions
- Drugs
  - Drug
    - Route
    - Dose
    - Duration
    - Interval
    - Stop-rules
    - Serious / common AEs (adverse effects)
    - Costs
    - Drug interactions
    - Genetic testing
- Endoscopy
  - Endoscopy procedures
- Surgery
  - Surgical options
- SSV
  - Screening, surveillance, vaccinations
- Special
  - Pregnancy

consideration
- Breast feeding
- Renal / hepatic dosing
- Drug interactions

If for example you were asked to give the treatment of GERD symptoms in a 55 year old man, yes you would confirm the symptoms / signs that supported the clinical suspicion of the diagnosis. But was there any testing to determine if the symptoms are actually linked to reflux, is there reflux, is there reflux damage, is there an alternate diagnosis such as ischemic heart disease or non-cardiac chest pain. Has there been a clear management plan agreed to be the patient, has he been compliant with the many and important lifestyle issue. Don't just give the name of the general class of drugs (e.g. PPIs), but state "I would recommend to this patient that he take a PPI such as pantoprazole 40 mg once a day, half an hour before breakfast, for two weeks". What is the "stop rule"? You would recommend that the patient contact you in two weeks to report their progress, and together you would review the treatment plan – continue, increase to bid therapy, perform endoscopy. The patient is over 50 years of age; did you discuss the benefit of screening colonoscopy, even in an average risk person. Does he need EGD because he is middle-aged Caucasian male with a 10 year history of moderately severe reflux symptoms occurring 3 times a week?

Even you are asked the management of some GI or Hepatology condition you have never heard of (e.g. malakoplakia or non-specific colonic ulcers), you will likely receives passing marks for mentioning all the non-drug considerations.

- Economic Issues

In many countries such as Canada, Europe, Australia and New Zealand, heath care costs are spread over the entire population. This leaves the sick person to deal with their illness, and not with their banker – "for the better good of all".

When faced with economic issues and health care, please refer to the excellent guidelines developed by WGO, World Gastroenterology Organization (www.worldgastroenterology.org/).

- No cost resources

No cost resource through **www.giandhepatology.com**

For no cost ("Democratization of Medicine") program of current treatment options, please go to the WGO website click "abrt@giandhepatology.com, and select desired reading material in the areas listed below.

For those who wish a less-than-cost paper book version, please go to www.amazon.com, and enter the ISBN number.

GASTROENTEROLOGY

First Principle of Gastroenterology and Hepatology (ISBN; 978-1461038467)

A concise introduction and update of common disorders, the diagnostic approach and management.

Recommended for the Senior Medical Student, Resident in General Internal Medicine, as well as for the practising clinician who wishes a refresher.

GI Practice Review (ISBN: 978-1475219951)

A detailed and in-depth consideration of common and less common disorders, with background material, OSCE and Board-focused questions, and extensive answers. To challenge the reader, there are also teasers on trivia, “So You Want to be a Gastroenterologist!”

Recommended for the advanced GI Trainees, Academic Clinicians and Seasoned Practitioners who wish to refresh and upgrade their excellence.

Endoscopy and Diagnostic Imaging 2 parts (Part I [ISBN: 9781477400579]; Part II [ISBN: 9781477400654])

We choose to be Clinicians, Gastroenterologists, and Hepatologists. We depend on diagnostic imaging consultants for their expertise. Yet we need to refresh or knowledge behind our endoscopic skills, and review what we are looking for when we “review the films” with radiologists. Know the language, know what to look for, and know you can’t be fooled.

Scientific Basis for Clinical Practice in Gastroenterology and Hepatology (ISBN: 978-1475226645)

A short and snappy illustrated approach helping the clinician understand and appreciate the scientific basis to their clinical practice.

Recommended for all of us want as painless away as possible to learn and to relearn how things work in the GI tract and liver, and why we do some of the things we do.

Guideline-Based Management in Gastroenterology (ISBN-13: 978-1515078623

In this text are presented recommendations of the indications for the treatment of disorders in hepatology, as derived from major guidelines.

GENERAL INTERNAL MEDICINE

Achieving Excellence in the OSCE - Part I [ISBN: 978-1475283037, 410 pages]; Part II [ISBN: 978-1475276978, 466 pages]

Mastering The Boards and Clinical Examinations in Internal Medicine – Part I [ISBN: 978-1461024842, 816 pages }Part II [ISBN: 978-1478392736, 788 pages]

The gastroenterologist and hepatologist practices against the background of General Internal medicine. For the Advance Trainee preparing for their OSCE or Board Exam, this book will help you enormously preparing for scenarios based around taking a Directed History and Perform a Focused Examination.

Recommended for the Internist in all of us who needs to keep up and brush up on more than Gastroenterology and Hepatology.

Bits and Bytes (ISBN: 978-1478295365)

When on Clinical Rounds, have you ever noticed how the really sharp residents seem like clever “namedroppers”, knowing just the right question at the right time” You can easily learn to do this too- when seeing / discussing the GIM / GI patient with “Such-and-Such” or “Something-or-Other”, a quick glance at sample bedside questions will attract the staff attention to rocket you forwards to the best program in your area of interest.

- Guidelines

Publication of guidelines from learned professional organizations (e.g. AGA, ACE, BSG, AASLD, CAG, etc.) help to sift through an extensive medical literature which is not always available to all of us, review the evidence, and making suggestions or recommendations of what we should do in our practise, as well as how and when. Sometimes the levels of evidence will be excellent, sometime recommendations are based only on the agreement of so-called experts, sometimes we have only a meta-analysis or a single publication to rely upon. Occasionally, even the evidence-based medicine approach may be challenged.

In this publication of “Guideline-Based Management”, the most recent guidelines in the English language are presented in their summary points (full details are available in the often extensive and well-referenced primary sources). Where management guidelines are available, these are provided, where appropriate and possible, considering the Nine Steps of Patient Care,

"DECAL DESS", an acronym for Diagnosis, Explanation, Consent, Association, Lifestyle Considerations, as well as Drugs, Endoscopy, Surgery, and SSV (screening, surveillance, vaccination).

The author has no conflict of any nature with any commercial, political or professional organization, and cannot / will not profit from any aspect of suggestions made from summarizing and where necessary editoralizing on the recommendations.

The trainee needs to be alert to what does the Seasonal and Respected Clinician say and do. When asked, for example, the causes of duodenal ulceration, she / he does not recite a catelog of possible and "you'll never see in your lifetime" diagnosis, but will provide a balanced list, balanced by what is Common and what is serous if missed.

The privileged physician who is in training in a very rich program or the clinician who does 40 endoscopic procedures per week with collectable billings of $200 each, may well be able to refer to and subscribe to the outstanding web-based Up-to-Date®. For the 90% of physician world-wide who are not so fortunate hopefully they we will find that this non-charge WGO-endorsed web-based and regularly updated source is refreshing, nicely detailed, and to-the-point.

This series of quality and up-to-date medical publication is provided by WGO through CAPstone publications to physicians and to physician trainees worldwide, with the intent that these be no discrimination of the cognitive component of the quality of healthcare around the world Gastrointestinal and Hepaticopancreaticobiliary Disorders.

Left to the politician, the tax payers, the NGOs, and the global perspective of benevolent agencies in time there will be the removal of the financial barriers of quality medical care to all. But we as proud and dedicated physicians have and will use our power of commitment to remove financial considerations as a gatekeeper to the knowledge of our fellow physicians worldwide, as we master our professional knowledge, while awaiting the opening of resources so that we may help to benefit "All God's Creatures", our Sisters and Brothers.

Sincerely,

A. B. R. Thomson

Disclaimer

The primary purpose of this publication is education. The author, editor and publisher acknowledge that the development of new material opens to way for possible errors – what is correct today might not be the standard of care tomorrow. Readers are advised to ensure that the doses of drugs which they use are in compliance with their country's product information, and that the use of any therapeutic agent, be it a pharmaceutical or a technology, should be directed by local guidelines. There is often a wide diversity of professional opinion, and guidelines from one country are not always congruent with another.

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Introduction and General Principles

The “Grade” of evidence relates to the strength of the recommendation. A strong recommendation suggests the recommendation should or should not be followed, whereas the clinical recommendation is one of “probably” – probably follow or do not follow the recommendation.

The evidence level relates to the quantity of the data which is available, upon which to make a consensus statement or to formulate a guideline. For example, consider the extremes of the reliability of two double-blind placebo-controlled randomized clinical trials with the appropriate power, versus the opinion expressed by a so-called expert, who is usually a middle-aged male physician in the “Ivory Tower” of an acclaimed institution, who spends most of his time teaching, doing research and traveling the words rather than engaging in a very busy clinical practice.

A further consideration is taken by the members of the guideline committee of the World Gastroenterology Organization, the WGO. The WGO guidelines also recognize the importance of the resources available to the patient and to their community health care facilities. For example, there may be Level I, grade A evidence to treat the constipated patient with lubiprostone, prucalopride or biofeedback, put even in a so-called “developed” and “have” (as compared to a “have not”) country, these pharmaceuticals may not be provided by a third-party coverage, and sophisticated testing, sacral nerve stimulation or biofeedback might only be provided hundreds of kilometers or miles away, and therefore rendering them in reality, unavailable, and as well awarding a worldwide common complaint of dyspepsia diarrhea or constipation with the subtext notation of “DOR”, a disease of the rich.

Thus, the physician and the patient need to consider treatment decisions in three dimensions: strength of the data, strength of the recommendation, and strength of the patients’ resources. This book will not release the limitation of the resources, but the no-cost internet access will remove the constraint of knowledge. And with knowledge, comes justice, social justice and equality of opportunity.

Dedication

To my special teachers

Robi Dunlop

Leslie Valberg

Sidney Truelove

Ivan Beck

John Dietschy

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LIVER

DIAGNOSTIC TESTS

- Laboratory tests

- Give 6 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)

Alkaline phosphatase (AP) and gamma-glutamyl transpeptidase (GGT)

- 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

➢ 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)
  - Development of cirrhosis
- Transaminitis is not specific for liver disease
  - Thyroid
    - Hyper / hypo thyroidism
  - Muscle
    - Acute rhabdomyolysis
    - Myopathy
    - Extreme exercise
  - GI disease
    - Celiac disease
  - Others
    - Macro – AST

- Give 10 common causes for elevation of aminotransferases.
  - Marked elevation (up to 20+ fold)
    - Acute hepatitis due to viruses, ischemia or drugs
  - Moderate elevation (up to 8 fold)
    - Chronic hepatitis, cirrhosis, cholestatic diseases, and replacement disease

- Minimal elevation (up to 2+ fold)
  - Non-alcoholic liver disease, chronic viral hepatitis (C and B), alcoholism, obesity

SO YOU WANT TO BE A HEPATOLOGIST!

The ALT is usually higher than AST, except with ALD, acute rhabdomyolysis, myopathy, severe exercise, hypothyroidism or macro-AST.

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

- 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

- Gamma glutamyl transpeptidase (GGT)
  - Sensitive but not specific for liver disease
  - May be increased with
    - Alcohol
    - Drugs, e.g. HAART, phenytoin, barbiturates

- 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

Clinical Tips

- An elevated serum bilirubin, AP (alkaline phosphatase) or GGT does not necessarily indicate 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

SO YOU WANT TO BE A HEPATOLOGIST!

- 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 related 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

- 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 these 2 **types of cholestasis**.

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

- Give the clinical and laboratory features which suggest the diagnosis of SOS (sinusoidal obstruction syndrome), aka VOD (veno-occlusive disease).

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

  - Obstruction of terminal hepatic venules and hepatic sinusoids → dilation of sinusoids → hepatocellular necrosis → centriobular fibrosis

  - Clinical associations
    - BMT (bone marrow transplantation)
    - Chemotherapy
    - Jamaican herbal teas
    - Azathioprine use

  - Symptoms / signs
    - Painful hepatomegaly
    - Rapid weight gain
    - Ascites

- Laboratory
  - Conjugated hyperbilirubinemia > 2 mg/dL
  - Thrombocytopenia
- Example of typical causative drugs
  - Azathioprine
  - Tetracycline

- Give clinical and laboratory features which suggest the diagnosis of **Peliosis hepatis (PH)**.

➢ Definition: PH is characterized by multiple blood-filled spaces in the parenchyma of the liver.

- Clinical associations
  - Anabolic steroids
  - Bartonella infection in HIV-immunosuppressed patients
  - Azathioprine
  - OCA (oral contraceptive agent)
  - Vitamin A
  - Hydroxyurea
- About 1/3 of patients with severe disease will have a symptomatic, harmless ↑ ALT.
- Examples of causative drugs
  - Azathioprine
  - Tamoxifen

- Give the detailed laboratory and diagnostic imaging investigation of the patient with suspected chronic liver disease.

➢ History and physical examination

- Fatigue, malaise, anorexia, fever, weight loss/gain, ankle swelling
- Following blood donation-positive hepatitis B or C test
- Blood transfusions
- Drug abuse
- MSM (men who have sex with men)
- Extrahepatic manifestations
- Following acute hepatitis-failure of recovery, whether clinical or biochemical or both

- Abnormal liver enzyme or function tests, or positive hepatitis B or C viral markers at routine check-up
- Abnormal physical findings
  - Hepatomegaly,
  - Signs of portal hypertension: splenomegaly, jaundice, peripheral edema, ascites, hepatic encephalopathy, renal dysfunction, bleeding (varices, coagulopathy)
  - Liver – big/normal/small
- Cutaneous and endocrine changes
  - Spider nevi, palmar erythema, Dupuytren's contractures
  - Gynecomastia, testicular atrophy, impotence
  - Amenorrhea
  - Parotid enlargement
- Coagulopathy
  - Hypoprothrombinemia
  - Thrombocytopenia
  - Dysfibrinogenemia
  - Slit lamp Kayser-Fleisher rings
- Circulatory changes
  - Hyperdynamic circulation
  - Arterial desaturation, clubbing

➢ Laboratory tests

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

- Hematology
  - Hemoglobin
  - White cell count
  - Platelet count
  - PPT
- Special tests
  - Serum antibodies
    - Nuclear
    - Smooth muscle
    - Mitochondrial
    - Liver/kidney microsomal
  - HBsAg
  - HBeAg
  - HBeAb
  - Anti-HCV and HCV RNA
  - Serum iron, transferrin, % saturation, genetic testing
  - Serum ferritin
  - 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)

- Abdominal ultrasound, CT, fibroscan

- Core liver biopsy
  - Hematoxylin and eosin, connective tissue stains, “special stains” (e.g. for iron, copper, HBV)

Adapted from: Simon JB. *First Principles of Gastroenterology* 2005. pg. 500-505.

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

- CNS
  - Depression
  - Anxiety
  - Hepatic encephalopathy (HE)
- Lung
  - Portopulmonary hypertension
  - Hepatopulmonary syndrome
  - Pleural effusion
  - Congestive heart failure
  - Aspiration
- Heart
  - Prolonged QT (from low Mg 2+)
  - Endocarditis
  - Peripheral intravascular vasodilation
  - ↓ systemic vascular resistance
  - ↑ HR
  - ↑ BP
  - ↑ CO
  - Vitamin K deficiency
- Blood
  - Coagulopathy (DIC, fibrinolysis)
  - Thrombocytopenia
  - Hypersplenism
  - ↓ thrombopoetin
  - Immune mediated destruction
  - ITP (especially with use of interferon for HCV)
  - Direct effect of alcohol
  - Cryoglobulinemia
- GI
  - Esophageal ulcers from sclerotherapy
  - GERD
  - Varices
  - Delayed gastric emptying
  - PHG

- GAVE
- Small bowel: slow transit
- Bacterial overgrowth syndrome

- Bone
  - Osteoporosis
  - Osteomalacia
  - Cholestasis
  - Liver transplantation
  - Malnutrition
  - Alcohol
  - Tobacco
  - ↓ motility
  - Hypogonadism
  - Malabsorption
- Renal
  - Hyponatremia
  - Ascites
  - Hepatorenal syndrome
  - Glomerulosclerosis (HCV)
  - Nephritic syndrome
  - Amyloidosis
- 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

Adapted from: Simon JB. *First Principles of Gastroenterology* 2005. pg. 502.

Surgery and Liver Disease

- Give when surgery should be **postponed** in acute viral hepatitis.
    - Acute viral hepatitis plus laparotomy
        - Operative mortality of ~ 10%
        - Do not perform elective surgery
    - Chronic hepatitis plus surgery, operative risk
        - Portal or interface hepatitis
            - Low
            - High
        - Liver biopsy for risk stratification may be useful in this setting
    - Cirrhosis Child Pugh (C-P) class, operative mortality
        - A, 10%
        - B, ~ 30%
        - C, ~ 80%

➢ **MELD Score** (model for end-stage liver disease)

- Derived from creatinine, bilirubin, INR
- Correlates with mortality rate for
    - Liver transplantation
    - Liver resection
    - Other abdominal operations
    - Cardiac surgery

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".

- Give 10 management considerations in the pre- and post-operative care of the patient with advanced liver disease (CHLD score).
    - Risk stratification
        - Child-Pugh score classification

- MELD score
- PHT (portal hypertension)
- Co-morbidities
- For high risk surgery, consider performing the surgery at a centre with hepatobiliary experience
- Consider pre-operative assessment for L-Tx (liver transplantation), in case patient does not do well post-operative

o Prevention of HE (hepatic encephalopathy)
- Correction of reversible metabolic factors (eg. hyponatremia, hypocalcemia)
- Oral lactulose administration, titrated to ~3-4 bowel movements per day
- Administration of nonabsorbable antibiotics
- Avoidance of nephrotoxic insult (eg. NSA|Ds, narcotics, benzo's))
- Supportive care
- Correction of reversible metabolic factors

o Treat complications of portal hypertension (PHT)
- Ascites, peripheral edema
- Oral diuretic therapy with spironolactone and furesomide
- Fluid restriction (if sodium concentration is <120 mmol/l)
- Avoidance of excessive saline administration
- Albumin infusion (with paracentesis volumes >5 l)
  - Antibiotics for spontaneous bacterial peritonitis
  - Steroids, as indicated
- Coagulopathy
  - Vitamin K supplementation (oral or parenteral)
  - Fresh, frozen plasma transfusions
  - Intravenous administration of cryoprecipitate
  - Intravenous administration of recombinant factor VIIa
  - Platelet transfusions
  - Paracentesis with analysis of ascitic fluid for evidence of infection

o 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
  - Avoid benzodiazepines, NSAIDs, narcotics

- Assess pulmonary function
  - Supplemental oxygen

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

- Give the **Child-Pugh classification** (CPC) 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	CPC
5-6	A
7-9	B
10-15	C

Abbreviation: CPC, Child-Pugh classification

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.

CPC	Surgical MR (%)
A	5-10
B	30
C	70-80

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

Source: Sterling RK. *ACG Annual Scientific Meeting Symposia Sessions* 2009; 71-77.

Infectious Hepatitis

There are certain "**buzz words**" which are meant to signal a likely diagnosis.

- Give 3 buzz words which when applied to the patient with acute hepatitis, suggest typhal fever from infection with either Salmonella typhi or Salmonella paratyphi.
  - Hepatitis plus
    - "Stepwise fever"
      - Stepwise increase temperature
    - "Temperature-pulse dissociation"
      - Pulse rate does not increase as much as expected for the temperature (i.e. relative bradycardia)
    - "Rose spots on skin"
      - Salmon-pink macules on skin of trunks

- Other clues that acute hepatitis might represent typhoid fever.
  - RLQ tenderness (ileitis / cecitis)
  - ALT / LDH < 4 (↑ 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 **Fitz-Hugn Curtis (FHC) syndrome** and violin string perihepatic adhesions on laparoscopy.

  - FHC syndrome is a gonococcal or chlamydia trachomatis infection of the female pelvic organs (usually salpingo-oophoritis) which involves the surface of peritoneum, causing the perihepatic fibrinous exudate (violin string adhesions).

  - The diagnosis of FHC syndrome would be suspected in a sexually active women with a painful pelvic examination.

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

Sepsis releases

- Exotoxins and endotoxins
  - Inhibits transport across hepatocyte sinusoidal and canalicular membrane
- TNF-α
  Same effect as exo- / endotoxins

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)

Please see "*Therapeutic Choices*, Ottawa, Canada: Canadian Pharmacists Association 2013, Chapter 59. Table 1: Characteristics of hepatitis viruses

The hepatitis alphabet Soup: What's it all about?

Serology	Type of infection
IgM anti HAV	Acute HAV
HBsAg for	
< 6 months	Acute HBV
> 6 months	Chronic HBV
Anti-HBs	HBV immunity
IgM HBeAg positive	Acute HBV Acute HBV flare of chronic HBV
IgM HBeAg negative	Excludes acute HBV
HBeAg	Infectivity
Anti-HCV	Marker for exposure (not for immunity to HCV)

- 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	Incubation (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%

Virus type	Trans-mission	Incubation (days)	Serologic diagnosis	Fulminant hepatitis	Risk of chronicity
- 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, men who have sex with men

Adapted from Therapeutic Choices, Canadian Pharmacist Association 2013, Chapter 59, Table 1, page 782.

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

- Give the screening, vaccination and prophylaxis which is recommended on 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

- Treatment when exposed (**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.

Hepatitis B Virus (HBV) Infection

➢ Molecular biology

- 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.

- Stages
  - Immune tolerant
    - Normal ALT level
    - Minimal or no inflammation or fibrosis
    - High levels of HBV DNA
    - Presence of HBeAg
  - 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.

- Pathogenesis
  - 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.

- Natural history
  - 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).

- 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.

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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.
- Explain 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

- Give the **mode of transmission** and the approximate **lifetime risk** of HBV infection in persons who reside in fifferent geographical areas.

Geographical Area	Mode of Transmission	Lifetime Risk of HBV Infection
o NA, WE, SA, Au	- Horizontal person-to-person, young adults - Sexual	< 20%
o SE, EE, ME, IS fUSSR, NAFR	- Infancy - Early childhood	20% to 40%
o 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

  - HBV progression

  Acute HBV → chronic HBV:

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

- List 5 **markers** of HBV infection, and what they signify.
  - HBsAg – appears first and if persists for > 6 months, the patient is chronically infected (exposed, chronic infection)
  - HBsAb – implies recovery or immunity to HBV, either naturally occurring or after vaccination
  - HBcAb-IgM – past or present HBV infection (newer and more sensitive assays may also be positive during reactivation of chronic infections)

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

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

- Define the following terms:

➢ Chronic active HBV (active HBsAg carrier)
- HBsAg positive for more than 6 mon HBe Hg positive
- HBV-DNA > 10^5 copies/mL (>20,000 Ik)
- Persistent or intermittent ALT/AST elevation
- Liver biopsy showing chronic hepatitis
- Evidence of on-going replication (active carrier), active chronic HBV infection

➢ 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)

➢ 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.

- Give the characteristics of the **different phases** 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	Inactive	Active/+ fibrosis	Inactive	Active/+ fibrosis
Treatment	Not recommended	Recommended	Not recommended	Recommended
Liver biopsy recommended	No progression of disease for about 3-6 months	HBeAg seroconversion with treatement		8-10% develops cirrhosis each year, compared with 2-6% of HBeAg positive patients

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

- Clinical
  - Active hepatitis
    - Circulating HBsAg – anti-HBs complexes activate complement
    - HBsAg – anti-HBs complexes are deposited in wall of the blood vessels of the skin synovium
    - Serum sickness-like prodrome, with 1/3 of patients developing jaundice
    - Low levels of HBV may persist in the serum
  - Fulminant hepatitis
    - Survival
      - spontaneous, 20%
      - liver transplant, 50%

- Inactive carrier
  - HBsAg lasting > 6 months
  - Falling levels of HBsAg may predict delayed clearance of HBsAg
  - ↓↓ HBV DNA (only PCR detection)
  - ALT normal
  - Seroconversion $HBeAg^+ \rightarrow HBeAg^-$ (anti-HBe positive)
  - Necroinflammation bodies
  - ↓ fibrosis
  - HBV replication
    - PCR-based, +
    - Non PCR-based, - (less sensitive)
  - AST, ALT
    - Normal, or slight increase
- Active 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%
- Fulminant HBV
  - Due to “massive immune-mediated lysis of infected hepatocytes”
  - Usual-onset
    - Within 4 weeks of symptoms of HBV
    - Untreated mortality rate, > 80%

- Late-onset liver failure after several months of onset of HBV symptoms
- May be associated with “flares” (exacerbations of disease)
  - ↑ ALT (2x the baseline value)
  - IgM anti-HBe
  - Associated with histological progression of disease

o 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

o Immune clearance
- ↓ HBV DNA
- ↑ ALT
- $HBeAg^{+}$
- Hepatic necroinflammation (immune-mediated lysis of HBV-infected hepatocytes)
- Optimal time for treatment

- Pathology

- 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 ccDNA 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

- 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
  - 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
    - Over time of titre of anti-HBs may have fallen to levels which are no longer protective (25% to 50% of vaccinated persons develop non-protective levels of anti-HBs over 5 to 10 years).
    - Initial hyporesponders, with the development of low and non-protective concentrations of anti-HBs
  - Some persons with low or no anti-HBs after vaccination appear to be protected.
  - Booster doses of vaccine is needed
    - In hemodialysis patients
    - In persons who are immunocompetent

- Give 8 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.

SO YOU WANT TO BE A HEPATOLOGIST!

- Give 10 reasons why a person immunized with HBs-Ag vaccine may not develop an adequate anti-HBs response.

Reasons for an inadequate anti-HBs response following vaccination with HBsAg:

- Persons
  - Very young, or old
  - Obese
  - Smoking
  - Chronic liver disease
  - Immunosuppressed
    - Transplantation
    - Chemotherapy
  - Administration of vaccine into buttock muscles
  - Genetic factors
    - HLA
      Alleles DR3, DR7, DQ2
      No HLA-A2
- Virus
  - Mutant HBV virus strains (mutation of "a" determinant of HBV, are not neutralized by vaccination with HBsAg, so are called HBV escapes mutants)

➢ Treatment

- General management strategy

- Baseline evaluation should include HBV genotype, particularly if peginterferon therapy considered
- The Centre for Disease Control (CDC) now recommends HBV diagnostic testing in all persons going on immunosuppressants or undergoing cancer chemotherapy
- 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
- Revised normal ALT levels (30 IU/L for men, and 19 IU/L for women) should be used as criteria for treatment
- Liver biopsy should be considered for patients with normal ALT levels, especially if age >35-40 years
- Baseline laboratory assessment; Baseline HBV DNA levels in patients aged 30-65 years are directly related to the likelihood of developing hepatocellular cancer (HCC) 10 years later
- Natural clearance of HBV occurs in 5% of neonates and 95% of adults infected with HBV
- 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.
- The longterm goal of HBV is to improve the patient's quality of life, and the prevention of progression of the disease to cirrhosis, HCC, and hepatic decompensation.
- 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.

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

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.

- 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.

- After HBV vaccination, subclinical HBV infection, 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

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.

Useful numbers

- 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%

- **Pre-therapeutic assessment** of liver disease
  - LEs (liver enzymes) – AST, ALT, GGT, AP
  - LFTs (liver "function" tests) – Bilirubin, albumin, globulins, INR
    – Scores based on blood work (e.g. MELD, DFT)

- HBV DNA (reflects HBV replication)
- Assess for possible other liver diseases
  - HAV, HCV, HIV; ALD, NAFLD: AIH, PABC
- Stratification of severity
  - FibroScan (transient elastography), liver biopsy
- All patients treated with NAs must have
  - Serum creatinine phosphate and creatinine clearance measurements before and during therapy
  - Assessment of baseline renal risk
    - Glomerulonephritis, active
    - Concomitant nephrotoxic drugs (e.g. NSAIDs)
    - CCR (creatinine clearance rate) < 60 ml/min
    - Hypertension, poorly controlled
    - Diabetes, uncontrolled
    - Cirrhosis, decompensated
    - Proteinuria
    - Organ transplant
  - Renal monitoring
    - Low renal risk q 3 mon for 1 yr; if no deterioration, then q 6 mon
    - High renal risk q 3 mon; if no deterioration, then q 3 mon for 9 mon; then q 6 mon
- 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

- 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.

- Principles – treat to maintain 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%

- Give 3 virological responses, which represent **acceptable end points** for HBV therapy.
  - Sustained off- therapy loss of HBsAg
  - Sustained off therapy loss of HBeAg (anti-HBe antibody positive)
  - Sustained off therapy HBe antigen negative patient who was HBe antigen negative at baseline
  - Undetectable HBV DNA (< 2000 IU/mL by sensitive PCR assay) while on anti-HBV therapy

Please see "*Therapeutic Choices*, Ottawa, Canada: Canadian Pharmacists Association 2013, Chapter 59. Table 3: Management of Chronic Hepatitis B

- Give 6 **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)
  - 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
- Improve patient quality of life
- 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])

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

Comparisons	HBeAg positive	HBeAg negative
○ Epidemiology	○ Most common type in North America	– Higher incidence in Asia, Europe and other Mediterranean countries
○ Natural History	○ Lower rate of progression to cirrhosis (10-20% /yr) (immune tolerance)	– Higher rate of progression to cirrhosis
○ Treatment response	○ Higher sustained response rate to IFN-α therapy	– Lower sustained response rate to IFN-α therapy

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

- Outcomes
  - 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)

- Give 5 factors that are **predictive of a viral response** (VR) to treatment of HBV infection.
  - Patient
    - Immunocompetent
  - HBV
    - Adult-acquired infection
    - Low HBV-DNA level
    - Absence of HDV or HIV co-infection
    - HBeAg +ve
  - Biopsy
    - Active liver disease—ALT > 5x upper limit of normal (ULN), active hepatitis on biopsy
  - Adherence to optimal therapeutic program
- 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 chronic hepatitis B (CHB)	Poor	High

- 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 the importance of HBeAg status
- HBeAg
  - Represents
    - ↑ viral replication
    - Active liver disease
    - Need for antiviral therapy
  - 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

- 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!
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

Menu of choices in HBV treatment

- IFN (interferon)
  - Non-pegylated
  - Pegylated (PEG-IFN)
- Nucleosides (NSs)
  - Lamivudine
  - Telbivudine
  - Emtricitabine
  - Entecavir
- Nucleotides (NTs)
  - Adefovir
  - Tenofovir
- Note:
  - Treatment does not completely eliminate HBV infection, since the HBV (a DNA virus) becomes integrated within the hepatocyte genome as CCC, (covalently closed circular) DNA

NA	High barrier to resistance	High efficacy	High cost
Entecavir	+	+	+
Tenofovir	+	+	+
Lamivudine	-	-	-
Adefovir	-	-	++
Telbivudine	-	+	+

Note:

- The dose of NAs (NTs and NSs) must be reduced if creatinine clearance < 50 mL / min.

- Give the **general management strategy** of the person with HBV.
  - Treatment strategies
    - PEG-IFN or NA monotherapy for finite duration
    - NA for longterm 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 longterm duration
  - Entecavir or tenofovir monotherapy for
    - HBeAg-positive patients who failed to seroconvert or HBeAg-negative patients
    - All HBV cirrhosis
  - 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 (166-8). 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

- "More than 90-95% of adults with acute HBV infection will recover spontaneously and seroconvert to anti-HBs without anti-viral therapy.

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One goal of therapy of HBV is to minimize HBV DNA levels. Give the reason why therapeutic elimination of the HBV is not possible.

- HBV genome is incorporated in host genome
- ccc DNA (covalently closed circle DNA persists in nuclei of infected hepatocytes)

- Indications for treatment
  - ↑ HBV DNA (> 2000 IU / mL)
  - ALT > ULN (upper limit of normal)
  - Necroinflammation (≥ moderate severe) and fibrosis (≥ moderate), by liver biopsy or standardized scoring system
    - Note
      - If HBV DNA > 2000 IU/mL and ≥ moderate severe necroinflammation, treatment may be undertaken even if ALT normal
      - HBeAg-positive
        - < 30 yr
          - ALT persistently normal (q 3 mon for q yr)
          - ↑ serum HBV DNA (> 2000 IU/mL)
          - No evidence of liver disease
          - No family history of cirrhosis or HCC

            ↓
          - FU q 3 to 6 mon
        - > 30
          - Family history of cirrhosis or HCC

            ↓
          - Liver biopsy, or HBV Rx

- HBV-Ag-negative
  - ALT normal q 3 mon for ≥ 1 yr
  - Serum HBV DNA > 2000 < 20,000 IU/mL
  - No evidence of liver disease

    ↓
  - FU ALT and HBV DNA q 3 mon for ≥ 3 yr

    ↓
  - After 3 yr continue to follow for life
    - Like inactive chronic HBV carrier (anti-HBe antibody positive, very low / underdetectable serum HBV-DNA
    - FibroScan
- Active CHB (chronic hepatitis B)
  - No cirrhosis
    - ALT > 2x ULN
    - Serum HBV DNA > 20,000 IU/mL

      ↓
    - Liver biopsy plus Rx, or
    - FibroScan plus Rx
  - Cirrhosis, compensated; serum HBV DNA detectable

    ↓

    Rx
  - Cirrhosis
    - NAs (nuceloside / nucleotide analogues
    - May require liver transplantation if viral replication continues despite NAs

Abbreviations: Rx, HBV treatment; ULN, upper limit of normal

- Choices
  - Nucleosides
    - Lamivudine
    - Telivudine
    - Emtricitabine
    - Entecavir
  - Nucleotides
    - Adefovir
    - Tenofovir

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

Resistant NA	Therapeutic strategy
○ 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.

Interferon (IFN / PEG IFN)

- Give 4 **contraindications** to the use of IFN / PEG-IFN.
  - Decompensated HBV cirrhosis (↑ risk of bacteremia and ↑ decompensation further)
  - Autoimmune disease
  - Uncontrolled severe depression / psychosis
  - Pregnancy
  - Renal transplant patients (↑ risk of rejection)

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NAs (nucleoside / nucleotide analogs) may be used for finite duration treatment periods in HBeAg-positive patients, or for long-term treatment in those "…. who are not expected or fail to achieve a sustained off-treatment virological response and require extended therapy, i.e. for HBeAg-positive patients who do not develop anti-HBe seroconversion and HBeAg-negative patients".

- Give the circumstance under which long-term treatment with NA's may be stopped.
  - After at least 12 mon of consolidation therapy, treatment might be stopped in HBeAg-positive patients if they achieve confirmed anti-HBe seroconversion.

PEG-IFN has some 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.

Nucleoside (NS) and 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".
- 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.
- Lamivudine
  - High rate of viral mutation and viral resistance
  - ~40% at 2 years, 65% at 5 year
  - Higher rate of resistance with treatment of co-infection with treatment of co-infection with HIV.
- Viral resistance may occur weeks to months before a virologic breakthrough
- 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

SO YOU WANT TO BE A HEPATOLOGIST!

- Give why interferon is **contraindicated** in HBV-associated cirrhosis.
  - In HBV-associated cirrhosis, giving interferon may cause an immune-mediated flare which could result in decompensation.
- Give the treatment of the HBV in the co-infected HBV plus HIV patient.
  - If the treatment of HBV is mediated in the HBV plus HIV patient:
  - If HIV does not need to be treated (CD4+ > 350 mm^3) - Anti-HBV therapy with no effect HIV, e.g. peg interferon or adefovir
  - If HIV does need to be treated (CD4+ < 350 mm^3) - Anti-HBV therapy with effect on HIV, (e.g. plus effect on HBV, e.g. tenofovir plus emtricitabine, or tenofovir plus lamivudine)

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

HBeAg positive	PEG-IFN		Nuclesoside analogs			Nucleotide analog	
	PEG-IFN-2a	PEG-IFN-2b	Lamivudine	Telbivudine	Entecavir	Adefovir	Tenofovir
Dose	180 µg	180 µg	100 µg	600 mg	0.5 mg	10 mg	245 mg
Anti-HBe seroconver-sion (%)	32	29	16-18	22	21	12-18	21
HBV DNA < 60-80 IU / mL (%)	14	7	36-44	60	67	13-21	76
ALT normalisation (%)	41	32	41-72	77	68	48-54	68
HBsAg loss (%)	3	7	0-1	0.5	2	0	3

HBeAg negative	PEG-IFN	Nuclesoside analogs			Nucleotide analog	
		Lamivudine	Telbivudine	Entecavir	Adefovir	Tenofovir
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

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 Seroconversion										
Year 1										
Year 2	20%	NP	13%[a]	NP	21%	NP	23%	NP	23%	NP
Year 3	26%	NP	29%[a]	NP	31%	NP	30%	NP	26%	NP
Year 4	40%	NP	37%[a]	NP	NA	NP	NA	NP	NA	NP
	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.

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

<u>Favoring lamivudine</u>

- Needle phobia
- HIV co-infection
- Other immunosuppression (e.g. transplantation)
- May be used in patients with
  - Depression
  - Renal failure
- Low WBC count
- Low platelet count

<u>Favoring IFN</u>

- Young Asian
- Genotype A
- Recent infection
- AST > 100
- Low serum HBV-DNA
- Active liver biopsy
- eAg+
- Possibility of seroconversion

- Autoimmune disease
- Decompensated cirrhosis
- Vertical transmission
- Cost concerns
- Pregnancy, may be used
- Has 70% resistance rate at 5 years. It acts as an immune modulatory 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 (eAg+→eAb+, 25%)
- PEG-IFN has advantages over nucleos(t)ide (NA) because of
  - The absence of resistance
  - 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.

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

"Let's see if there is mechanistic information that

we can tease out."

Grandad

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

Agent	Advantages	Disadvantages
○ Interferon	– HBsAg loss – Short treatment duration – No drug resistance	• Parenteral administration • Frequent side effects
○ Peg-IFN	– HBsAg loss – Fixed duration of treatment – No drug resistance	• Parenteral administration • Frequent side effects but less than interferon
○ Lamivudine	– Oral administration – Excellent tolerance – Use in ESLD – Use in adefovir failures	• Drug resistance: common (~20%/year, and up to 70% with 4-5 years of therapy)
○ Adefovir	– Oral administration – Excellent tolerance – Use in ESLD – Use in lamivudine failures	• Less potent, with suboptimal responses not uncommon • Drug resistance: delayed and less common (0% at year 1, 2% at year 2, 7% at year 3, 15% at year 4, and 29% at year 5 of therapy)
○ Entecavir	– Oral administration – Excellent tolerance – High potency in lowering HBV DNA levels – Use in adefovir failures	• Drug resistance: rare in nucleoside naïve patients (0.1% at year 1, 0.4% at year 2 and 1.1% at year 3), but common in patients with lamivudine resistance (6% at year 1, 14% at year 2, and 32% at year 3)
○ Telbivudine	– Oral administration – Excellent tolerance – High potency in lowering HBV DNA levels	• Drug resistance: intermediate rates (5% at year 1, and 21.6% at year 2 in HBeAg-positive patients, 8.6% in HBeAg-negative pts)

Abbreviation: ESLD, end-stage liver disease

Printed with permission: Keeffe EB. *2007 AGA Institute Postgraduate Course*: 76.

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

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

Useful background: 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 potential management strategies for HBV by **on-treatment virologic response** categories.

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

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

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

OSCE AND BOARDS ALERT

- Give 5 causes of "**flares**" of acute hepatitis (reactivation, decompensation) in persons with chronic HBV.

Cause of flares	Comment
○ Spontaneous	– Seroconversion HBeAg+ →HBeAg- – Reappearance of IgM anti-HBC
○ Drugs – Immunosuppressive therapy – Steroids Interferon (systemic (interferon), common; oral agents, rare – Antiviral therapy – Lamivudine	– Flares are often observed during withdrawal of immunosuppressants; requires preemptive antiviral therapy – Flares are often observed during the second to third month: may herald virologic response
○ During treatment	– Flares are no more common than with placebo
○ YMDD mutant	– Can have severe consequences in patients with advanced liver disease
○ Adefovir, entecavir	– On withdrawal, flares are caused by rapid reemergence of wild-type HBV; can have severe consequences in patients with advanced liver disease
○ HIV treatment	– Flares also can occur with immune reconstitution or secondary to antiretroviral drug hepatotoxictity
○ Genotypic variation – Precore and core promoter mutants	– Fluctuations in serum ALT levels are common with precore and core promoter mutants

- Superimposed infection with
- Other hepatitis viruses
- Alcohol use

- HAV, HCV, HDV may be associated with suppression of
- HBV replication

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

More Boards Alerts

- 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
- 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.
- Mutations in the Precore, Basal Core Promoter and Core Genes

- More common in HBe-Ag-negative persons
- Stop the synthesis of HbeAg
- ↑ development of fulminant HBV
- ↑ risk of HCC
- ↓ response to interferon

- Mutations in HBV DNA polymerase
  - "HBV reverse transcriptase function of the polymerase gene is highly preserved…." (Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier, Philadelphia, 2010, page 1291).

- Give the reason why acute liver failure (ALF) may occur during steroid withdrawal for treatment of 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.

Abbreviations: LT, liver transplantation; NA, nucleos(t)ide; NS, nucleoside; NT, nucleotide

- Give the treatment of anti-viral resistant HBV.

o 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)
o 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

- 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.

- 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 IU/ml	Normal	– No treatment: majority inactive HBsAg carrier – Monitor every 6-12 months
≥2,000 IU/ml	Normal	– Consider biopsy; treat longterm 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.
≥2,000IU/ml	Elevated	– Adefovir, entecavir, peginterferon alfa-2a, or possibly telbivudine are preferred – Longterm treatment required for oral agents

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

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

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

- 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

Monitoring and stopping HBV treatments

- Give when HBV therapy should be reassessed or stopped.
  - HBeAg+: HBeAg seroconversion and – HBV DNA
  - HBeAg-: ? Longterm 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.

- PEG-IFN
  - HBeAg-positve
    - 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.

- Give the treatment of HBV infection in 6 of the following **special circumstances**.

The special circumstances include:

- Chronic renal failure
- Dialysis, and transplantation
- HIV, co-infection
- HCV co-infection
- HDV co-infection
- Post-LT (liver transplantation)
- ALF (acute liver failure)
- Healthcare worker
- Pregnancy
- Before immune- or chemotherapy

- Immune rebound
- HBV carriers and HCC

- **Chronic renal failure**
  - The dose of NAs (NTs and NSs) must be reduced if creatinine clearance < 50 mL / min.
  - Dialysis and renal transplantation
    - Vaccinate HBV serogate 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 day which is active against HIV
  - Early dual anti-HIV and anti-HBV therapy, using usual indications for anti-HBV
    - HBV DNA
    - Serum ALT
    - Histological feature
  - Tenofovir plus emtricitabine plus emtricitabine or lamivudine, plus third anti-HIV drug
  - Risk of HBV flare with immune reconstitution from treatment of HIV
- **HCV co-infection**
  - Treat HCV in usual manner
  - Monitor HBV DNA for possible ↓ HBV → Rx with NA and treat HBV activation with NAs (activity of HBV is often suppressed in presence of HCV).

- **HDV-coinfection**
  - Diagnose HDV co-infection with HBV
    - HDV-RNA
    - HDV antigen on IMC (immunohistochemical staining of liver)
    - Anti-HDV IgM
  - PEG-IFN for 1 yr, with assessment q 3 mon of HDV RNA

- **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) from 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)
  - Renal patient-di88.alysis
    - Screen all persons with renal disease for HBV
    - HBV seronegative
      - Vaccination
    - HBV seropositive
      - PEG-IFN or NAs with dose adjustment and monitoring of creatinine, blood sugar and HgA1c, as well as systemic blood pressure
      - If renal transplant patient, do not use IFN (risk of rejection)
- **Healthcare workers' HBsAg-positive, HBV DNA ≥ 2000 IU / mL - entecavir or tenofovir to reduce HBV DNA to undetectable levels.**
  - Healthcare workers (such as surgeons)
    - HBsAg-positive plus HBV DNA ≥ 2000 IU/mL
    - Tenofovir or entecavir to achieve HBV DNA
    - "Monitor for compliance and < 2000 IU/mL efficacy in practicing surgeon is required
  - Follow HBV DNA and monitor patient compliance to Rx.
  - Treat reactivation of chronic hepatitis B

- NA(nucleos(t)ide) (NS [nucleoside] or NT [nucleotide])

- **Pregnancy**
- Give the management of the **woman** with active HBV infection who becomes **pregnant**.
  - Pregnancy
    - Discuss planning for pregnancy, as well as FDA category of drugs
      - PEG-IFN, **X** contraindicated
      - Lamivudine, adefovir, entecavir, C
      - Tenofovir, telbivudine, B
    - FDA category
      - B tenofovir (preferred), telbivudine
      - C lamivudine, adefovir, entecavir

Treatment Caution

- **X PEG-IFN: do not use in pregnancy**

    - 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
  - Infants of HBV CHB patients
    - HBIG plus HBV vaccination

- For infants of mothers with serum HBV DNA > 10^{6-7} IU/mL, often also being HBeAg-positive, add lamivudine or telbivudine in T3 (third trimester of pregnancy) plus post-partum HBIC and HBV vaccination
- If ant-HBV therapy is inappropriately stopped or never started / taken
  - Monitor during and after pregnancy for HBV flare
- During lactation
  - NA, especially tenofovir
  - "… breast feeding may not be considered a contraindication in HBsAg-positive mothers"

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

- Before starting **immunosuppressive therapy or chemotherapy**
  - HBe-Ag-positive
    - NA before, during and for 12 months after immunosuppressive therapy or (preferable entecair 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,
    - HBV-DNA level low prophylactic lamivudine high (and/or long or repeated cycles of immunosuppression), tenofovir, or entecavir
    - 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-positve donor – indefinite lamivudine prophylaxis

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 occurs when the patient with HBV infection is placed on corticosteroids which are then stopped.

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

- **HBV Carriers and Hepatocellular Cancer (HCC)**

- Give 5 characteristics of healthy HBV carriers (no cirrhosis) who are candidates for HCC screening.
    - African males/ females > 20 years
    - Asian male >40 years
    - Asian female >50 years
    - Caucasian inactive or active disease with cirrhosis*
    - Family history of HCC
    - Co-infection with HCV, HIV

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

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

- Give factors associated with ↑ **risk of HCC in HBV infection**.
  - HBeAg
  - Patient
    - Male
    - > 45 years
    - 1º relative with HCC
    - Race (African > Asian men > Asia women)
  - Serology
    - HBeAg-positive
    - Reversion of anti-HBe to $HBeAg^+$
    - Cirrhosis
  - Fibrosing cholestatic hepatitis reactivation of HBV immunosuppressants given for organ transplantation ↑↑↑ HBsAg and HBeAg in liver tissue
  - Infection with other (A_1C_1D) hepatotrophic viruses
  - Extrahepatic manifestation
    - Fever, arthralgias (proximal interphalangeal pints), angioneurotic edema
    - PAN (polyarteritis nodosa)
    - HBV-associated
      - Glomerulonephropathy
      - Membranous glomerulonephritis
      - Membranoproliferative glomerulonephritis
      - Immune-complex glomerulonephritis
      - Nephrotic syndrome
      - Renal failure
      - Cryoglobulinemia

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! HBV, 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

HEPATITIS C VIRUS (HCV) INFECTION

- Transmission
  - 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
- Pathogenesis
  - Usually immune-mediated
  - 75% of persons with acute HCV progress to chronic HCV infection because of ineffective immune against the HCV
  - HCV-enters hepatocytes by attachment and transport, using proteins
    - E1 and E2 envelope proteins
    - CD81 tetraspan superfamily
    - SR-B1 scavenger receptor class B type 1
    - LDL-R LDL receptor
    - HDL unknown low HDL marked by increases infectivity of HCV
  - Mutational rate of HCV

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.

- Risk factors

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

Groups at risk	Estimated prevalence (range %)
○ 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

Abbreviation: ALT, alanine aminotransferase

- 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 Rx considered
    Anti-HCV negative but immunocompromised or suspected as having HCV

↓ Anti-HCV positive

HCV positive → interpret HCV → HCV genotyping

↓ Give advice re measures to avoid transmission of HCV

↓ HCV genotyping: Access for possible fibrosis, FibroScan, or Liver biopsy

Access for treatment
- Indications
- Contraindications
- Individualized therapy

Not determined by ALT vlue
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

  Followed by 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

↓ ↓ ↓

Wk 12-24, HCV RNA undetectable

↓

Continue Rx for 72 wk

↓

HCV RNA negative, retest 24 wk later when off Rx (SVR, sustained virological response)

↓

Wk 12, HCV RNA still detectable

↓ continue Rx another12 wk

Wk 24, retest, and if HCV RNA still present, stop treatment

Wk 12, EVR < 2 log ↓ HCV RNA, stop treatment (EVR, early virological response, ≥ 2 log ↓ HCV RNA)

If cirrhosis present, monitor q 6-12 mon for HCC

➢ Screening

- Give the types of persons who should be screened for HCV.
    - Concurrent disease
        - Hemodialysis patients
        - Transplanted patients
        - Immunosuppressed patients
        - Hemophylics
        - Blood transfusion before approximately 1990 (depends on country)
    - At risk occupations
        - Needle stick injury
        - Inmates
    - At risk behavious
        - HIV-positive patients
        - Men who have sex with men (MSM)
        - Sex trade workers (STWs)
        - Those with > 50 lifetime sexual partners
        - Those with a history of STD
        - STDs
        - IV drug users
    - Regular folks
        - Those with unexplained elevated ALT
        - Immigrants
        - There is discussion as to possible benefit of screening everyone

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

➢ Clinical

- Give 10 **extrahepatic manifestations** of Hepatitis C (HCV) infections.
    - Skin
        - Vitiligo
        - Lichen planus

  - Positive antibodies: ANA2 anti-ASM, anti-LKM microsomal antibodies, peroxidase
- 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
- Thyroid
  - Autoimmune thyroiditis
  - Thyroid cancer
- Lung
  - Idiopathic pulmonary fibrosis
- Endocrine
  - Diabetes mellitus
  - Autoimmune thyroiditis
- MSK
  - Chronic polyarthritis
  - Sicca syndrome
- Kidney
  - Membranous nephropathy
  - Cryoglobulinemic nephropathy
  - Non cryoglobulinemic nephropathies
  - MPEN (membranoproliferative) glomerulonephritis
  - Renal cell carcinoma
- Hematology
  - B cell non Hodgkin 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 5 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

Clinical Challenge

- A patient presents with abdominal pain, leucocytoclastic vasculitis, plapable purpura, and ↓ complement. Give the likely diagnosis.
  - Young adult
    - HSP (Henoch-Schonlein purpura)
  - Older adult
    - Mixed cryoglobulinemia (e.g. associated with HCV)

Clinical Alert!

- HCV and autoimmune conditions
  - Because autoantibodies are common in HCV, they are not necessarily associated with disease, so be cautious about 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

➢ Laboratory

- 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 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

➢ Pathology

- 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
    - – Panels
    - – Indirect makers of fibrosis included (fibrotest ™)
    - – Direct markers of fibrosis
    - – Combination of indirect and direct markers of fibrosis

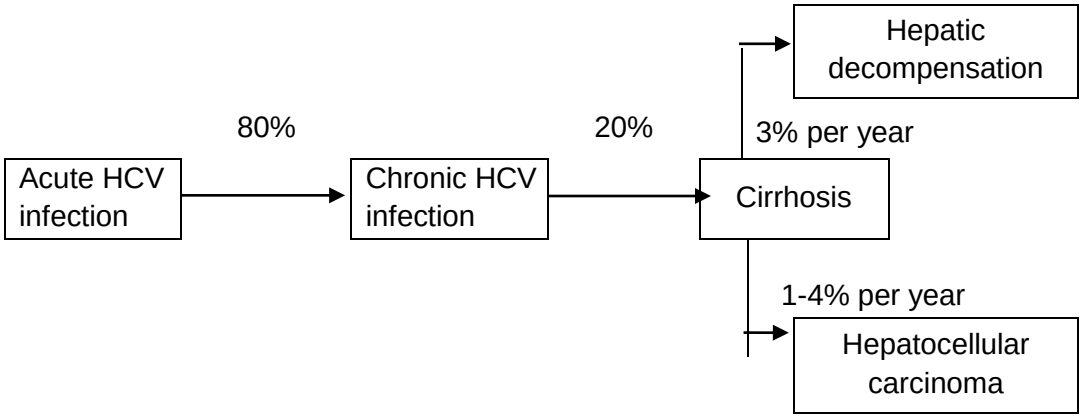
    - Hepascore ™
    - Fibrometer ™
  - Transient elastography (TE)
- Give 10 modifiable as well as non-modifiable factors which are associated with the **histological progression** of HCV infection.

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

	Established	Likely
o Patient	– Age > 40 yr – Males – Caucasian	
o Life style	– Alcohol > 50 g / day	– Obesity – Elevated serum ALT levels (elevated) – Smoking – Cannabis use (marijuana)
o Co-morbidities	– Immunosuppression (especially humoral immune impairment) – Immunosuppression (HIV coinfection, agammaglobulinemia, organ transplantation)	– Steatosis – Insulin resistance – Diabetes (genotypes 1 and 4) – Iron overload – HBV co-infection – Schistosomiasis – Histology - Moderate to marked necroinflammation

Note: Progression of HCV is **not** associated with HCV load or genotype

- Progression of HCV



- 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) without cirrhosis
4		Cirrhosis – Focal – Diffuse – Marked

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

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.

- 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.

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- 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

- Give a **non-biopsy grading system of fibrosis** in HCV

➢ Blood tests
  - FibroSure ®
    - Composite score
      - Age
      - Gender
    - A2-macroglobulin
      - Haptoglobulin
      - Apolipoproteins A-1
      - GGT
      - Bilirubin
  - ↑ AST and ↑ ALT, ALT > AST, APR1 (AST-to-platelet index)

➢ 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

➢ Natural history of HCV
  - Acute → chronic HCV 55% to 89%
  - Chronic HCV → compensated cirrhosis ~1% per year after infection
  - Compensated cirrhosis → HCC ~2% per year
    → decompensation ~3% per year

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

- 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.

- 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

Please see "*Therapeutic Choices*, Ottawa, Canada: Canadian Pharmacists Association 2013, Chapter 59. Table 4: Management of Chronic Hepatitis C

- ○ Note
  - With the remarkable efficacy of the new pharmaceutical therapies for HCV, some of the agents discussed below may soon pass from use.
  - Until this happens, the complete menu of therapies is included.

- Give the management of persons with HCV.
    - Chronic compensated HCV liver disease with moderate or severe fibrosis
        - Regardless of symptoms or concentration of serum ALT
        - No contraindications
    - Assess severity of liver disease
    - Assessment of possible relative or absolute contraindications
    - Assessment of factors predictive of viral response
    - Prevention, screening, vaccination (none), prophylaxis on exposure
    - General management strategy
    - 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.

    - Another way to approach the answer is to consider the converse to the following question (factors which predict a good treatment response in HCV)

- Give the **pretreatment assessment**: of treatment of HCV.

➢ *Necessary*

    - Medical history, including complications of liver disease, presence of significant extrahepatic disease, and symptoms of chronic HCV that may diminish quality of life
    - Psychiatric history, including past or ongoing psychiatric, and substance use disorders
    - Screening for depression and alcohol use
    - Biochemical markers of liver injury and assessment of hepatic function, including serum ALT, serum albumin, serum bilirubin (including direct bilirubin), and prothrombin time
    - Hemoglobin, hematocrit, WBC with differential, and platelet count

- TSH
- Serum creatinine
- Serum glucose
- Uric acid (while receiving TVR)
- Serum ferritin, iron saturation, and serum ANA
- Pregnancy test (in women of childbearing age)
- HIV serology
- Serum HBsAg, antiHBc, antiHBs, antiHAV (total)
- Quantitative HCV RNA measurement
- HCV genotype
- Previous antiviral therapies and response
- ECG in patients with preexisting cardiac disease

➢ *Recommended*

- Liver biopsy (if results will influence management)
- IL28B genotype (if results will influence management)
- Eye exam for retinopathy in patients with diabetes or hypertension
- Urine toxicology screen for opiates, cocaine, and amphetamines

➢ "Factoids"

- Benefit of routine screening for HCV in pregnancy is not proven.
- Interferon and ribavirin given to breastfeeding mother with HCV is not recommended, even if mother's breast nipples are not cracked and bleeding.

Abbreviations: [a] ALT, alanine transaminase; ANA, antinuclear antibodies; antiHAV, antibody to hepatitis A virus; antiHBs, antibodies to HBsAg; AntiHBc, antibody to hepatitis b core antigen; ECG, electrocardiogram; HbsAg, hepatitis B surface antigen; HCV, hepatitis C virus; TSH, thyroid-stimulating hormone; TVR, telaprevir; WBC, white blood cell.

Printed with permission: Yee HS, et al. Update on the Management and Treatment of Hepatitis C Virus Infection: Recommendations from the Department of Veterans Affairs Hepatitis C Resource Center Program and the National Hepatitis C Program Office. Am J Gastroenterol 2012; 107: Table 2, 669-689.

- The endpoint of treatment is to obtain SVR (sustained virologic response HCV RNA < 50 IU / mL, 24 weeks after stopping treatment), which represents a cure of the HCV infection in 99% of HCV-infected persons.

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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%

Predictors of response to HCV treatment to HCV treatment include:

- Genetic polymorphisms located in chromosome 19 near the region coding for IL-28b (especially in persons who are genotype I)
- Genotype (treat response 2 > 3 >> 1)
- Severity of liver disease (stage of fibrosis)
- Therapy: type, dose, duration, compliance
- Host- age, gender, BMI, insulin resistance

- The likelihood of obtaining a treatment-induced SVR is assessed from measuring HCV RNA at weeks 4, 12 and 24 of treatment.

Types of responses

- Responders after 12 weeks
  - ↓ 2 log HCV RNA IU/mL
  - After 24 weeks
    - Undetectable HCV RNA
- Non-responders

- Fail to achieve above endpoints
  - Retreatment response (genotype 1) with PEG IFN is only 4% to 14%
  - Retreat genotype 1 non-responders with PEG-IFN, ribavirin plus PI (protease inhibitor)
  - Retreat non-genotype 1 non-responders with PEG-IFN

- Relapsers
  - Undetectable HCV RNA at end of treatment, but then relapse and do not achieve SVR (15% to 25%)

- Types of response to anti-HCV therapy
  - NR > pEVR > cEVR > RVR

- 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)

- Expected SVR rate from Standards-of-care therapy (PEG IFNα plus ribavirin) and doses:

  - PEG-IFN α 2a 180 μg / week
  - PEG-IFN α 2b 1.5 μg / kg / wk
  - Ribavirin 15 mg / kg / day
  - Genotype 1
    - 40% to 54% SVR at week 48

  - Genotype 2 or 3
    - 0.5% to 82% SVR at week 24

  - Note:
    - PEG-IFN α 2b and ribavirin are dosed on a weight basis; it is optimal if the patient achieves their ideal body weight to achieve the optimal rates of SVR
    - Avoid alcohol intake

- Give the **contraindications** of treatment of HCV.

- Absolute
  - History of
    - Depression
    - Psychosis
    - Seizure disorder
  - Pregnancy, or inadequate contraception
  - Severe concurrent medical condition
    - Autoimmune disease
    - Severe or uncontrolled DM (diabetes mellitus)
    - Cardiopulmnary disorders
    - COPD (chronic obstructive pulmonary disease)
    - HF (heart failure)
    - HBP (systemic hypertension)
    - ↑ serum creatinine
    - Untreated thyroid disease
    - Decompensated liver disease
  - These will change with the use of interferon-free anti-HCV therapies

- Relative (treat those conditions which might otherwise represent a contraindication)

  - "penias"
    - Anemia (< 10 g /dL)
    - Neutropenia (< 70 mm^3)
    - Thrombocytopenia (< 50,oo mm^3)
  - Note
    - These may respond to adjustment of the dose of PEG-IFN (α 2a and α2b) and ribavirin, but should be stopped if the neutrophil count is < 500 / mm^3 or if the platelet count is < 25,000 / mm^3
    - Rather than reducing the dose of ribavirin if anemia develops, use erythropoietin (EPO); the use of G-CSF (granulocyte colony-stimulating factor is not recommended.

➢ Predictors of response to treatment

- Good response

- Non-I
- 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 interferon monotherapy: 5-15%, to combined interferon and ribavirin: 30-40%, to combined pegylated interferon and ribavirin: 54-56%.

- Poor response
  - Virus
    - Genotype I
    - High baseline viral load
  - Host
    - IL-28 B CT, TT genotype
    - African, Latino ancestry (related to IL-28B)
    - Older males
    - ↑ BMI (obesity)
    - Insulin resistance
  - Liver
    - Advanced fibrosis score
    - Steatosis
    - Severe necroinflammatory activity

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
- CNS
    - ↑ retinopathy DM
    - Optic tract neuropathy
    - CNS (neuropsychiatric)
- GI
    - Weight loss
    - Diarrhea
    - Anorexia
    - IBD worsens
- Endocrine
    - Worsening thyroid disease
- MSK
    - Muscle aches
- Hematology
    - Bone-marrow suppression
- Autoimmune
    - Autoimmune autoantibodies
    - Autoimmune diseases worsen
- Skin
    - Alopecia
    - Lichen planus worsens
- Pregnancy class C
- Infection
    - ↑ Bacterial infections

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

PegIFN dose recommendation, based on hematological parameters

- WBC count

$<1.5 \times 10^9$/l	– PegIFN alfa-2b: reduce dose to 1 mcg/kg per week, then to 0.5 mcg/kg per week if needed
$<1.0 \times 10^9$/l	– Discontinue PegIFN alfa-2b until resolution

PegIFN dose recommendation, based on hematological parameters

○ ANC[a] (absolute neutrophil count)	
<0.75 × 10^9/l	– PegIFN alfa-2a: reduce dose to 135 mcg per week PegIFN alfa-2b: reduce dose to 1 mcg/kg per week, then to 0.5 mcg/kg per week if needed
<0.50 × 10^9/l	– Discontinue PegIFN until resolution
○ Platelets[b]	
<50 k/mm^3	– PegIFN alfa-2a: reduce dose to 90 mcg per week – PegIFN alfa-2b: reduce dose to 1 mcg/kg per week, then to 0.5 mcg/kg per week if needed
<25 k/mm^3	– Discontinue PegIFN until resolution
○ Hb concentration	
<11.0, but >10 g/dl	– No change in RBV dose if patient has minimal symptoms – In a symptomatic patient, consider RBV dose reduction
<10.0, but >8.5 g/dl	– Decrease RBV, consider starting an erythropoietic growth factor – In patients with a cardiac history, reduce RBV dose and reduce PegIFN alfa-2b dose by 50%
<8.5 g/dl	– Discontinue RBV until resolution – If RBV is stopped for ≥7 days or discontinued in patients who are concomitantly receiving BOC or TVR, then BOC or TVR must be permanently discontinued

Abbreviations: BOC, boceprevir; GCSF, granulocyte colony-stimulating factor; Hb, hemoglobin; HCV, hepatitis C virus; PegIFN, peginterferon; RBV, ribavirin; TVR, telaprevir; WBC, white blood cell counts.

[a] If dose is maintained outside of manufacturer recommendations, monitor ANC more frequently, and counsel patient on neutropenic precautions. In post-liver transplantation or HIV/HCV-coinfected patients who remain neutropenic despite dose reduction, consider starting GCSF until resolution.

[b] If dose is maintained outside of manufacturer recommendations, monitor platelet counts, and signs or symptoms of unusual bleeding or bruising more frequently.

Printed with permission: Yee HS, et al. Update on the Management and Treatment of Hepatitis C Virus Infection: Recommendations from the Department of Veterans Affairs Hepatitis C Resource Center Program and the National Hepatitis C Program Office. Am J Gastroenterol 2012; 107: 107: Table 5, 669-689.

- Duration of treatment

Genotype	Response	HCV RNA ≤ 50 IU /mL
1	RVR	4 wk
2 and 3	RVR	4 wk
1,4	EVR	12 wk
1,2,3	DVR	24 wk

	weeks
– Low baseline HCV RNA (< 400,000 to 800,000 IU / mL)	24
– High baseline HCV RBA	48
– Low baseline HCV RNA	16
– Low baseline special factors (regardless of baseline)*	24
	48
	72

- Following-up
  - Cirrhosis: surveillance
    - For HCC, every 6 months
    - For esophageal varices, every 1-2 years
  - Non-cirrhotic at week 48 and 96, test for HCV RNA and ALT

Ribavirin

- Give 6 relative or absolute **contraindications** to the use of Ribavirin.
  - Pregnancy
  - Inadequate contraception

- End-stage renal disease
- Anemia
- Angina pectoris (possible)
- Old age (possible)
- Known allergy to ribavirin

- Give the management of major hematological adverse effects of ribavirin.

Cell type	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 peg IFN 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
○ Platelets	50,000/μL	- Reduce peg IFN by 50%	Individualize dose adjustment
	25,000/μL	- Stop IFN	Consider platelet transfusion or platelet stimulating factor

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- Give the common adverse effects (AEs)of Ribavirin (RIB) in the treatment of HCV, and give the management of these AEs.
  - Common AEs: “flu-like symptoms”, fatigue, anorexia, nausea, nasal congestion, irritability, cognitive impairment, insomnia
  - Overall dose reduction in19% of Ribavirin treated persons, with discontinuation in 10%
  - Major AEs of Ribavirin
    - ↓ RBC, ↓ WBC, ↓ platelets
  - Ribavirin (RBR)
    - Skin drug reaction with eosinophilia – stop TVR/Boc
    - RBR dose ↓ for anemia does not affect all with TVR/Boc
    - Contraception with RBV: no conception for 6 months after RBV stopped

Nucleoside polymerase inhibitor plus protease inhibitor

- Single-stranded positive-sense RNA virus
- Objective of therapy
  - Eradicate HCV (SVR)
- SVR (sustained viral response)
  - Absent serum HCV RNA 6 months after
- Treatment-associated SVR depends on HCV genotype and therapy used
- I/R (interferon plus ribavirin)
  - Genotype I 40% to 50%
  - Genotype II 70% to 80%

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

➢ CC genotype

- 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 genotype
  - 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

- 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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Protease Inhibitors

- In the past 35 years, three Nobel prizes have been won in the area of gastroenterology / hepatology: the H2-receptor and its antagonists (Black), the LDL receptor (Brown and Goldstein), and the rediscovery of Helicobacter pylori and the establishment of its importance in ulcer disease (Warren and Marshall).
- With the identification of the hepatitis C virus (HCV) by Heyden and the recent "game changing" development of protease inhibitors, the hope for the sustained eradication of HCV has gone from 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.
- 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.

- Overview of new protease inhibitors
  - PEG IFN (peg interferon) + RBV (ribavirin)
    - HCV genotypes
      - 1, 4, 5, 6 48 wk
      - 2,3 24 wk
  - New for genotype1
    - DAA (direct-acting antiviral agents (inhibitors of N53/4A [non-structural protein 3/4A] serine protease)
    - BOC, boceprevir 300 mg pot id
    - TVR, telaprevir 750 mg po q 8 h, with food
  - Treatment-naïve
    - use PEG IFN plus RBV / weight-based for 4 wk, followed by BOC 300 mg pot id with food or TVR 750 mg po q 8 h with food, for 24 to 44 wk
  - Without cirrhosis

- PEG IFN, RBV plus BOC or TVR for 28 wk, if HCV RNA is undetectable at 8 and 24 wk
- If HCV RNA > 100 IU/mL at week 12 or detectable at 24, stop PEGIFN, RBV any BOC TVR
- PEG IFN, RBV plus TVR for 12 wk, followed by PEG IFN and RBV for 12-36 wk longer
- PEG, IFN, RBV plus TVR for 24 wk, if HCV RNA is undetectable at 4 and 12 wk

o With cirrhosis
- PEG IFN, RNA plus BOC or TVR for 48 wk
- If HCV RNA > 1000 IU/mL at wk 4 to 12 and/or detectable at wk 24, stop PEG IFN, RBV and VVR
- Previously treated (treatment experienced patients) CHC (chronic hepatitis C) failing Rx
- Rel or PR after PEG IFN-α / TNF-α plus WB (weight based) RBV
- NR after INF-α / PEG INFα and/or WB-RBV
- If HCV RNA > 100 IU at wk 12 after retreatment with PEG IFN, RBV, BOC, stop retreatment (likely to develop HCV resistance)
- If HCV RNA > 1000 IU at wk 4 or 12 after retreatment with PEG IFN, RBV, TVR, stop retreatment (likely to develop HCV resistance)
- Rel or PR of treatment-experienced with BOCOR TVR may be considered using response-guided therapy

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

<u>These AASLD / IDSA recommendations are available online at</u>

http://www.aasld.org/PRACTICEGUIDELINES/Pages/default.aspx

http://www.idsociety.org/IDSA_Practice_Guidelines/

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

Pharmaceutical therapy recommendations, genotypes and interferon eligibility

Interferon (IFN) eligibility

Genotype I

➢ Treatment naïve

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
• *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 not 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

Not recommended

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

- PEG / RBV with or without telaprevir or boceprevir for 24 to 48 weeks
  Rating: Class IIb, Level A

- Monotherapy with PEG, RBV, or a DAA
  Rating: Class III, Level A

Genotype 2 – Regardless of interferon eligibility

- *Recommended regimen for treatment-naïve patients with HCV genotype 2, regardless of eligibility of IFN therapy:*
  - Daily sofosbuvir (400 mg) and weight-based RBV (1000 mg [< 75 kg] to 1200 mg [≥ 75 kg]) for 12 weeks is recommended for treatment-naïve patients with HCV genotype 2 infection.

Rating: Class I, level A

Not recommended

- The following regimens are **NOT** recommended for treatment-naïve patients with HCV genotype 2.
  - PEG / RBV for 24 weeks

    Rating: Class IIb, Level A

  - Monotherapy with PEG, RBV, or a DAA

    Rating: Class III, Level A

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

    Rating: Class III, Level IA

Genotype 3– Regardless of interferon eligibility

- *Recommended regimen for treatment-naïve patients with HCV genotype 3, regardless of eligibility for IFN therapy:*
  - Daily sofosbuvir (400 mg) and weight-based RBV (1000 mg [< 75 kg] to 1200 mg [≥ 75 kg]) for 24 weeks is recommended for treatment-naïve

patients with HCV genotype 3 infection.

Rating: Class I, Level B

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

Rating: Class IIa, level A

Not recommended

- The following regimens are **NOT** recommended for treatment-naïve genotype 3.
  - PEG / RBV for 24 to 48 weeks

    Rating: Class IIb, 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.* o 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 o Alternative regimens for treatment-naïve patients with HCV genotype 4 who are eligible to receive IFN. o Daily simeprevir (10 mg) for 12 weeks and weight-based RBV (1000 mg [< 75	• *Recommended regimen for treatment-naïve patients with genotype 4 who are not eligible to receive IFN.* o 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

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

SO YOU WANT TO BE A HEPATOLOGIST!

- Give the common adverse effects (AEs) of BOC (boceprevir) and TVR (telaprevir).
  - BOC
    - Anemia (~50%)
    - Dysgeusia
    - Cytochrome P450 drug-drug interactions
  - TVR
    - Anemia
    - Skin
      - Rash (56%)
        - Eczamatous
        - Maculopapular
        - Steven Johnson syndrome
      - Pruritis (50%)
    - GI
      - Nausea
      - Diarrhea
    - Cytochrome P450 drug-drug interactions

SO YOU WANT TO BE A HEPATOLOGIST!

- The hepatocyte damage from HCV is not immune-mediated, as is HBV.
- About 75% of persons with acute HBV develop chronic HCV because the HBV escapes the immune response to clear the infection.

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

- What clinical feature of acute HCV infection suggests that the patient will be in the lucky group and clear their HCV.
  - Persons with acute HCV associated with jaundice have an increased chance of clearing in HCV.

- Give the reasons why the ALT or AST is not a useful marker for the progress of HCV.
  - The transaminases
    - Fluctuate widely in HCV
    - A normal level may occur even though chronic HCV infection is present
    - Women with low levels of HCV RNA may more commonly have low ALT, less inflammation and less fibrosis.

- **Summary**

- **Treatment**

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)
	○ IFN ineligible: SOF + SMV ± RBV x 12 weeks	- IFN ineligible: 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
4	○ IFN eligible: SOF + PEG / RBV x 12 weeks ○ IFN ineligible: 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 - SOF + RBV x 24 weeks - SMV x 12 weeks + PEG / RBV x 48 weeks**	▪ PEG / RBV ± telaprevir or boceprevir ▪ Monotherapy with PEG, RBV, or a DAA ▪ Do not treat decompensated cirrhosis with PEG or SMV
2	○ SOF + RBV x 12 weeks	- SOF + PEG / RBV x 12 weeks	▪ PEG / RBV ± telaprevir or boceprevir ▪ Monotherapy with PEG, or direct-acting anti-viral agent ▪ Do not treat decompensated cirrhosis with PEG
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
Genotype	Recommended	Alternative	**Not recommended**
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

Genotype 1

- Non responders

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	○ Eligbility to receive IFN: - Daily sofosbuvir (400 mg) for 24 weeks and weight-based RBV (1000 mg [< 75 kg] to 1200 mg [≥ 75 kg]) for 24 weeks is an alternative for retreatment of IFN-ineligible persons with HCV genotype 1

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

infection, regardless of subtype.

Rating: Class IIb, Level C

Eligible	Not eligible

- *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 PEG / RBV (with or without an HCV protease inhibitor) non-responder patients with HCV genotype 1:

- PEG / RBV with or without telaprevir or boceprevir

Rating: Class IIb, Level A

- Monotherapy with PEG, RBV, or a DAA

Rating: Class III, Level A

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

Genotype 2– Regardless of interferon eligibility

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

  Rating: Class I, Level A
- *Alternative regimen for PEG / RBV non-responder patients with HCV genotype 2 infection who are eligible to receive IFN.*
    - Retreatment with daily sofosbuvir (400 mg) and weight-based RBV (1000 mg [< 75 kg] to 1200 mg [≥ 75 kg]) plus weekly PEG for 12 weeks is an alternative for IFN-eligible persons with HCV genotype 2 infection.

  Rating: Class IIa, Level B

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

- PEG / RBV with or without telaprevir, boceprevir or simeprevir
  Rating: Class IIb, Level A
- Monotherapy with PEG, RBV, or a DAA

  Rating: Class III, Level A

Genotype 3

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

  Rating: Class IIa, Level A

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

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

Rating: Class IIa, Level B

Not recommended

- *The following regimens are **NOT** recommended for non-responder patients with HCV genotype 3 infection:*
  - PEG / RBV with or without telaprevir, boceprevir or simeprevir
    Rating: Class IIb, Level A
  - Monotherapy with PEG, RBV, or a DAA
    Rating: Class III, Level A

Genotype 4

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

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

Rating: Class IIa, Level C

- *Alternative regimen for HCV genotype 4, PEG / RBV non-responder patients.*
  - Daily sofosbuvir (400 mg) and weight-based RBV (1000 mg [< 75 kg] to 1200 mg [≥ 75 kg]) for 24 weeks is recommended for retreatment of HCV genotype 4 infection.

Rating: Class IIa, Level B

Not recommended

- *The following regimens are **NOT** recommended for non-responder patients with genotype 4 HCV infection:*
  - PEG / RBV with or without telaprevir or boceprevir

    Rating: Class IIb, Level A

  - Monotherapy with PEG, RBV, or a DAA

    Rating: Class III, Level A

Genotype 5, 6

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

  Rating: Class IIa, Level C

- Alternate regimen for PEG / RBV non-responder patients with HCV genotype 5 or 6.
  - None

Not recommended

- *The following regimens are **NOT** recommended for non-responder patients with HCV genotype 5 or 6.*
  - PEG / RBV with or without telaprevir or boceprevir

    Rating: Class IIb, Level A

- Monotherapy with PEG, RBV, or a DAA

Rating: Class III, Level A

Clinical Pride

The subspecialty of Gastroenterology / Hepatology has several Nobel Prizes.

Special considerations

Unique patient populations: **Renal impairment**: Dose adjustments

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

Unique patient populations: HIV / HCV coinfection box. Recommendations for HCV co-infected patients who are being treated for HCV, by genotype

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

Genotype	Recommended	Alternative	NOT Recommended	Allowable anti-retroviralherapy
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

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

  - Determine stage of HCV
    - 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.
  - Determine prognosis
    - Given the variable natural history and the complexity and cost of treatment, informed decision can only be made based on histology.
  - Determine treatability

  - 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 (to distinguish between acute cellular rejection or HCV recurrence).

- Give 3 circumstances when an HCV infection is likely to be diagnosed.

Asymptomatic	– Abnormal liver enzymes on health examination – Presence of chronic liver disease
Symptomatic, acute HCV	– Development of flu-like symptoms (from acute hepatitis) – Seroconversion – Known clinical exposure
Chronic HCV	– Cirrhosis ▪ Compensate ▪ Decompensate – Development of HCC (hepatocellular cancer)

- Give the `Stopping Rules`for the treatment of HCV infection.
  - Uncontrolled depression
  - Hepatitis flare (ALT > 10 x ULN)
  - Neutropenia (< 500 / mm^3)
  - Thrombocytopenia (< 25,000 / mm^3)
  - Sepsis

- Give the management of HCV in 4 of the following **special conditions**.
  - Co-infection with
    - HIV
    - HBV
  - Chronic renal failure /hemodialysis
  - Renal transplantation
  - Acute HCV

- Give the new alternate name for SJS (Stevens Johnson Syndrome).
  - DRESS (drug-related eruption with systemic symptoms)

Recommended Doses:

Generic (Trade name)	Recommended dose	Recommended dose in renal or hepatic dysfunction
○ PegIFN alfa-2a (Pegasys®)	180 mcg SC once weekly	ClCr <30 ml/min: 135 mcg SC once weekly Hemodialysis: 135 mcg SC once weekly
○ PegIFN alfa-2b (PEG-Intron®)	1.5 mc/kg SC once weekly	ClCr 30–50 ml/min: reduce dose by 25% ClCr 10–29 ml/min: reduce dose by 50%
○ RBV (Copegus®, Rebetol®, Ribasphere®, RibaPak®)	Genotype 1: 1,000 mg (if ≤ 75 kg) or 1,200 mg (if >75 kg) PO daily in two divided doses, or <65 kg: 800 mg PO daily in two divided doses 65–85 kg: 1,000 mg PO daily in two divided doses >85–105 kg: 1,200 mg PO daily in two divided doses >105 kg: 1,400 mg PO daily in two divided doses -- Genotype 2 or 3: 800 PO daily in two divided doses	ClCr 30–50 ml/min: 200 mg PO daily, alternating with 400 mg PO daily ClCr <30 ml/min: 200 mg PO daily
○ PIs for treatment of HCV genotype 1		
– Boceprevir (Victrelis™)	800 mg (4 × 200 mg capsules) PO every 7–9 apart with food in combination with PegIFN–RBV following a 4-week lead-in with PegIFN–RBV	Dose adjustments not necessary for renal or hepatic impairment (Child-Pugh <7)
– Telaprevir (Incivek™)	750 mg (2 × 375 mg tablets) PO every 7–9 h with food (20 grams fat) for 12 weeks, plus PegIFN–RBV for 24 or 48 weeks	Dose adjustments not necessary for renal or hepatic impairment (Child-Pugh <7)

Abbreviations: ClCr, clearance of creatinine; HCV, hepatitis C virus; PegIFN, peginterferon; PI, protease inhibitor; PO, orally; RBV, ribavirin; SC, subcutaneous; TVR.

Printed with permission: Yee HS, et al. Update on the Management and Treatment of Hepatitis C Virus Infection: Recommendations from the Department of Veterans Affairs Hepatitis C Resource Center Program and the National Hepatitis C Program Office. Am J Gastroenterol 2012; 107: 669-689.

Interpretation and **Treatment Approach** for HCV RNA Levels During Treatment with Interferon and Ribavirin

Week First Became HCV RNA Undetectable	Description	% of Patients	Relapse Rate	SVR Rate	Treatment Strategy
• Genotype 1					
4	Rapid response	15	10	90	Keep patients on treatment for 48 weeks even if have to reduce dose. If shorten therapy, SVR still very high
12	Early response	35	33	66	Complete 48 weeks of treatment
24	Slow to respond	15	55	45	Extend therapy to 72 weeks
Never	Null response	20	0	0	Stop treatment as soon as pattern recognized at 12 weeks
Never	Non-response	15	0	0	Stop treatment as soon as pattern recognized at 24 weeks
• Genotype 2 and 3					
4	Rapid response	66	10	90	Keep patients on treatment for 24 weeks even if have to reduce dose. If shorten therapy, SVR still very high.
After week 4	Early response	33	50	50	Consider extending therapy to 48 weeks
Never	Non-response	3	0	0	Stop treatment as soon as pattern recognized at 12 weeks

Printed with permission: Spiegel BM, Karsan AA. Acing the hepatology questions on the GI board exam. Slack Incorporated 2012, Table 64-1.

Clinical GEMS in HCV

The sexual transmission rate of HCV is usually low, except with

- MSP (multiple sexual partners)
- MSM (men who have sex with men, especially receptive anal intercourse)
- HIV co-infection

Liver transplantation

- Pre-LT
  - C-P (Child-Pugh) A (indication for LT is HCC)
  - Genotypes 2 and 3 — PEG-IFN plus ribavirin
  - Low baseline HCV RNA
  - C-P B — patient-by-patient basis
  - C-P C — no Rx
- Post-LT
  - About 3/4 of HCV RNA RBA before LT
  - Histologically proven chronic hepatitis HCV (to distinguish from rare graft rejection)

Co-infection with HIV

- All HIV-infected persons, test for
  - Anti-HCV positive
    - Test for HCV RNA
  - Anti-HCV negative, but presence of unexplained liver disease
    - Test for HCV RNA
- For HIV / HCV co-infection
  - Compensated liver disease
    - Treat if favourable balance between severity of liver biopsy, likely treatment response, and likely AEs.

        - PEG IFN-α plus RBV, as per guidelines for HCV monotherapy given above, and for 48 wk.
        - Please see most recent studies for non-guideline-based triple therapy using PI (protein inhibitors)
    - Decompensated liver disease
      Do not use PEG IFN +RBV; instead
      Access for possible liver transplantation

- Acceleration of liver disease with HCV-HIV co-infection
- No difference in indications for treatment of HCV if HIV-positive vs. negative
- SVR for HCV lower when co-infection with HIV

	Weeks of
- Genotype 1, week 12 HCV RNA	
▪ Negative	48
▪ Positive	72
- Genotype 2 or 3	
▪ Low baseline HCV / RNA and only mild fibrosis	24

Co-infection with HBV

- No difference in indications for treatment of HCV-positive vs. negative
- If HBV infection is active (HBV DNA is usually low / undetectable in presence in HCV), treat with nucleus(t)ide, as per usual choice and doses.

Chronic Renal Failure and Hemodialysis

- Acceleration of liver disease with HCV and chronic renal dysfunction or renal transplantation
- Ribavirin undergoes renal clearance, so in chronic renal failure (CRF), the dose of ribavirin must be reduced (no need to reduce dose of ribavirin if patient is on hemodialysis).
- PEG-IFNα 2b is cleared by kidney (PEG-IFNα 2a cleared by liver), but no dose adjustment is needed in HCV plus CRF.

Renal transplantation (RT)

- Acceleration of liver disease with HCV plus RT
- Ideally, treat HCV before RT, since treatment of HCV in RT (PEG-IFN plus ribavirin) carries a 30 risk of acute or chronic rejection

Acute HCV

- PEG-IFNα 2a/b (no need for adding ribavirin) for 24 week result in > 90% SVR, especially if patients are symptomatic.
- Failure of SVR in 10% is treated with PEG-IFN plus ribavirin for a duration determined by genotype and level of HCV RNA.

Please see: Peltekian KM, Hirsch G. Chapter 59. In: Therapeutic Choices. Grey J, Ed. 6th Edition, Canadian Pharmacists Association: Ottawa, ON, 2011, Table 4: Hepatitis C, page 793.

Abbreviations and definitions

- Rel, relapse:
- HCV RNA → undetectable while on Rx (PI), then reappeared with stopping BOCOR TVR
- PR, partial responders: wk 12 HCV RNA ↓ ≥ 2 log IU/mL, but wk 24 HCV RNA still present
- NR, null responders: wk 12 HCV RNA did not drop by at least 2 log IU/mL

Note: For futrher information re cytochrome P450 drug-drug interactions and the use of protease inhibitors boceprevir (BOC) and telaprevir (TVR), please refer to
www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm
http//:222.drug-interactions.com
www.hep-druginteractions.org

Anemia developing while on BOC or TVR

- ↓ dose of RBV

↑ HCV RNA > 1 log above

- Stop BOC or TVR

Do not cross-over treatment (BOV → TVR → BOC) for relapse, failed response, or breakthrough

- Genotype 2 or 3 HCV RNA

  PEG IFN α plus RBV 800 mg for 24 wk
  ↓
  wk 24, HCV RNA negative stop Rx
  ↓
  wk 48 HCV RNA negative
  → SVR
  ↓
  If cirrhosis present, monitor q 6 to 12 mon for HCV

- Treatment failure
  - Failure to achieve SVR with
    - PEG IFN +RBV
    - (Non-PEG) IFN +RBV
  - Do not retreat
  - Consider retreating, especially if biopsy shows bridging fibrosis or cirrhosis

For recommendation for treating HCV **in children**, please see Hepatology 2009; 49: 1335-1374.

➢ **Cirrhosis**

- Compensated cirrhosis from HCV
  - PEG IFN plus RBV in usual doses, but with careful monitoring for AEs
- Decompensated cirrhosis from HCV
  - Access for possible liver transplantation
  - Low dose IFN plus RBV as a bridge to liver transplant

➢ Post-liver transplantation recurrent HCV

- Usual PEG IFN +/- RBV, with careful monitoring for AEs
- PEG/ IFN plus RBV for fibrosing cholestatic hepatitis

- Non-hepatic solid organ transplantations (kidney, heart, lung) plus HCV
  - No IFN plus RBV, except

- **Chronic renal disease**
  - Not on renal replacement therapy
    - Anti-HCV → HCV RNA
    - Access need for HCV treatment
    - GFR > 6o mL/min
      - Usual PEG IFN plus RNV
    - GFR < 60 mL/min
      - PEG IFN-α 2a 135 mcg/wk, plus
      - RBV 200 to 800 mg/d, or
      - PEG IFN-α 2b 1 mcg/kg per wk, plus
      - RBV 200 to 800 mg/d
  - On dialysis
    - IFN 2a or 2b 3 mU tid, or
    - PEG IFN 2a 135 mcg/wk, or
    - PEG IFN 2b 1 mcg/kg per wk, plus
    - RBV 200 mg/d with monitoring for anemia, as well as other AEs
  - Renal transplantation
    - No IFN plus RBV, except
    - PEG/IFN plus RBV for fibrosing cholestatic hepatitis

- **Cryoglobulinemia**
  - Mild-moderate proteinuria
    - IFN in standard doses or PEG IFN in ↓ doses, plus RBV
  - Severe proteinuria, plus
    - Progressive renal disease
    - Acute flare of cryoglobulinemia

      ↓
    - Rituximab, or cyclophosphamide plus methylprednisolone, or plasma exchange

      ↓
    - Once acute cryoglobulinemia resolved, IFN-based Rx

OTHER HEPATITIS VIRUS INFECTIONS

- **Hepatitis D Virus (HDV)**
  - RNA virus
  - 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

- **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 5 types of hepatobiliary disorders associated with CMV infection.
  - Transaminitis
  - Hepatitis
    - Acute
    - Granulomatous
    - Cholestatic
  - Fulminant hepatic failure
  - Post liver transplantation
    - Fibrosing cholestatic hepatitis
  - Graft rejection-like picture
  - Typical pathological changes on liver biopsy
    - Multinucleated giant cells
    - Owl’s eye nuclear inclusions
    - Mononuclear portal and parenchymal inflammatory infiltration

- **Herpes Simplex Virus (HSV)**
  - Microcutaneous and genital HSV lesions
  - Transaminitis
    - Immune suppressed persons
  - Pregnant women
    - 3rd trimester
    - Fulminant hepatic failure

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

- Give 4 laboratory features and which should alert the physician about the possibility of HSV hepatitis and the need to begin empiric therapy with acyclovir.
  - ↑↑ ALT, AST (> 1000)
  - ↓ WBC
  - Fever / abdominal pain
  - Associated HSV
    - Pneumonitis
    - Encephalopathy

- 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
    - Focal or extensive
      - Hemorrhage
      - Necrosis, extensive
    - 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.

Leptospirosis (aka Weil syndrome)

Leptospira interrogans

- Acute hepatitis plus
  - General
    - Fever
    - Rigors
  - Clinical
    - Eyes
      - Conjunctival suffusion
    - Heart
      - Temperature-pulse dissociation
    - Lung
      - Cough, no sputum
    - MSK
      - Myalgias
    - Kidney
      - ↓ Na^+, ↓K^+
      - Renal insufficiency
    - Hematology
      - Lymphadenopathy
      - Bleeding
    - Liver
      - ALF (rare)
  - Laboratory
    - ↑AST, ↑ bilirubin

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.

SO YOU WANT TO BE A HEPATOLOGIST!

- In the context of a "zoonosal infection", give the clinical findings of **Weil syndrome**.

Weil syndrome (leptospirosis)

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

ALCOHOLISM

Alcohol abuse, tolerance and addiction

"I keep drinking because I like the way it makes me feel"

- Definition: Alcohol dependence is "….. a maladaptive pattern of use associated with 3 or more of the following
  - There may be a biological predisposition to alcoholism (my brother, my father, my grandfather were alcoholics".

- 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
- 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

Useful background

- 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

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

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

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.

ALCOHOLIC LIVER DISEASE (ALD)

➢ Treatment

- 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)

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

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

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

ALCOHOLIC HEPATITIS

- 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

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.

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

➢ Risk assessment

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

Name of prognostic test	Components	Poor prognosis score
○ MADDREY Score MDF, modified Maddrey discriminant function	MDF = 4.6 (patients PT – control PT) + total bilirubin (mg / dL)	≥ 32

- ○ Maddrey discriminant function (MDF)
  - MDF (aka Maddrey score) is obtained from the PT (prothrombin time) and serum bilirubin concentration
  - MDF > 32 in severe alcoholic hepatitis, treated with steroids

Presence of HE (hepatic encephalopathy)	1-mon mortality rate
Yes	45%
No	35%

- ○ **MELD** (Model for End-Stage Liver Disease) Score
  - Obtained from INR, serum bilirubin and creatinine concentration

Name of prognostic test	Components	Poor prognosis score
○ 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

- 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
PT	+		+	+	
INR		+			+
BILI	+	+	+	+	+
Cr		+		+	+
BUN			+		
WBC			+		
ALB				+	
Age				+	+

Abbreviations: GAH, Glasgon alcoholic hepatitis score; MDF, modified Maddry discriminant function; MELD, model of end-stage liver disease

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- Give the name of a NOS (nitric oxide synthase) inhibitor and a genetic variant which have been suggested to be markers for a poor prognosis (mortality) in ALD.
  - Asymmetric dimethylarginine and its stereoisomer are equivalent to MDF and MELD to predict mortality in person with acute alcoholic hepatitis against the background of alcoholic cirrhosis.
  - The PNPLA3 gene predisposes the heavy alcohol user to develop ALD, including steatohepatitis and fibrosis

➢ Treatment

- 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 the evidence for the benefit of metadoxine in ALD.
  - Metadoxine
    - Pyroxene plus pyrrolidine
    - In alcoholics with ultrasound-demonstrated fatty liver, 3 month of metadoxine reduced steatosis by 72%, vs. 30% for placebo; relationship to overall mortality unclear.

NON-ALCOHOLIC FATTY LIVER DISEASES (NAFLD)

- Demography
  - Natural history of NAFLD

NAFLD —20%→ NASH —~1% / year→ cirrhosis, HCC —~4% / year→ decompensation

  - Patients with NASH cirrhosis may come to liver transplantation (LT).
  - 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.

- Causes / associations
  - Metabolic syndrome
  - Insulin resistance
  - ↑↑ / ↓↓ BMI
  - Drugs
  - Food choices
  - Endocrine
    - Hypothyroidism
    - Hypopituitarism
    - Hypogonadism
    - Hyperuricemia
    - Vitamin D deficiency
  - Ovary
    - Polycystic ovary syndrome (PCOS)
  - Pulmonary
    - Obstructive sleep apnea
  - GI
    - Pancreaticoduodenal resection
    - Colonic adenomatous polyps

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Alcoholic liver disease is suspected if the average drinks of alcohol per week is > 14 in women and > 21 in men.

- Give the “allowable” average drinks of alcohol per week when evaluating persons with suspected NAFLD.
  - Women, < 14; men, < 21 (Hepatology 2011; 54: 344-353)

➢ Pathophysiology

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

- GI tract
  - ↑ intake of fat, carbohydrate
  - Alered intestinal microbiotica

- Hepatic steatosis
  - ↑ dietary fat or delivery of fat to the liver (from ↑↑↑ FFA from adipocytes)
  - ↑ carbohydrate transport to the liver, with formation of fatty acids (↑ lipogenesis)
  - Bacterial flora
  - ↑ oxidative stress
  - ↑ peripheral insulin resistance (↑ leptin, ↓adiponectin ;↑insulin, ↑TNFα)
  - ↑ mitochondrial synthesis of fatty acids (FA's)
    - Mitochondrial dysfunction
      - ↓ respiratory chain complexes
      - ↑ ROS
      - ↑ TNF-α
      - ↓ ATP
      - Mitochondrial DNA damage
  - ↑ fat synthesis (increased insulin activates SREBP-1, the sterol regulatory element binding protein 1-c, and increases CHREBP, the carbohydrate regulatory element binding protein)
  - ↓ lipolysis
  - ↓ transport of FA's out of the liver (↓β-oxygenation), ↓Apolipoprotein B-100

- Hepatocyte injury, inflammation and fibrosis
  - ↑ FFA
    - ↑ NFkB
    - ↑ IL-6
    - ↓ adiponectin

    - ↑ leptin, ↑ leptin resistance
    - Lysosomal destabilization (↑ TNF-α)
  - ↑ ROS, ↑ CYP 2E1
  - FFA form fatty acid ethyl esters
    - Toxic to mitochondrial membranes
  - Accumulation of triglyceride-derived toxic lipid metabolites activates intracellular inflammatory pathways within hepatocytes and Kupffer and other immune cells, similar to defects within adipocytes.
  - ↑ Oxidative stress
  - ↑ PPAR-α
    - ↑ FA oxidation
    - ↑ oxidative stress
    - 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.
  - Regulation by
    - Insulin
    - Catecholamines
    - Glucagon
    - Growth hormone
    - Leptin
    - Adiponectin
  - ↑ Lipotoxicity
  - ↑ Death receptors
  - ↑ apoptosis
  - ↓ DNGA (transcriptional sensitizer)
  - Stellate cell activation

- Pro-inflammation
  - Endo-/ exotoxin-mediated release of proinflammatory cytokines
  - 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.
  - Inflammasome-dependent processing of IL-1β and IL-18 could be important in NAFLD / NASH.

- Stellate cell 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
  - Activation of hepatic stellate cells leads to collagen deposition and the potential for cirrhosis.

- Adipose tissue
  - Adipose tissue is composed of adipocytes and the stromal vascular fraction, macrophages and other immune cells
  - Activation of macrophages/immune system → dysfunctional, insulin-resistant adipocytes → release ↑↑↑ FFA → insulin resistance and lipoapoptosis in distant tissues (liver, muscle, pancreatic beta cells, vascular bed, other).

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

- 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	▪ 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.

- Clinical cautions
  - NAFLD, both simple steatosis as well as NASH (steatosis hepatitis with / without fibrosis) is a risk factor for HCC (hepatocellular cancer),
  - NAFLD worsens the prognosis of liver disease associated with HCV and HH (hereditary hemochromatosis).

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).

- Testing for NAFLD
  - High risk groups (please see below)
  - 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
  - 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%
  - NAFLD and NASH may be distinguished using **Kleiner's scoring system**, also known as "NAS" (**NASH activity score**) (Kleiner DE, et al. *Hepatology* 2005;41:1313-21.)
  - Based on:
    - Simple steatosis
    - Steatosis plus inflammation alone
    - Steatosis plus ballooning
    - Steatosis plus fibrosis (Matteoni CA, et al. *Gastroenterology* 1999:1413-9.)

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

  - NAFLD is often associated with metabolic syndrome (which is diagnosed as well as with laboratory measurements) as well as with insulin resistance.
  - Insulin resistance is easily measured using HOMA (homeostatic model assessment)

➢ Progression

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

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

- 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

- 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%

- Diagnostic imaging
    - Ultrasound (US) - ↑ echogenicity
    - CT - liver density = spleen
    - MRI - bright T1 – weighted imaging of liver

        - Detection of > 33%, fat in liver; sensitivity
            - Sensitivity
                - US, 100%
                - CT, 93%
            - PPV
                - US, 62%
                - CT, 76%
    - Support the diagnosis of NAFLD
    - US, CT, MRI do not predict severity: do not distinguish simple steatosis from NASH

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

    - FibroScan® (aka TE [transient elastography])
        - Useful to identify advanced but not early cirrhosis from

        - HCV
        - PBC (primary biliary cirrhosis)
        - HH (hereditary hematomachrosis)
        - NAFLD
        - Recurrent chronic hepatitis after liver transplantation

- 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)

- Liver biopsy
    - "Gold standard", but is actually only the "bronze standard" because of considerable sampling variation (patchy changes)
    - Severe steatosis (centrilobular, macrosteatosis)
    - ↑ Stainable iron
    - Signs of cirrhosis
    - Performance characteristics for fibrosis, cut-off value
        - High cut-off (0.70)
            - PPV, 73%
            - Specificity, 98%
        - 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)

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.

- 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

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

Bariatric surgery

- Severe morbid obesity
- Failed treatment of obesity
- NASH recurring after previous LT (retransplantation)
- Severe morbid obesity
- Failed treatment of obesity
- Progressive NASH with fibrosis in allograft

Liver Transplantation (LT) for Non-alcoholic Steatohepatitis (NASH)

- Pre-transplantation
  - Diagnosis of NASH
  - Liver biopsy showing
    - NASH, or
    - Cryptogenic cirrhosis plus ≥ 3 criteria for metabolic syndrome
  - Because the ↑↑↑ risk of coronary heart disease, in HASH, NASH patients should have preoperative risk stratification by cardiologists.
  - If already on non-selective B-blocker, continue, or start NSBB if indicated
  - Statin given 1 wk before liver transplantation

    Do not use simvastatin or atorvastatin → interact with calcineurin inhibitors
  - Treat obesity preoperatively if possible

- Especially if > 40 kg/m^2, unless patient has decompensated ESLD (end stage liver disease) because of risk of protein calorie malnutrition
- Compensated cirrhosis and HCC

- Post-transplantation
  - Continue statin
  - Blood glucose control
    - 6 to 10 mmol/L
  - Immunosuppression
    - Induction therapy
    - Anti-thymocyte globulin, or
    - IL-2 receptor antagonist
    - If corticosteroids used, stop within 3 mon
    - Calcineurin, plus anti-metabolite (myophenolate)

DRUG INDUCED LIVER INJURY (DILI)

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

➢ Histopathology

- Give 12 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)
  - 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
  - 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

- 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
  → SOS (sinusoidal obstruction syndrome)
  → B-CS (Budd-Chiari syndrome)
- Hepatic vein (HV) thrombosis
  - B-CS (Budd-Chiari syndrome)
  - Associated with

        - Coagulation disorders
        - Myeloproliferative disorders
        - Use of OCA (oral contraceptive agent)
    - Obstruction of HV or IVC (inferior vena cava)

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

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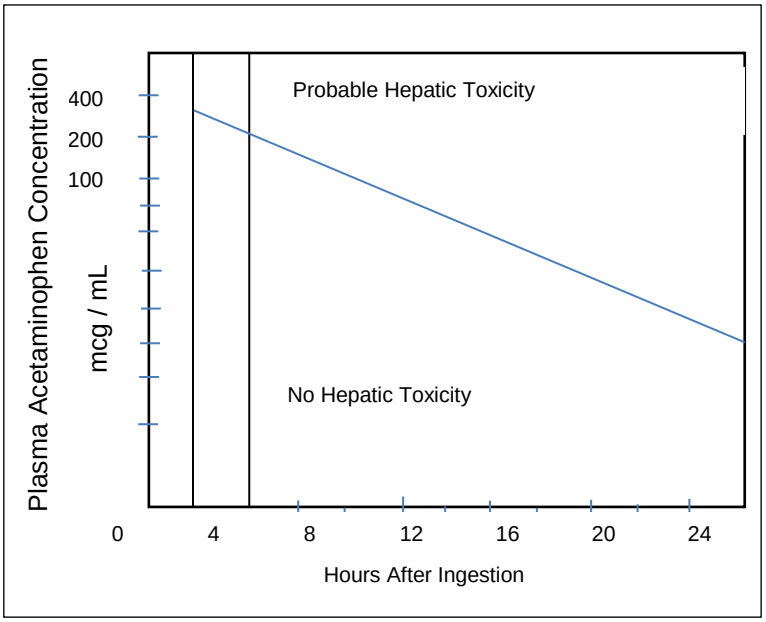
A toxic nomogram is available to predict how long after ingestion NAC remains effective. Because of the relative safety of the use of NAC, and that it may be efficacious even 48 hours after overdose, or in persons with non-acetaminophen ALF, the nomogram is not always strictly followed. In addition, the nomogram may have limitations.

- Give 3 examples of when the standard acetaminophen toxicity nomogram may not correctly reflect possible severe liver disease.
    - Multiple doses of acetaminophen taken, rather > 4 g at once
    - Unknown time of overdose ingestion
    - Alcoholic patient
    - Fasting patient

Acetaminophen toxicity nomogram

- Very common cause of ALF



Printed with permission: Spiegel BM, Karsan AA. Acing the hepatology questions on the GI board exam. Slack Incorporated 2012, Figure 27-1, page 83.

- Give the management of patients with acetaminophen (ACM) overdose.
- Initial measures
  - ABC's
  - Rule out other co-ingestions
  - Contact liver centre
  - Supportive care
  - Risk stratification for possible liver transplantation (KCC, King's College Criteria)
  - Serum ACM level, urine toxicology screen, LFT's, INR, arterial lactate
  - Determine likelihood of hepatotoxicity from normal nomogram (except in non-intentional cases)
  - Within 4 hrs of ingestion of acetaminophen, charcoal may be given prior to starting NAC

- For persons with ALF though to be due to acetaminophen overdose,
  - Immediately give activated charcoal (1gm/kg body weight [BW] po in a slurry (does not reduce the effect of NAC [N-acetylcysteine]).

- IV N-Acetylcysteine (NAC)
  - Dose 1. Loading dose: 140 mg/kg NAC in 200 ml D5W over 1 hr.
  - Dose 2. 50 mg/kg NAC in 500 ml D5W over 4 hours.
  - Dose 3. 125 mg/kg NAC in 1000 ml D5W over 19 hrs.
  - Dose 4. 150 mg/kg NAC in 1000 ml D5W over 24 hrs.
  - Dose 5. 150 mg/kg NAC in 1000 ml D5W over 24 hrs.

- Oral N-Acetylcysteine (NAC)
  - Loading dose: 140 mg/kg po/NG x1
  - 70 mg/kg q 4 hours x 17 doses
  - Compazine/raglan for nausea prn
  - Cimetidine (P450 inducer)
  - NAC should be given within 4 hours of overdose, but may still be of value 48 or more hours after ingestion.
  - For causes of ALF other than acetaminophen, and in patients with stages I or II encephalopathy, NAC may improve outcomes.
  - 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. hypertension or CV collapse).
  - Give NAC
    - IV
      - 150 mg/kg BW IV loading dose in 5% dextrose over 15 min, followed by 500 mg/kg over 4 hours, then 100 mg/kg over 16 hours or 6 mg/kg/hr

mg/kg	Frequency (hr)
150	0.25
50	4
100	16

    - Oral administration also possible
      - 140 mg/kg po / NG tube, then 70 mg/kg po q 4 hr for 17 doses

- Stopping rules after 72 hours, or when liver chemistry improves
- Some evidence that NAC plus prednisolone (pred) for 4 weeks is better than prednisolone alone for treatment of acetaminophen toxicity.

Treatment	1-month	3-month	6-month
- NAC plus Pred	8%	22%	27%
- Pred	24%	34%	38%
P value	< 0.01	0.06	0.07

Treatment Caution

- Do not administer NAC to patients with known sulfa allergy
- Administer IV formulation of oral NAC through a leukopore filter in a monitored setting after consent obtained from patient/family.
- IV infusion of NAC leads to anaphylactic/hypersensitive reactions in 3 to 5% most commonly during loading dose.
- Hold and reduce infusion rate by 50% if rash/nausea occurs (rare). Administer fluids, IV Benadryl, IV steroids as needed.

➢ Psychological assessment

➢ Seek transplant centre assessment if hepatic failure (encephalopathy of grade 1 → 4, ATN, hepatorental syndrome, jaundice, coagulopathy)

➢ 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

LIVER TRANSPLANTATION (LT)

- Complications

- Give 10 complications of liver transplantation (LT).
  - Liver
    - Infections*
    - Jaundice
    - Hepatobiliary complications
    - Acute cellular rejection
    - Recurrence of original liver disease
  - CNS
    - Neurological complications*
    - Hearing impairment
  - Endocrine
    - Metabolic syndrome*
    - Hyperuricemia
    - Diabetes
    - Dyslipidemia
    - Obesity
    - Fatigue and sexual dysfunction
  - Kidney
    - Chronic renal failure
  - CVS

    - Hypertension*
    - Cardiovascular disease
  - Vessels
    - Hepatic artery thrombosis
    - Malignancy

* risk is approximately 50%

- Give the 10 most common complications after liver transplantation.

Group	Approximate risk	Complications
1	50%	○ Serious infections ○ Metabolic syndrome ○ Hypertension ○ Neurological disease ○ Hyperuricemia ○ Fatigue and sexual dysfunction
2	20%-25%	○ Diabetes (at 1 yr) ○ Obesity ○ Dyslipedemia ○ Chronic renal failure ○ Acute cellular rejection
3	10-15%	○ Malignancy

Group 1 – approximate risk of 50%

➢ 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

- 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

- 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 4 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%

- Hyperuricemia and gout
  - 2-year post-LT
    - Hyperuricemia, 47%
    - Gout, 6%
  - Treatment
    - Acute, colchicine
    - Maintenance, allopurinol (note: may ↑ azathioprine concentration)

- Hearing impairment
  - Loss, 52%
  - Tinnitus, 38%
  - Otalgia, 30%

- Hepatobiliary complications
  - Biliary leaks and strictures
  - Acute and chronic rejection

Group 2 – approximate risk of 20% - 25%

- Metabolic syndrome (MS)
  - 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

- Diabetes
  - 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 m² post-LT

Time post-LT (years)	Incidence
3	14%
5	18%

- Give 10 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

- 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!

Group 3 – approximate risk 10% - 15%

- Jaundice
  - Biliary tract obstruction
  - HAT (hepatic artery thrombosis)
  - Graft non-function
  - Acute rejection
- Cardiovascular (CV) disease

- Give 5 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 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%

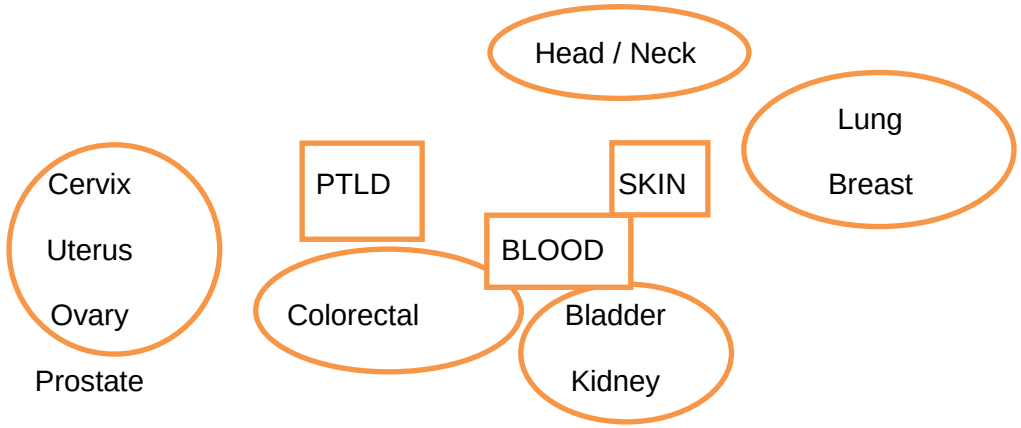
➢ **Malignancy**

- Give 6 common tumors after liver transplantation, and their average time-to-develop (TTD).
  - The liver disease associated with HCC may influence the site and the type of post-LT malignancy. For example,
    - ALD
      - (18% in 10 yr) head and neck, as well as esophageal squamous cancer
    - PSC
      - (22% in 10 yr) cholangiocarcinoma
    - HBC
      - Associated liver disease – 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.

1-year	2 years	3 years	4 years



Abbreviation: PTLD, post-transplant lymphoproliferative disorder

- 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)

- Give the relative order of the immunosuppressants in causing the components of the metabolic syndrome ("C-T").

    - Cyclosporin > tacrolimus (calcineurin inhibitors CNIs)
        - Hypertension
        - Obesity
        - Dyslipidemia

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 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	Systemic hypertension	Dyslipidemia	New onset of DM
Corticosteroids	++	++	+	+	++
CNI	-	+	++	++	++
Antimetabolites	-	-	-	-	-
mToRi	-	-	-	+++	+/-

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

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

➢ Pathophysiology

- Give the immunopathological steps involved in liver rejection after orthoptic liver transplantation, and the pharmaceutical agents which block these steps.

➢ T-cell activation

- Alloantigenic recognition
  - 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

CLINICAL TIP:

- Drug interaction
  - Cyclosporin → ↓ HCV replication → ↓ metabolism of CNIs, → ↑ blood levels of CNIs)

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.

Immunosuppressive Drugs and Biologicals used Post Liver Transplantation (LT)

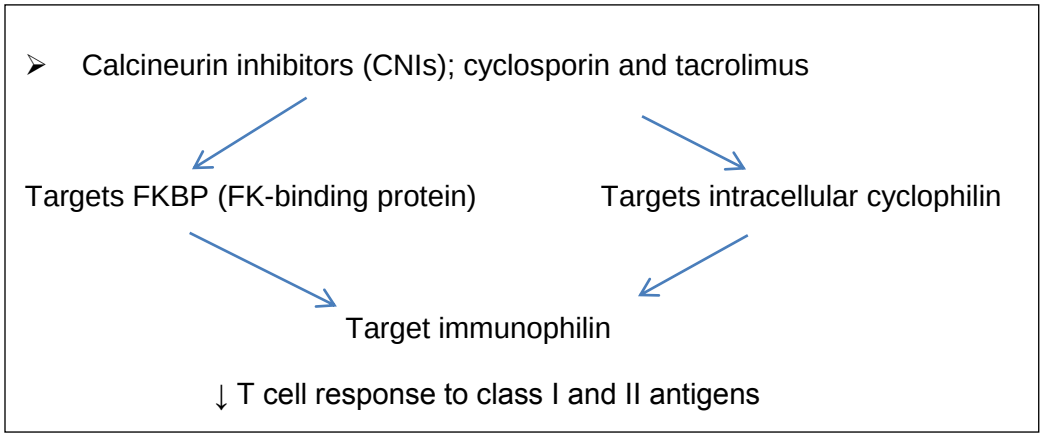
To be covered here:

- Cyclosporin
- Tacrolimus
- Corticosteroids

- MMF / MPA
- Biologicals

➢ **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 4 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

- **Tacrolimus**
  - A macrolide antibiotic derived from Streptomyces tsukubaensis
  - Binds FKBP (FK binding protein)
  - Also a calcineurin inhibitor (CNI)
  - 100x more potent than cyclosporin
  - Metabolized by hepatic CYP 3A4
  - Not removed by dialysis
  - Adverse effects, comparable to cyclosporin
  - 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 6 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)

➢ **Glucocorticorsteroids**

➢ Corticosteroids
- ↓ cell-mediated cytotoxicity
- ↓ antibody binding
- ↓complement binding
- ↓ T cell synthesis of IL-2, IL-6, IFN-γ (interferon gamma)
- ↑ IL-10

- 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.

➢ **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

- Monoclonal antibodies to IL-2R basiliximab
- mTor (mammalian target of rapamycin) bound by sirolimus

CLINICAL COMMENT

- Even persons who are not “Fat” may have on-alcoholic fatty liver disease.
- With the epidermic of obesity in developed as well as less developed countries, there is an urgent need to l
- The prediction for t to train larger numbe of hepatologists and liver transplantation experts has been lessened by the remarkable success of the protease inhibitors / DAAs in curing HCV infection.

“Use diagnostic imaging to guide your clinical impression, not to make the diagnosis.”

Dr. Joel Hurwitz

ACUTE LIVER FAILURE (ALF)

- Definitions
  - Coagulopathy (INR ≥ 1.5) and encephalopathy in patient without previous cirrhosis and with an illness of < 26 weeks duration
  - A sudden (usually < 24 weeks length of illness) loss of hepatic function in a patient without preexisting liver disease, with the development of coagulopathy) INR > 1.5) and hepatic encephalopathy (Ritt DJ, et al. *Medicine (Baltimore)* 1969:151-72.)
  - ALT is defined as “….the rapid development of hepatocellular dysfunction, specifically coagulopathy and mental status changes (encephalopathy) [and often jaundice] in a patient without prior liver disease”.
  - Coagulopathy (INR ≥ 1.5) and encephalopathy in patient without previous cirrhosis and with an illness of < 26 weeks duration

- ALF is "….a clinical syndrome that represents the final common pathway of severe liver injury resulting from numerous infections, immunologic, metabolic, vascular and infiltrative disorders", leading to severe cellular or mitochondrial dysfunction and hepatocellular necrosis".
- "Hepatic encephalopathy is a defining criteria" for ALF. (Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. *Saunders/Elsevier* 2010, page 1557).

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The AASLD Position Paper on ALF defines ALF as coagulopathy and encephalopathy
"……. In a patient without pre-existing cirrhosis and with an illness of < 26 weeks duration".

- Give the 3 hepatic conditions in which often unrecognized pre-existing cirrhosis may be present.
  - AIH (autoimmune hepatitis)
  - HBV, vertically-acquired
  - WD (Wilson disease)

➢ Demography

< 1 / 10^5

1-year survival ~ 2/3

- The time interval between the onset of illness and the development of ALF is < 8 weeks, although some authors suggest a range of different time intervals:

– Hyperacute	≤ 1 week
– Acute	1 to 4 weeks

- Subacute 4 to 24 weeks

- Clinical
  - ALF (acute liver failure) syndrome
    - HE (hepatic encephalopathy)
    - Coagulation
    - Jaundice
    - No prior liver disease
    - ↑ inflammatory cytokines
    - ↓ immunity
    - ↓ metabolism of albumin-bound toxins
  - Acute on chronic liver failure (AoCLF)
    - ↑ NO (nitric oxide)
    - ↑ vasodilation
    - ↓ cardiac output

- Causes / associations
  - The causes of ALF in America are as follows:
    - Acetaminophen overdose, 46%
    - Indeterminate, 14%
    - Drug-related, 11%
    - HBV, 7%
    - Other causes, 7%
    - Autoimmune, 5%
    - Ischemic, 4%
    - HDV, 3%
    - Wilson disease, 2%

Worldwide the commonest known causes of ALF are acetaminophen overdose, HBV, HAV, and DILI (drug-induced liver injury) from drugs other than acetaminophen. Other less common drugs and toxins causing ALF are isoniazid,

propylthiouracil, phenytoin, valproic acid; and don't forget the mushroom! – Amanita phalloides poisoning). These comprise about 60% of cases.

- Give a classification of the causes of acute hepatic failure (ALF), and give 15 examples.
    - Viral Infection
        - 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
    - ALF (acute liver failure) may occur from HBV caused by use and then withdrawal of
        - Steroids
        - Chemotherapy
        - Anti-TNF drugs (immune suppression, followed by immune reconstitution with withdrawal of these drugs).
    - Drugs (Iatrogenic)
        - Acetaminophen, isoniazid, NSAIDs, sulfonamides
        - Tetracycline, rifampin, valproic acid, phenytoin, halothane
        - Telithromycin, orlistat, amiodarone
        - Drug withdrawal in HBV
    - Immune reconstitution

    - In HBV use and then withdrawal of steroids, chemotherapy or anti-TNF drugs (immune suppression, followed by immune reconstitution with withdrawal of these drugs).
- Inherited
    - Wilson disease
    - Alpha-1 antitrypsin deficiency
    - Galactosemia
    - Tyrosinemia, Reye's syndrome, hereditary fructose intolerance
    - Neonatal iron storage disease
    - Lecithin-cholesterol acyltransferase deficiency
- Ischemic
    - Left heart failure
    - Shock (cardiogenic / non-cardiogenic)
    - Venocclusive disease (SOS, sinusoidal obstruction syndrome)
    - Budd-Chiari syndrome (BCS)
    - Heat stroke (Inadvertent occlusion 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

Adapted from: Khashab M, et al. *Curr Gastroenterol Rep* 2007;9(1):66-73.

- Differential
  - The diagnosis of ALF is based on clinical findings, and must be differentiated from conditions with similar clinical findings (eg. HEV infection)

- Give the 7 important hepatic and non-hepatic conditions which may mimic the clinical presentation of alcoholic liver failure (ALF).
  - Acute decompensation of chronic liver disease
  - Acute HBV
  - Acute flares of chronic HCV
  - Alcoholic hepatitis
  - Sepsis (low factor VIII; normal factor VIII in ALF)
  - SLE (systemic lupus erythematosus)
  - TTP (thrombotic thrombocytopenic purpura)

- 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°
    - 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°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.

- Acute adrenal insufficiency

- 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

- 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

INHERITED METABOLIC DISORDERS OF LIVER

- Hereditary hemochromatosis (HH) – HFE- and hepcidin-associated disorder
- Wilson disease (WD)
- Cystic fibrosis
- α1 anti trypsin deficiency (α AT)
- Bile acid transport defects

Hereditary Hemochromatosis (HH)

➢ Definition

- HH is an autosomal recessive disorder in the HFE gene on chromosome 6, leading to either the C282Y or the H63D mutation, low expression of hepcidin (the hepatic iron-regulatory protein), and iron loading of the hepatocytes as well as some other tissues.

➢ Pathophysiology

- Give the role of **hepcidin** in iron homeostasis.
  - Hepcidin
    - 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

➢ Causes of iron overload
  - Inherited – HFE
  - Secondary – Non-HFE

- Give the **non-HFE forms of HH**.
  - 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
- 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

- Give the mechanisms of Fe overload in ALD and HCV.
  - In ALD (alcoholic disease) and HCV, ROS (reactive oxygen species) are formed
  - ↑ ROS
    - Acts on a C/EBP (CCAAT / enhancer binding protein → ↓ hepcidin expression
    - ↑ Fe in hepatocytes
  - This leads to ↑ iron absorption and release of iron in macrophages, the iron overload in the conditions

➢ Genetics

- Persons with HH are homozygous for C282Y, or heterozygous for C284Y plus H63D, but phenotypic expression requires a trigger such as HCV, alcohol, or down-regulation of a modifier gene
- 24-58% of C284Y homozygotes have a normal serum ferritin concentration

*Remember, there is non-expression of the phenotypic abnormality in 50% of the hereditary hemochromatosis genotype

- Give the interpretation of the following genetic test results in persons suspected as having hemochromatosis.

➢ C282Y homozygote
  - Seen in >90% of genetic Hemochromatosis.
  - 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 biochemical iron studies suggest significant iron overload (e.g. serum ferritin >1000µg/L), and 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.

- Clinical

- Give the physical findings in patients with HH.
  - Skin
    - Increased pigmentation
    - Porphyria cutanea tarda (PCT)
  - Liver
    - Hepatomegaly
    - Cutaneous stigmata of chronic liver disease
    - Splenomegaly
    - Signs of PHT (ascites, encephalopathy, jaundice, coagulopathy)
  - Joints
    - Arthritis
    - Joint swelling
    - Chondrocalcinosis

- Heart
  - Dilated cardiomyopathy
  - Heart failure (HF)
  - Arrhythmias
- Endocrine
  - Testicular atrophy
  - Hypogonadism
  - Hypothyroidism

Abbreviations: PHT, portal hypertension

Adapted from: Bacon BR, et al. Hepatology. 2011;54(1):328-43.

CLINICAL POINTER:

Skin hyperpigmentation in HH is in the sun-exposed regions and is either from deposit of iron in skin, as well as from ↑ melanin synthesis in melanocytes

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

➢ Laboratory

- 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.

- 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%

➢ Liver biopsy

- 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 vein concentration is > 16, 000 µg/g liver dry weight

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
  - HIC (hepatic iron concentration)
    - Normal, < 1500 µg/gm liver, dry weight
    - HH with symptoms, > 10,000
    - HIC level when fibrosis / cirrhosis occurs, > 20,000
    - Note: if patient has HH and for example HCV or NASH, fibrosis / cirrhosis will develop at HIC < 20,000 µg/gm liver, dry weight
  - HII (hepatic iron index) HIC / age of patient (years)
    - > 1.9, HH
    - < 1.9, likely secondary iron overload

➢ Diagnostic imaging

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.

- 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

- 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

"Science is never cast in stone and ideas are written with a finger on shifting sand."

Anonymous

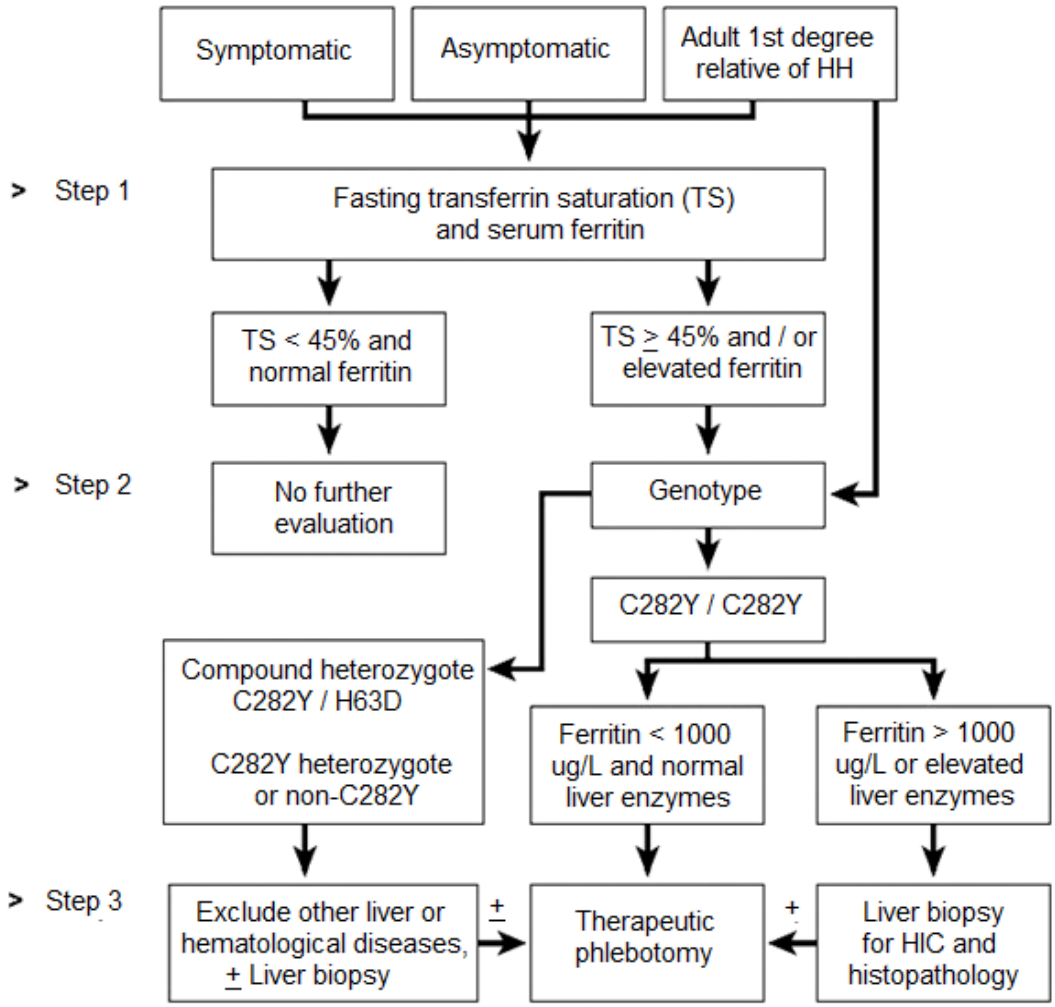
CLINICAL SCENARIO

- A 30-year-old man's biological father died of cryptogenic cirrhosis, and the young man requests genetic testing for hemochromatosis. He is found to be a C282Y homozygote (C282Y +/+). What are the next steps for him and his family?*
  - Normal iron studies - repeat iron studies every 5 years.
  - Abnormal iron studies - liver biopsy and liver iron index, needed if >40years, ferritin >1000, ↑ AST; exclude HCV, alcohol, NAFLD/NASH
  - Assess liver enzymes and function – blood, ultrasound
  - Education

➢ Assess and treat
  - Extraintestinal manifestations (diabetes, heart, arthritis)
  - Avoid liver toxins, including alcohol
  - Screen for HCV, HCC
  - Preventative care: vaccinate against HAV, HBV
  - Phlebotomy if ↑ liver iron index

➢ Screen
  - Siblings – screen
  - Spouse - screen to determine if their children should be screened
  - Avoid high intake of Fe, vitamin C

- Give a **suggested algorithm** to investigate HH based on serum transferrin saturation, serum ferritin concentration, and HFE genotype.



Printed with permission: Bacon BR, et al. Diagnosis and management of hemochromatosis: 2011 practice guideline by the American Association for the Study of Liver Diseases. Hepatology. 2011;54(1):328-43.

- Give a diagnostic algorithm for when to perform liver biopsy in possible HH.
  - TS (transferrin saturation) > 45% → testing for C282Y and H63D → for C282Y+, measure serum ferritin;
    - If > 1000 mg/mL → liver biopsy
    - If < 1000 mg/mL but ↑ ALT or ↑ AST → liver biopsy

Printed with permission: Adams PC. Evaluation of cirrhosis with an elevated ferritin. Clin Gastroenterol Hepatol. 2012;10(4):368-70.

➢ Treatment

- Hereditary hemochromatosis
  - 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
  - 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
  - General comments
    - Target - 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
      - Normalization of elevated liver enzymes
      - Reversal of hepatic fibrosis (in approximately 30% of cases)
      - Elimination of risk of HH-related HCC if iron removal is achieved before development of cirrhosis
      - ↓ portal hypertension in patients with cirrhosis
    - Extrahepatic
      - Improved cardiac function
      - Improved control of diabetes
    - Note
      - No reversal of established cirrhosis
      - No (or minimal) improvement in arthropathy
      - No reversal of testicular atrophy

Adapted from: Bacon BR, et al. Hepatology. 2011;54(1):328-43.

- Give the common **causes of death** after liver transplantation (LT) for HH.
  - HCC

- Infections (↑ risk of infection in iron-loade patients)
- Cardiac and ventricular dysrhythmias
- CHF (congestive heart failure)

- Celiac disease
  - 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

Wilson Disease (WD)

- Definition: Autosomal recessive defect of cellular copper export, leading to accumulation of copper in liver, brain, kidney, eye, as well as in other tissues.
  - 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.
  - Be sure to associate WD 5th 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.

- Diagnosis

Diagnostic Cautions

- Caution: NAFLD is common and WD is rare; fatty liver is common in WD, so when you see a person with NAFLD, always ask yourself,- could this be WD?

- 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

Clinical Cautions

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

- Give 4 **routine tests** for diagnosis of Wilson disease, and give examples for each of false positive and false negative findings for these tests.

Test	Typical finding	False negative*	False positive*
Serum ceruloplasmin	> 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	- Incorrect collection - Children without liver disease	- Hepatocellular necrosis - Cholestasis - Urine contamination
Serum "free" copper	> 1.6 µmol / L		
Hepatic copper	> 4 µmol/g dry weight	Due to regional variation - In patients with active liver	Cholestatic syndromes

		disease - In patients with regenerative nodules	
○ Kayser-Fleischer rings by slit lamp examination	Present	Absent - ≤ 50% of patients with hepatic Wilson - In most asymptomatic siblings	Primary biliary cirrhosis and other cholestatic hepatic conditions of long duration

Printed with permission: European Association for Study of Liver. EASL Clinical Practice Guidelines: Wilson's disease. J Hepatol. 2012;56(3):671-85, Table 4.

- Diagnostic scoring system

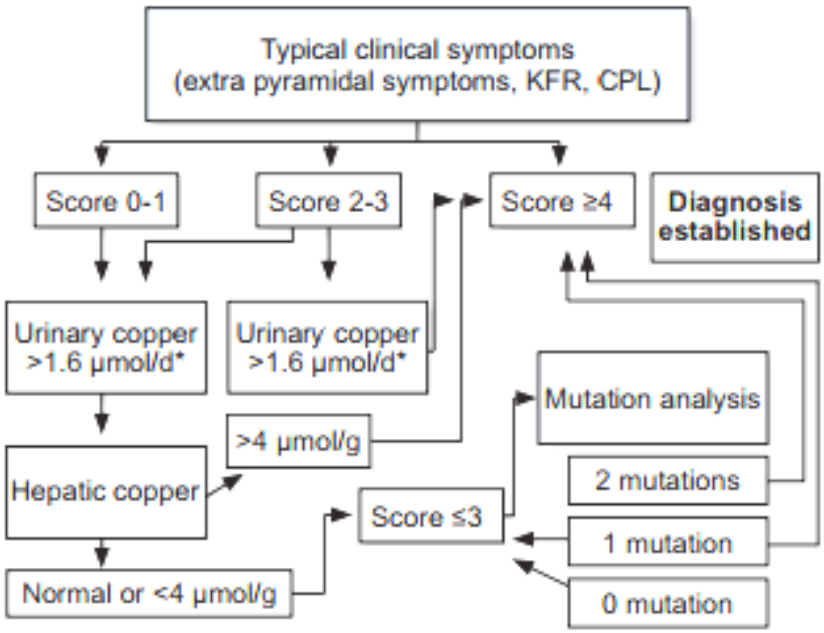
Typical clinical symptoms and signs		Other tests	
○ KF rings		○ Liver copper (in the absence)	
Present	2	> 5x ULN (>4 µmol/g)	2
Absent	0	0.8-4 µmol/kg	1
		Normal (< 0.8 µmol/g)	-1
○ Neurologic symptoms**		Rhodamine-positive granules	1
Severe	2	○ Urinary copper (in the absence)	
Mild	1	Normal	0
Absent	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.

- Suggested Diagnostic algorithms for Wilson disease based on the Leipzig Score.



∗In children the cut off can be lowered to 0.64 µmol/d.

Abbreviations: CPL, ceruloplasmin; KFR, Kayser-Fleischer rings

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

SO YOU WANT TO BE A HEPATOENTEROLOGIST!

In the patient on penicillamine with pre-existing or new neurological symptoms, give cotherapy plus zinc po. Space the intake of zinc 1 hr before or 2 hr after the penicillamine.

- Give the reason why the blood hemoglobin concentration needs to be monitored in WD patients treated with both penicillamine and zinc.
    - This treatment regimen increases the risk of developing sideroblastic anemia.

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.

➢ 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 • Gastritis• Aplastic anemia rare• Sideroblastic anemia • Sideroblastic anemia	– ↓ dose before surgery – During pregnancy – Maximum dose 20 mg/kg/day; reduce by 25% when clinically stable
Zinc	– Metallothionein inducer – ↓ copper absorption	Rare	• Gastritis; biochemical pancreatitis • Zinc accumulation • Possible changes in immune function	– No dosage reduction for surgery or pregnancy – Usual dose in adults: 50 mg elemental Zn three times daily; *minimum* dose in adults: 50 mg elemental Zn twice daily
Tetrathio-Molybdate	– Chelator – ↓ copper absorption	Rare	• Anemia; neutropenia • Hepatotoxicity	– Experimental in the United States and Canada

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

Penicillamine (D-penicillamine)

- 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

- 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.

- 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.

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

- Give the special considerations for treatment of Wilson disease in pregnancy, preoperatively, and with acute liver failure in children.

- 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 the intervention which may be used to treat 4 liver diseases, in which the treatment may lead to the reversal of hepatic fibrosis.

Liver disease	Intervention
o Hemochromatosis	– Phlebotomy
o Secondary iron overload	– Desforoximine
o Hepatitis B	– Antiviral therapy (entecavir)
o Hepatitis C	– Antiviral therapy (protease inhibitors)
o Non-alcoholic steatohepatitis	– Weight reduction

Source: Adams P. Gastroenterology 2011; 1142-1143

AUTOIMMUNE HEPATITIS

➢ Types

- Give the 8 differences between type 1 and 2 AIH (autoimmune hepatitis), including the **classification** of autoimmune hepatitis (AIH) based on autoantibody profiles of patients

Feature	Type 1 AIH	Type 2 AIH
o Geographical variation	Worldwide	Worldwide
o Age at presentation	All ages	Usually childhood and young adulthood
o Sex (F:M)	3:1	10:1
o Clinical phenotype	Variable	Generally severe
o Characteristic autoantibodies	ANA* ASMA Anti-actin antibody Anti-SLA/LP antibodies	Anti-LKM-1 antibody Anti-LC-1 antibody

Feature	Type 1 AIH	Type 2 AIH
	*25% of patients negative ANA	
○ Histopathological features at presentation	Mild disease to cirrhosis	Generally advanced, ↑ inflammation/cirrhosis common
○ Treatment failure	Rare	Common
○ Relapse after drug withdrawal	Variable	Common
○ Need for longterm maintenance	Variable	Approximately 100%

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

- Give the alternate **descriptive criteria for diagnosis of autoimmune hepatitis (AIH):** (adapted from the revised International Autoimmune Hepatitis Group (IAIHG) criteria, 1999103).

Features	Definite AIH	Probable AIH
○ Liver histology	– Interface hepatitis of +/- lobular hepatitis or bridging necrosis. – No biliary lesions, granulomas or other prominent changes	▪ Same as for definite AIH
○ Laboratory features	– ↑ aminotransferase abnormality, especially if alkaline phosphatase activity normal.	▪ Same as for definite AIH but patients with abnormal levels of copper and caeruloplasmin may be included contingent on the exlusion of WD

	Features	Definite AIH	Probable AIH
		– Normal levels of alpha-1-anti-trypsin, copper and caeruloplasmin	
○	Serum immunoglobulins	– Globulin, γ-globulin or IgG concentrations >1.5× upper normal limit.	▪ Any elevation in globulin, γ-globulin or IgG concentrations above the upper normal limit
○	Serum autoantibodies	– ANA, SMA or anti-LKM-1 antibodies at titres ≥1:80. – Lower titres acceptable for children, especially anti-LKM-1. – Negative AMA.	▪ ANA, SMA or anti-LKM-1 antibodies at titres ≥1:40, or presence of other specified autoantibodies
○	Viral markers	– No markers of current infection with hepatitis A, B and C viruses	▪ Same as for definite AIH
○	Other exposures	– Average alcohol consumption <25 g/day. – No recent use of known hepatotoxic drugs	▪ Average alcohol consumption <50 g/day ▪ No recent use of known hepatotoxic drugs. ▪ Patients who have consumed larger amounts of alcohol or have had exposure to known hepatotoxic drugs may be considered if ongoing damage after abstinence/withdrawal

Abbreviations: AMA, antimitochondrial antibodies; ANA, antinuclear antibody; SMA, smooth muscle antibody; LKM-1, liver kidney microsomal-1 antibody.

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, Table3.

Laboratory Alert

- Autoantibodies may be absent in up to 30% of persons with ALF from AIH
- Liver biopsy (transjugular because of coagulopathy) may be necessary to make the diagnosis.

➢ **Modified diagnostic criteria** for the diagnosis of autoimmune hepatitis (AIH).

Parameter/feature	Score
○ Female sex	+2
○ ALP:AST (or ALT) ratio	
– <1.5	+2
– 1.5–3.0	0
– >3.0	−2
○ Serum globulins or IgG above normal	
– >2.0	+3
– 1.5–2.0	+2
– 1.0–1.5	+1
– <1.0	0
○ ANA, SMA or LKM-1	
– >1:80	+3
– 1:80	+2
– 1:40	+1
– <1:40	0
○ AMA positive	4
○ Hepatitis viral markers	
– Positive	−3
– Negative	+3
○ Drug history	
– Positive	−4
– Negative	+1
○ Average alcohol intake	
– <25 g/day	+2
– >60 g/day	−2

Parameter/feature	Score
○ Liver histology	
– Interface hepatitis	+3
– Predominantly lymphoplasmacytic infiltrate	+1
– Rosetting of liver cells	+1
– None of the above	−5
– Biliary changes	−3
– Atypical features	−3
○ Other autoimmune disease(s)	
– In either patient or first-degree relative	+2
○ Optional additional parameters	
– Seropositivity for other defined antibodies	+2
– HLA DR3 or DR4	+1
○ Response to therapy	
– Remission alone	+2
– Remission with relapse	+3
○ Interpretation of aggregate scores	
– Pre-treatment	
▪ Definite AIH	>15
▪ Probable AIH	10–15
– Post-treatment	
▪ Definite AIH	>17
▪ Probable AIH	12–17

Abbreviations: AMA, antimitochondrial antibodies; ANA, antinuclear antibody; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; LKM-1, liver kidney microsomal-1 antibody; SMA, smooth muscle antibody.

Printed with permission: Gleeson D, Heneghan MA; Gut. 2011;60(12):1611-29.

Simplified diagnostic criteria for the diagnosis of autoimmune hepatitis (AIH)

Feature/parameter	Discriminator	Score
○ ANA or SMA+	≥1:40	+1*
○ ANA or SMA+, or	≥1:80	+2*

Feature/parameter	Discriminator	Score
LKM+, or	≥1:40	
SLA+	Any titre	
○ IgG or immunoglobulin level	>Upper limit of normal	+1
	>1.1× Upper limit	+2
○ Liver histology	Compatible with AIH	+1
	Typical of AIH	+2
○ Absence of viral hepatitis	No	0
	Yes	+2

≥6 points: probable AIH; ≥7 points: definite AIH.

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

Abbreviations: ANA, antinuclear antibody; LKM, liver kidney microsomal antibody; SLA, soluble live antigen; SMA, smooth muscle antibody.

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 5.

➢ Treatment

- 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.

CIRRHOSIS

- Pathphysiology

- Give 7 pathophysiological factors responsible for the development of hepatic fibrosis.
  - Extracellular matrix proteins (EMP)
  - Hepatic stellate cells (HSC)
  - Activation of HSC to form myofibroblasts
  - Other mesenchymal cell populations and bone marrow-derived cells
  - Hepatocyte growth factor (HGF)
  - TGF-β
  - Renin-angiotensin system (RAS)
  - Angiotensin-converting enzyme (ACE)
  - Angiotensin I and II receptors
  - Endotoxin, lipopolysaccharide (LPS)
  - Toll-like receptor (TLR4)
  - Angiogenesis
    - Vascular endothelial growth factor (VEGF)
    - Angioporetin 1, 2

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

➢ Causes / associations

- Give 8 causes of cirrhosis.
  - Viral hepatitis
    - HBV, HCV, HDV
  - Metabolic
    - Autoimmune
    - Autoimmune Hepatitis (AIH)
    - NASH
    - Primary biliary cirrhosis (PBC)
    - Sclerosing cholangitis (primary and secondary)
  - Drugs/toxins

    - Alcohol
  - Congestive
    - Cardiac failure
    - Budd-Chiari Syndrome
  - Inherited
    - α1-antitrypsin deficiency
    - Cystic fibrosis
    - Galactosemia
    - Hemochromatosis (HH)
    - Tyrosinemia
    - Wilson disease

- Give 6 hepatic/extrahepatic signs of **cirrhosis** on hepatic DI (diagnostic imaging), CT and/or MR.

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

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 cirrhosis 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 2 examples of the effect of cirrhosis on the **assessment of endocrine function**.
  - Hypothyroidism
    - ↓ T3
    - N/↑ thyroxine binding globulin level
  - Hyperthyroidism
    - ↑ ALT/AST (seen with liver disease, as well as 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.

- Give 10 factors to consider in the **preventive care** of the patient with cirrhosis.
    - Prevention of first variceal hemorrhage: EGD q3 years, with banding or beta blockers (primary prophylaxis)
    - Prevention of recurrent variceal hemorrhage (secondary prophylaxis)
        - Non-selective beta-blockers (NSBB)
        - Banding
        - Sclerotherapy
        - Shunts (TIPS)
    - Prevention of bacterial infections after GI bleeding
        - Antibiotic prophylaxis
    - Prevention of spontaneous bacterial peritonitis (SBP) antibiotics for previous SBP
    - Assess for minimal (subclinical) HE (grade 0), and treat appropriately; test for driving competence
    - Vaccination – Influenza, Pneumococcus, HAV, HBV
    - Nutritional assessment and treatment
    - Avoid hepatotoxic drugs, eg., alcohol, benzodiazepines, NSAIDs, vasodilators, Viagra, hepatotoxic herbs
    - 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

PORTAL HYPERTENSION (PHT)

- Definition:
  - Hepatic sinusoidal pressure ≥ 6 mm Hg
    - Note: Not all persons with portal hypertension have cirrhosis, and not all persons with cirrhosis have portal hypertension.
- Physiology background
  - 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 HA, and vice versa, through an autoregulatory mechanism
    - Recall that we are dealing with three distinct vascular beds
      - Intrahepatic
      - Splanchnic
      - Systemic

"Life isn't a matter of milestones, but of moments."

Rose Kennedy

- Give the 12 components 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)

➢ 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

  $\Delta P = FxR$

  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)

- 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)
  - Give NO in cirrhosis will restore the intrahepatic vasodilation arising from the endothelial cells, but the HSC in cirrhosis contribute to the vasoconstriction and are less responsive to NO. Replacement in cirrhosis, so benefit of restoring ↓ NO levels does not fully restore the vessel diameter to normal
  - 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

Printed with permission: Møller S, and Henriksen JH. *Gut* 2008; 58:271.

- 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.

Portal and Hepatic Venous Blood Flow

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

Laboratory Alert

- 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 anit-mitochondral antibodies.

- Give 4 sites of portal vein-systemic circulation which develop in portal hypertension, and name the involved and 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 esophageal varices to develop ▪ > 12 mm Hg for esophageal varices to bleed ▪ > 16 mm Hg for gastric varices to bleed - Most common site of bleeding, the palisade zone, does not drain to periesophageal veins, and from there to the azygous system

- 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 SVT 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.
  - The usual surgical treatment for isolated gastric fundal varices due to the splenic vein thrombosis (SVT).

➢ Diagnostic imaging

- Give 4 clinical uses of **Doppler ultrasound** in patients with suspected liver disease.
  - Portal vein (PV)
    - Patency
    - Anatomical abnormalities (pre liver pretransplantation)
    - Acute flow changes

- Direction of flow

- Hepatic artery (HA)
  - Patency
  - Anatomical abnormalities
- Hepatic veins (HV)
  - Patency (Budd-Chiari syndrome)

Adapted from: Robinson KA, et al. *Ultrasound Q* 2009;25(1):3-13.

➢ **Presinusoidal Portal Hypertension**

- Give 5 causes of liver disease in which there may be **portal hypertension without cirrhosis**, due to a presinusoidal component of the intrahepatic disease.

  - ALD (alcoholic liver disease) presinusoidal perivenular lesions
  - HCC or 2º liver malignancy
  - HH (hereditary hemochromatosis)

  - AIH (autoimmune hepatitis)
  - PBC (primary biliary cirrhosis)
  - Sarcoidosis (early disease; later the site of ↑ intrahepatic resistance is postsinusoidal)
  - Schistosomiasis (S. mansoni, S. japonicum)
    - Presinusoidal granulomas
    - Inflammation
    - Periportal fibrosis

- Give the anatomical site of increased resistance when liver disease is associated with ↑ portal pressure (PP) and yet HVPG is normal.

  - There will be ↑ PP but normal HVPG when the site of increased resistance is presinusoidal.

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

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

- Histopathology

- 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.

- Pathophysiology
  - Clinical manifestations are the result of the development of shunts between the hepatic artery (HA), hepatic vein (HV), or portal vein (PV).

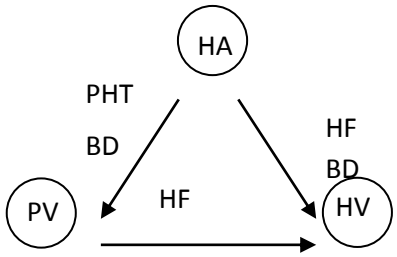
- Clinical

- Give the **diagnostic criteria** for HHT / OWRD.

  - Positive family history

- Epistaxis
- Telangiectasias
- AV fistulas (lung, liver)

- Give the clinical presentations arising from shunting between HA (hepatic artery), HV (hepatic vein) and PV (portal vein) in HHT (hereditary hemorrhagic telangiectasia)



- High-output heart failure (HF) (hepatic artery [HA] and/or portal vein [PV] to hepatic vein [HV] shunt) HA → PV / HV
  - Shortness of breath on exertion
  - Orthopnea
  - Ascites
  - Edema

- Biliary disease (BD; hepatic artery [HA] to hepatic vein [HV] and/or portal vein [PV] shunt, HA → PV)
  - Severe cholestasis
  - Recurrent cholangitis

- Portal hypertension (PHT) (hepatic artery [HA] to portal vein [HV] shunt, HA → PV / HV)
  - Esophageal varices
  - Nodular regenerative hyperplasia

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.

A patient without previous liver disease, but with a history of recurrent nose bleeds and telangiectasias on the lips presents with the sudden onset of ascites, bleeding varices, and new onset of an abdominal bruits. BCS (Budd-Chiari syndrome) has been excluded.

- Give the likely diagnosis, based on the location of the bruit.
    - A splanchnic artery which forms a fistula with a mesenteric vein causes a sudden and dramatic increase in portal pressure (from > 6 mm Hg to > 100 mm Hg), leading to sudden onset of ascites and varices, with bleeding from the varices.
    - The likely diagnosis is HHT (hereditary hemorrhagic telangiectasial
    - AV fistulas to the lung or liver are common in HHT.

➢ Treatment

- Give the mechanism(s) of action of **5 drugs** used to treat portal hypertension (PHT).

Drugs used for treatment of PHT generally are selected to act to

- ↓ portal blood flow, or (↓ Portal Blood Flow → ↓ PP [Portal Pressure])
- ↓ intrahepatic resistance

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

"The covers of the book are too far apart."

Anonymous

ASCITES

➢ Definition
- Free fluid (> 25 mL) in the peritoneal cavity

➢ Tips about Ascites

- If ascitic fluid contains ↑ lymphocytes (not PMNs), suspect
  - Tuberculous peritonitis
  - HCC / hepatic metastases
  - Pancreatitis

- When malignancy causes the ascitic fluid, it is due to
  - Peritoneal carcinomatosis (commonest causes)
  - Hepatic metastases
  - HCC (hepatocellular cancer)

- 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

- 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 (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.

- Give 7 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!

➢ **When the SAAG "sags"**

- Which laboratory value predicts that an ascitic patient is 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.

  - 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 low 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 these two causes of ascites:

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

Abbreviation: pbNP, pro-brain-type naturetic peptide

- Give the serum ascites albumin gradient (SAAG) and ascites protein to determine the cause of ascites.

SAAG, g/dL	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

➢ Pathogenesis

- Give the current theory of the pathogenesis of ascites.

PHT → ↑ NO → vasodilation →↓ effective arterial BM
→ ↑ vasoconstrictors
→ ↑ vasopressin
→ ↑ renin-aldosterone
→ ↑ sympathetic nervous system activity
→ ↑ Na+ -retaining hormones
→ ↑ renal vasoconstriction → ↓ renal function → ↑ retention of Na+ / H2O → Ascites

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.

Staff Stumpers !!!!!

In the context of the patient with ascites, give the meaning of “ovarian hyperstimulation syndrome” (OHS), “Poems syndrome”, and “hemophagocytic syndrome”.

Condition	Association with Ascites
○ OHS	– Excess stimulation of the ovaries with sex hormones may lead to ascites
○ Poems syndrome	– Polyneuropathy, organomegaly, endocrinopathy, M component, skin changes → may be associated with ascites
○ Hemophagocytic syndrome	– Leukemia or lymphoma, associated with ascites

- Treatment
  - 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

- 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

CLINICAL CAUTION

- BB (beta blockers, including non-specific BB)
  - 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.

- 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 underlying liver disease / condition
- Undertake vaccinations
  - 1^o / 2^o prevention of bleeding from esophageal / gastric varices
- Consider diagnostic paracentesis to rule out spontaneous bacterial peritonitis (SBP)
- Diuretics
  - Lasix 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 $\downarrow K^+$)
  - Transjugular intrahepatic portosystemic shunt (TIPS) decreases sinusoidal portal pressure, and decreases Na^+ reabsorption in the proximal renal tubules, producing a diereses
  - 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

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.

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.

- Give 8 examples of **non-diuretic treatments** for ascites.
  - Peritoneal carcinomatous from ovarian cancer – Surgical debulking
  - Alcoholic cirrhosis – Stop drinking alcohol
  - Chlamydia ascites – Tetracycline
  - HAC HCV – Interferon plus ribavirin plus third agent
  - HBV – Interferon, or oral nucleoside
  - Lupus – Glucocorticosteroids
  - NASH – Weight loss
    – Treatment of metabolic syndrome
    – Vitamin E (possibly)
  - Nephrogenous ascites – Hemodialysis
  - Paracentesis – Continue regular paracentesis

- Preoperative – Change IV from normal saline
- TIPS – Doppler ultrasound to exclude possible obstruction
  – Consider inserting new stent if TIPs becomes occluded
- Tuberculous ascites – Appropriate antituberculous therapy

- Restriction of oral Na+ intake to 2 g/day of salt
  - With salt restriction to < 120 mmol / day (~ no added salt), spironolactone 100 mg / day → 400 mg / day plus furosemide 40 mg / day → 160 mg / day, aim for daily weight loss of
    - 0.5 kg when there is no edema
    - 1.0 kg when there is edema
- Restriction of fluid intake
  - Because of the avid renal retention of Na^+ and water, the cirrhotic with ascites may have hyponatremia, but the total body Na^+ is actually increased.
  - About 1% of cirrhotics will have serum $Na^+ < 120$ mEq／L (from hypervolemia hyponatremia), and these patients will require restriction of fluid intake (to a volume that is < daily urinary output).
  - Do not give patient IV 0.9% saline or increase serum Na^+ concentration quickly for fear of causing osmotic demyelination
- No restriction on exercise (curiously, swimming ["water immersion"] may accelerated clearance of ascites)

- **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

Trivia

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

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)

TRANJUGULAR INTRAHEPATIC PORTOSYSTEMIC SHUNT (TIPS)

- Therapeutic paracentesis
  - Measure the total protein concentration in ascitic fluid
    - Ascitic fluid protein < 15 g / L is associated with ↑ risk of SBP
    - When ascitic fluid protein < 15 g / L, use antibiotics (to prevent SBP)
- TIPS
  - As long as **no** history of hepatic encephalopathy (HE)
- Evaluation for possible liver transplantation

TIPS ABOUT

- In about 10% 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 pseudointinal hyperplasia will occur in the parenchymal tract or outflow hepatic vein, associated with development of a coating of collagenous matrix and covered by endothelial cells.
- Doppler ultrasound may be used to establish the potency of the TIPS.
- There are numerous signs repeated 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%).
- Potency of TIPS is best demonstrated with re-catheterization of the TIPS.
- Overall, TIPS causes less rebleeding from esophageal varices (EV), more HE (hepatic encephalopathy), and no change in overall survival.
- Proven benefit of TIPS
  - Primary prophylaxis of bleeding from EV or GV **No**
    - EV, GV Yes
    - PHG failing NSBB therapy Yes
  - Secondary prophylaxis
    - Refractory cirrhotic ascites, intolerant to LVP Yes
    - Hepatic hydrothorax, unresponsive ↓ Na^+ & diuretics Yes
    - Budd-Chiari syndrome, moderate, failed anti-coagulation Yes
- No proven benefits of TIPS
  - GAVE

Abbreviations: EctV, ectopic varices; EV, esophageal varices; GAVE , gastric antral vascular hyperplasia; GV, gastric varices; HRS, heptorenal syndrome; LVP, large volume paracentesis; NSBB, non-specific beta blocker; PHG, portal hypertensive gastropathy

- Give the relative **contraindications** of TIPS.
  - Liver failure
    - HE (hepatic encephalopathy)

  - Jaundice (serum bilirubin > 5 mg / dL)
  - Coagulopathy (INR > 2)
- Progressive renal failure
- Associated acute infection
- Severe cardiopulmonary disease
- Portal vein thrombosis (PVT)
- Polycystic liver disease
- Wrong indication
  - Primary prevention of bleeding of EV, GV, EctV
  - GAVE (gastric antral vascular ectasia)

Abbreviations: EV, esophageal varices; EctV, ectopic varices; GV, gastric varices; HE, hepatic encephalopathy; PVT, portal vein thrombosis; TIPS, transjugular intrahepatic portosystemic shunts

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.

DIURETIC RESISTANT ASCITES / DIURETIC INTRACTABLE ASCITIS

➢ Definition

- Diuretic Resistant Ascites (DRA)
  - 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.
  - 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 80 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 o initial mobilization

- Diuretic Intractable Ascites (DIA)
  - 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)
  - Diuretic-induced complications:
    - Diuretic-induced hepatic encephalopathy (HE) is the development of encephalopathy in the absence of any 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 hypo- or hyperkalaemia is defined as a change in serum potassium to < 3 mmol/L or >6 mmol/L despite appropriate measures
    - Diuretic-induced hyponatremia is defined as a decrease of serum sodium by >10 mmol/L to a serum sodium of <125 mmol/L
  - If urinary Na^+ (measured on a 24-hr sample, or spot urine $Na^+ / K^+ > 1$ or > 2.5) is < 88 mEq / day, while the patient is on a daily dietary intake of ≤ 2 gm (88 mEq) Na^+; or
  - If patient cannot tolerate diuretics because of
    - ↑ azotemia
    - HE (hepatic encephalopathy)
    - Difficult-to-control electrolyte imbalance, and
  - Exclusion of other associated causes of ascites, e.g.
    - HCC (hepatocellular cancer)
    - BCS (Budd-Chiari syndrome)
    - PVT (portal vein thrombosis)
    - ESRD (end-stage renal disease), on regular renal dialysis
  - Total paracentesis +I.V. albumin (6-8 g of albumin per liter of ascites removed)

- 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

SO YOU WANT TO BE A HEPATOLOGIST!

- Give 4 **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

- Definition
  - "…..ascites unresponsive to a sodium-restricted diet [2 gm per day] and high-dose diuretic treatment [e.g. furosemide 10 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).
  - The development of refractory ascites ("ascites that cannot be mobilized or the early recurrence of which [i.e, after LVP] cannot be satisfactorily prevented by medical therapy"; 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)
  - Due to inappropriately high neurohumoral activation
  - Refractory ascites signals a poor prognosis and the need for assessment for possible liver transplant (LT).
  - Usually develops slowly over weeks to months,
  - Consider the possible benefit from
    - Serial therapeutic paracentesis
    - TIPS (transjugular intrahepatic portosystemic stent shunt)
    - Peritoneovenous shunt
    - Listing for LT (liver transplantation)
  - First-line treatment for refractory ascites
    - Tense
      - Therapeutic paracentesis, with or without albumin infusion
    - Non-tense
      - TIPS
  - 1 year mortality rate for ascites refractory to medical care ~ 68%
- Treatment
  - Diuretics
    - High dose IV furosemide plus hypertonic saline for short interval may restore response to diuretics.
    - Stop diuretics if Na^{+}_{u} > 30 mmol / day

- Large volume paracentesis (LVP)
  - Serial therapeutic paracentesis, including LVP, with albumin replacement for paracentesis > 5 L/day
  - Only if rapid removal of ascites is necessary
  - < 5 L removal, no albumin necessary
  - > 5 L removal, survival advantage to give albumin with LVP (large volume paracentesis) in order to prevent PCD (post-paracentesis circulatory dysfunction)
  - Remove as much fluid as possible from each treatment.
  - Test fluid for WBC and differential, protein (also measure serum albumin to calculate SAAG [serum-ascites albumin gradient]), amylase and cultures
  - When can paracentesis not be done safely?
    - The “battle field abdomen”, i.e. multiple surgical scars, making paracentesis unsafe.
    - “morbid obesity”
- TIPS (transjugular intrahepatic portosystemic stent shunt)
  - TIPS for patients who require frequent paracentesis (every 1-2 weeks) and whose CHLD score is <11
- Benefits
  - ↓ ascites
  - ↓ return of ascites
  - ↓ HRS (hepatorenal syndrome)
  - ↑ return of diuretic sensitivity
  - ↑ survival
- Selection of patients for TIPS
  - Diuretic-resistant cirrhotic ascites
  - C-P (Child-Pugh) class A or B (score < 12)
  - MELD score < 18 predicts 90-day mortality.
  - No history of severe previous HE
  - Cardiac ejection fraction > 60%
- TIPS versus LVP
  - ↓ likelihood of ascites returning, OR, 0.14
  - ↓ HRS (hepatorenal syndrome)
  - ↓ mortality (trend only), OR, 0.74
  - ↓ liver-related death

  - ↑ transplant-free survival
  - ↑ conversion of diuretic-resistant to diuretic-responsive (sensitive)
  - ↑ risk of HE (hepatic encephalopathy), OR, 2.26; occurs in about 30%
- Side-to-side portocaval shunt, placed through the right internal jugular vein.

- Peritoneovenous shunt for patients who are not TIPS
  - Considered when
    - Diuretic-resistant ascites
    - Paracentesis unsafe
      - Multiple previous abdominal surgeries, with multiple abdominal wall scar.
    - Not a candidate for LT
  - LT (liver transplantation) listing

BACTERIAL PERITONITIS

Spontaneous Bacterial Peritonitis

- Definition
  - 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.

- 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.

➢ Types

- Give the types of SBP.

	>250 neutrophils	Ascitic culture
1º		
– Classical SBP	+	+
– Culture-negative neutrocytic ascites (CNNA)	+	-
– Monomicrobial nonneutrocytic (MNB)	-	+
2º		
– Nonneutrocytic* polymicrobial	-	+

*Usually from needle perforation of the gut, is associated with severe symptoms and signs, low ascetic glucose (< 50 mg/dl), high LDH, and polymicrobial anaerobic infection

Abbreviations: SBP, spontaneous bacterial peritonitis; TIPS, transjugular intrahepatic portosystemic shunt; 1º, primary; 2º, secondary

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

- Give 3 types of bacterial peritonitis, which may be considered in the term SBP (ie.,excludes non-neutrocytic polymicrobial / secondary bacterial peritonitis).

Types of primary bacterial peritonitis	PMNs > 250	Bacterial culture of ascites
○ SBP (neutrocytic, culture positive monomicrobial ascites)	+	+
○ CNNA (culture-negative neutrocytic ascites)	+	-
○ MNB (monomicrobial non-neutrocytic bacterial ascites, aka bacterascites)	-	+

  - In the cirrhotic with ascites admitted to hospital
    - About 1/3 have bacterial peritonitis
    - 2/3 SBP, 1/3 MNB
    - Commonest monomicrobial organisms: E. Coli, Streptococci (pneumococci), Klebsiella
  - ○ 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).
  - ○ 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)

- 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)
  - SBP patients do not usually have
    - Peripheral blood leucocytosis
    - Fever
    - Abdominal tenderness
  - 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 8 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)

Secondary Polymicrobial Bacterial Peritonitis (Non-Neutrocytic Polymicrobial)

- Definition
    - 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 abdominal, excluded perforation rather than diagnosing neutrocytic spontaneous bacterial peritonitis (SBP).
        - Total protein > 1 g/dL
        - Glucose < 50 mg/dL
        - LDH > ULN for serum

- Microbiology
    - 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. SO gram stain may be useful in 2º BP (bacterial peritonitis [2º] to intestinal perforation), but not in SBP.
- In neutrocytic ascites, bed side inoculation of ascite fluid placed in blood culture bottles demonstrates bacterial growth in ~ 80%
- Ascitic fluid concentration < 2.5 g/dL 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).

➢ Diagnosing

- PMNs contain LDH, so when PMNs increase in SBP, there is ↑ LDH; in secondary BP, there is ↑↑↑ PMNs, so ↑↑↑ LDH (LDH is ascites > serum LDH)
- ↑ ascitic fluid amylase (> 2000 U/L, or 5x serum amylase) suggests
  - Acute pancreatitis
  - Intestinal perforation

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.

Clinical Gem: when it comes to ascites, treat CNNA as SBP

- Culture negative neutrocytic ascites Rx = spontaneous bacterial peritonitis

- Diagnosis
  - Consider SBP and perform diagnostic paracentesis if:
    - Symptoms/signs (abdominal pain, fever, chills)
    - Patient is in emergency room or admitted
    - Worsening renal function or encephalopathy
  - SBP is present if ascites PMN count >250 cells/uL (if fluid bloody, subtract 1PMN per 250 RBC/µL)
  - Clinical Challenge

Ascitic fluid neutrophils ≥ 250 / mm^3	Ascitic fluid culture positive	Treatment for SBP
Yes	Yes	Yes
Yes	No	Yes
No	Yes	- Repeat diagnostic paracentesis, and if - Neutrophils < 250 / mm^3 / no symptoms, follow patient - Neutrophils > 250 / mm^3 / treat symptoms - Remember ▪ In the cirrhotic patient who is hospitalized for GI bleeding, 40% develop SBP (that's why treatment of cirrhotics with GI bleeding and ascites are given prophylactic antibiotics).

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.

➢ Treatment (SBP, MNB and CNNA)

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 the indications for treatment of spontaneous bacterial peritonitis (SBP), including recurrent SBP.
  - In the cirrhotic patient with ascites, suspect SBP when there is
    - All persons with SBP
    - Prior history of SBP
    - GI bleeding, with ascites (even without SBP [PMN > 250; WBC > 500])
    - Low ascitic fluid protein concentration
  - General
    - Avoid therapeutic paracentesis during active infection
    - Intravenous albumin (1g/kg of body weight) if BUN>30mg/dL, creatinine >1mg/dL, bilirubin >4 mg/dl, and repeat at day 3 if renal dysfunction persists
    - Avoid aminoglycosides
  - The empiric antibiotic of choice for treating SBP would be
    - Cefotaxime plus metronidazole
    - Cefotaxime, 2 g IV q 8 hr (plus albumin 1.5 g / kg body weight (BW), IV for 2 days, then 1 g / kg BW IV for 3 days) (98% of organisms are susceptible) for 5 days
    - Ceftriaxone (2g IV every 24h) or
    - If there is penicillin allergy, or cefotaxime-resistance use levofloxacin empirically.
    - If there is possible / secondary bacterial peritonitis / polymicrobial bacterascites, use cefotaxime plus metronidazole.
    - Alternative antibiotic program
      - Ciprofloxacin 200 mg IV q 12 for 2 days, then 500 mg po q 12 hr for 5 days
      - TMP-SMX 1 double strength tablet p.o q.d
      - (Patients who develop quinolone resistant organisms may also have resistance to TMP-SMX)

        - Continue therapy for 7 days
    - Treatment duration is 5 days to 10 days (clinical response is usually rapid, within 2 days of treatment)

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 **not** use quinolones for an empiric treatment of SBP, and instead start with
    - Cefotaxime, 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)
    - In 80% of patient treated with cefotaxime have ↓ PMN in ascitic fluid within 48 hours
    - Follow up
        - 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
    - Prognosis
        - "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).
        - Early treatment of SBP is associated with a mortality rate (MR) of (only) 5%, with high MP with creatinine > 350 µmol/L, or if shock has developed.
        - "….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).

- 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)

- 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 plus albumin	Cefotaxime alone
- HRS type 1	10%	30%
- Mortality	10%	29%

  - 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 that all patients who develop SBP should be treated with broad spectrum antibiotics and intravenous albumin" (EASL Clinical Practice Guidelines, J. Hepatol 2010; 53: 399-417).

➢ Prophylaxis

  - Prophylaxis should be continued until the disappearance of ascites or until liver transplantation

- Give the management strategy in the prevention of recurrent SBP.

  - Recommended therapy
    - Oral norfloxacin 400mg po qd (preferred) or
    - Oral ciprofloxacin 250-500 mg qd* or
    - Oral levofloxacin 250 mg q.d*

o Alternative therapy	– TMP-SMX 1 double strength tablet po qd – Patients who develop quinolone resistant organisms may also have resistance to TMP-SMX
o 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.

- Give 4 criteria for using antibody prophylaxis for SBP.
  - Previous SBP
  - Previous EVB (esophageal variceal bleeding)
  - Total protein in ascitic fluid > 1 g/dL
  - Need for repeated LVP (large volume paracentesis)

➢ Treatment regimens
  - Ciprofloxacin 750 mg po qw (each week)
  - TMP-SMX 1 double strength tablet po 5 days per week
  - Norfloxacin 400 mg po od
  - ↓ incidence of SBP, antibiotic vs. placebo
    - Ciprofloxacin 3.6% vs. 22%
    - TMP-SMX vs. 27%\

Abbreviation: TMP-SMX, trimethoprim-sulfamethoxazole; SBP, spontaneous bacterial peritonitis; HRS, hepatorenal syndrome; MR, mortality rate

➢ Albumin

- Give the evidence for routine use of IV albumin infusion in patients with SBP.

	SBP antibiotics plus IV albumin	No IV albumin
o Irreversible renal impairment	10%	33%
o Mortality		
– in hospital	10%	29%
– 3-month	22%	41%

o 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 that all patients who develop SBP should be treated with broad spectrum antibiotics and intravenous albumin" (EASL Clinical Practice Guidelines, J. Hepatol 2010; 53: 399-417).

➢ Large volume paracentesis (> 5 L) is safe in ascites and spontaneous bacterial peritonitis (SBP)as long as 6-8 g albumin are given per liter fluid removed

- Norfloxacin (NOR) vs. placebo (PLA)

Outcomes	NOR	PLA
o # episodes of recurrent of SBP	7%	61%
o HRS	28%	41%
o MR		
– 3 month	6%	38%
– 12 month	40%	52%

These benefits are more likely if ascitic fluid total protein < 1 g/ dL

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 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 gram-negative bacteria (GNB)
            - ↑ incidence of gram-positive bacteria (GPB)
            - 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

Spontaneous Bacterial Hydrothorax (SBH)

- SBH may develop in cirrhotic pleural effusion (hydrothorax) with / without ascites.
- Perfom DP (diagnostic paracentesis) of hydothorax.
- If hydrothorax fluid
    - > 250 /mm^3 neutrophils, plus positive culture → treat > 500 /mm^3 but negative culture (in the absence of pneumonia)
- Why ascites matters
    - Once ascites develops in the patient with cirrhosis, the 2 year mortality rate is 50%

- Ascites may become complicated by SBP (spontaneous bacterial peritonitis), which may cause or worsen decompensation.

➢ Clinical

- 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%

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

- Then 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).

Malignant Ascites

- Give 4 causes of **malignancy-related ascites**.
  - Peritoneal carcinoma (1°, 2°)
  - Massive liver metastases
  - Peritoneal carcinomatosis with massive liver metastases
  - Hepatocellular carcinoma

- Malignant lymph node obstruction
- Malignant Budd-Chiari syndrome (tumour emboli in hepatic veins)

Source: Runyon, Bruce A. *Sleisenger & Fordtran's gastrointestinal and liver disease: Pathophysiology/Diagnosis/Management* 2006*:* pg. 1946.
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; HCC, hepatocellular cancer; IVC, inferior vena cava

- Give 4 types of tumors with commonly metastasize to the peritoneum.
  - Adenocarcinoma – GI
    - Stomach
    - Colon
    - Pancreas
  - Lymphoma – Non-GI
    - Ovary
    - Lung
  - Sarcoma

- Give 4 mechanisms by which tumors may cause ascites.

- Peritoneal carcinomatosis
- Extraperitoneal carcinomatosis
  - Hepatic 2º
  - Hepatic 1º (HCC), 2º (metastases)
- Lymph node obstruction
- Budd-Chiari syndrome ± IVC obstruction

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.

SO YOU WANT TO BE A GASTROENTEROLOGIST!

- Give 4 mechanisms by which tumors may cause ascites.
  - Carcinomatosis
    - Peritoneal
    - Extraperitoneal
      - Hepatic 2º
      - Hepatic 1º (HCC), 2º (metastases)
  - Obstruction
    - Lymphatics and lymph node
    - Hepatic vein (Budd-Chiari syndrome) ± IVC obstruction

HEPATORENAL SYNDROME (HRS)

- Definition
  - A functional and potentially reversible form of prerenal azotemia with a cascade of events associated with intense dilation of the splanchnic arterial vasodilation in the setting of cirrhosis or acute liver injury and resulting in profound renal arterial vasoconstriction and progressive renal failure" (Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. *Saunders/Elsevier* 2010, page 1546).
  - Functional renal failure in the person with cirrhosis and ascites
  - Type I, rapidly progressive; type II, slowly progressive
  - Another definition

- In the presence of acute or chronic liver disease
- ↓↓ urinary Na^+
- Baseline ↑ Cr (creatinine) > 1.5 mg/dL (133 μmol/L), or change in serum Cr concentration
- No abnormal urinary sediment < 50 RBC / hpf (no catheter used); protein < 500 mg/day
- Note: hyperbilirubinemia may be associated with granular and epithelial cell casts.
- Oliguria (only premorbid)
- Most have < 500 mL urine per day, but < 400 mL/day
- Diuretics do not cause HRS, they cause diuretic-associated azotemia which improves when the diuretics are stopped.
- Diuretics should be discontinued and intravascular volume expanded with i.v albumin
- If renal dysfunction persists despite above, diagnose HRS
- May be precipitated by
- Previous renal insufficiency
- Bleeding

➢ 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, 25%
- Reduces 3 year survival from liver transplant to 60% versus ~75%, when no HRS
- Cirrhosis, ascites, but no azotemia

  HRS development

1-yr	5-yr
18%	39%

- Acute severe alcoholic hepatitis, and no cirrhosis
  - HRS develops in 28%
  - Risk of HRS is less in PBC
- Some useful figures
  - Cirrhosis plus ascites 2-yr survival rate, of only 50%
  - Diuretic-resistant ascites (develops in ~10%), 6-month survival rate of only 50%, and 1-yr survival rate, 25%

- Ascites, spontaneous bacterial peritonitis and HRS are on different parts of the same pathophysiological spectrum

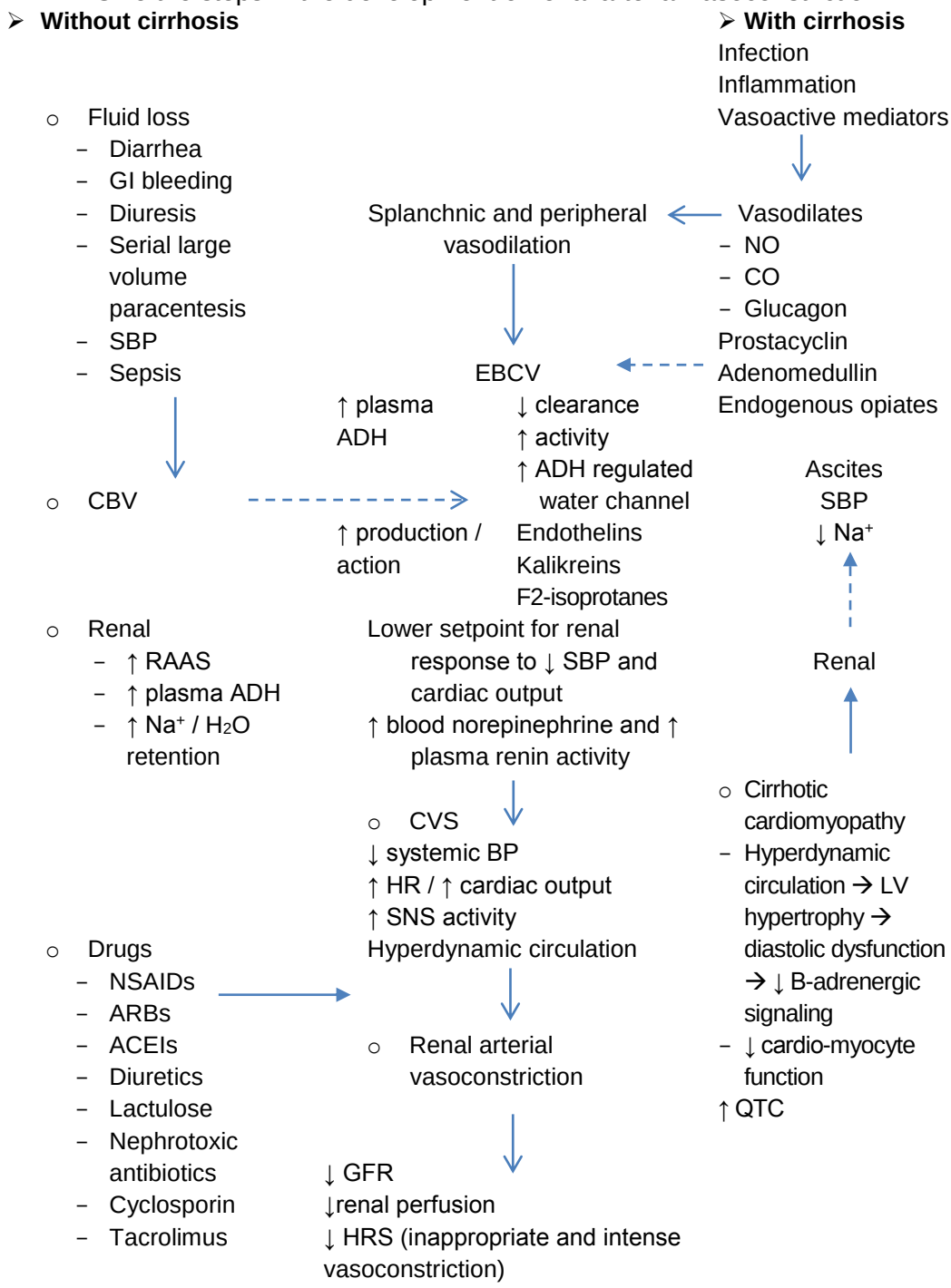
- Pathophysiology
  - Systemic hypotension → activation of renin-angiotensin as well as sympathetic nervous system → renal artery vasoconstriction → ↓ GFR and renal Na^+ excretion

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.
- 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, give norfloxacin 400 mg/day po to ↓ risk of SBP and death.

- Types

- Give the steps in the development of renal arterial vasoconstriction



- Give 5 features to distinguish between Type 1 and Type 2 HRS.

Characteristics	Type 1	Type 2
○ Progression	Fast (< 2 wks)	Slow
○ Serum creatinine	> 2.5 mg/dL	< 2.5 mg/dL (221 µmol/L)
○ Triggers	Bacterial infection (SBP) GI bleeding Surgery	Diuretic resistant ascites
○ ↓ Systolic blood pressure	↓↓↓	↓
○ Adrenal insufficiency with sepsis	Common (80%)	Uncommon
○ Cross-over	No	Yes (HRS 2 → HRS1)

Abbreviation: SBP, spontaneous bacterial peritonitis

- Criteria for diagnosis
  - Cirrhosis with ascites
  - Consider HRS in a patient with cirrhosis and ascites, who has a serum creatinine level of >1.5 mg/dl
  - HRS is a diagnosis of exclusion. Before making the diagnosisof HRS, rule out and treat:
    - Sepsis
    - Shock
    - Vasodilators, NSAIDs
    - Organic renal failure (urine sediment, kidney ultrasound)
  - Absence of parenchymal renal disease as defined by proteinuria <0.5 g/day, no microhematuria (<50 red cells/high powered field), and normal renal ultrasonography
  - Diuretics should be discontinued and intravascular volume expanded with i.v albumin
  - If renal dysfunction persists despite above, diagnose HRS
  - Serum creatinine >1.5 mg/dl (133 mol/L)

- Absence of hypovolemia (from hemorrhage, diarrhea, overdiuresis)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
- No or insufficient improvement in serum creatinine level (remains > 1.5 mg/dL) 48 hr after
  - Diuretic withdrawal
  - Adequate volume expansion with intravenous albumin and 1.5 L of 0.9% saline

Printed with permission: EASL clinical practice guidelines J Hepatol. 2010;53(3):397-417, Table 8.

- Give the major and minor criteria for the diagnosis of the hepatorenal syndrome (HRS), and distinguish this from acute tubular necrosis (ATN).

➢ Major criteria

- Presence of cirrhosis
  - Renal failure (creatinine >1.5mg/dl); if no previous renal impairment, or a serum a ↑ by 50% over baseline
- Lack of improvement in serum creatinine after ≥48 hrs of diuretic withdrawal and volume expansion with 1.5 L of 0.9% saline
- 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

- 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

- Give the laboratory changes which differentiate perenal azotemia and acute renal failure (ARF) from hepatorenal syndrome. (HRS).

Variable	Prerenal azotemia	Hepatorenal syndrome	Acute renal failure
○ Urinary sodium concentration, mEq/L	<10	<10	>30
○ Urine to plasma creatinine ratio	>30:1	>30:1	<20:1
○ Urine osmolality	At least 100 mOsm >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

- Give the reason why a 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.

- 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 DILEMNA:

- Does HRS cause acute tubular necrosis (ATN)?
- The 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:
    - Aminoglycosides
    - Radiocontrast material, e.g. CT contrast
- 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.

➢ Treatment

- 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).
- 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 data for the efficacy of norepinephrine or midodrine, plus octreotide plus albumin.
  - Midodrine
    - Selective alpha-1 adrenergic agonist, acting as a systemic vasoconstrictor

        - 7.5 mg to 15 mg tid, plus
    - Octreotide 100 µg to 200 µg SC tid, plus
    - Albumin infusion, 1 g/kg for volume expansion

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

- 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).

➢ Prevention

- Severe alcoholic hepatitis
    - Pentoxifylline
- Severe cirrhosis
    - Norfloxacin to ↓ 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

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.

- Titrate doses of midodrine and octreotide to maintain MAP (mean arterial pressure) > 15 mm Hg.
- Other agents, **not** established
  - Other pressors
  - Norepinephrine
  - Albumin, by itself
  - Vasopressin analog, terlipressin plus albumin
  - Microprostol
  - NAC (N-acetylcysteine)

- Renal dialysis
  - Dialysis
    - May be useful when there is no response to vasoconstrictors
    - "Bridge" for patient recovery from hepatic injury e.g.
      - Drug-induced liver injury (DILI)
      - Acute liver failure (ALF) which is potentially reversible
    - "Bridge" to transplantation
    - Continuous renal replacement is promising
    - Reinfusion dialysis
  - Liver transplantation
    - For patients who do / do not respond to vasopressin therapy
  - Combined kidney-liver transplantation
    - HRS, non-response to vasopressors, prolonged renal support > 12 weeks
  - Combined kidney-liver transplantation
    - HRS, non-response to vasopressors, prolonged renal support > 12 weeks

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.

- No response to vasopressors

- Renal support (dialysis) beneficial

- TIPS (transjugular intrahepatic portosystemic stent shunt)
  - Use for MELD score < 18
  - Small, short-term benefit
  - 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).

CLINICAL PEARLS:

- Although some cirrhotic patient with ascites may become confused, febrile, and develop abdominal pain ± tenderness, SBP is often asymptomatic
- The rule of thumb is to perform a diagnostic peritoneal tap (paracentesis) routinely in all patients admitted with ascites, or with new onset ascites.

Hepatic Encephalopathy (Aka PSE, Portosystemic Encephalopathy)

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

- Pathophysiology

- Outline the contribution of the small and large intestine, liver, skeletal muscle, kidney and brain in patients with liver failure and HE.

- Small bowel and large intestine

glutaminase (deamination)

glutamine → glutamate + NH_3

← glutamine synthetase (amidation)

- ↑ production of ammonia by

  - urease-producing bacteria in GI tract
  - Proteolytic bacteria
- ↑ gut glutaminase increased in liver disease
- ↑ production of ammonia and glutamate from increased action of intestinal glutaminase on chelating amino acids
- ↑ absorption of glutamate plus NH3

- Liver
  - Portosystemic shunting, by-passing portovenous system with less hepatic detoxification of ammonia via the urea cycle → ↑ NH3
  - ↓ hepatocytes → ↓ hepatocyte detoxification of NH3
  - In presence of hyponatremia, myoinositol falls, with less compensation for ↑ intracellular glutamine

- Skeletal muscle
  - Skeletal muscle normally take up to 50% of NH_3
  - Atrophy of skeletal muscles, in liver disease → ↓ utilization of NH3 (NH3 + glutamate → muscle glutamate, large nuclei and nucleoli, margination of chromatin→ Alzheimer type II astrocytes

- Kidney
  - Increased NH_3 production in presence of hypokalemia

- Brain
  - NH_3 and glutamate normally converted to and detoxified to glutamine by glutamine synthetase in astrocytes
  - In cirrhosis, increased brain blood flow and ↑ blood brain barrier permeability: ↑ brain NH_3 and ↑ glutamate
  - Abnormal form and function of astrocytes → ↓ glutamine synthetase and peripheral type benzodiazepine receptors (PTBR)
  - Increased brain glutamine increases mitochondrial permeability → brain edema
  - Glutamate normally taken up by synaptic excitatory amino acid transporters; reduced glutamate uptake leads to the accumulation of extracellular brain levels of glutamate, with impairment of the glutamatergic neurotransmitter system

- Hyperammonemia activates N-methyl-D-aspartate-nitric oxide-C-guanylate cyclase (NMDA-NO-CGC) signal transduction pathway, impairing memory, learning and sleep
- ↑NH_3 ↑glutamate cross BBB, and causes osteocyte swelling and cerebral edema
- 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
- CNS neurotransmitter disorder in HE

➢ Neurotransmitter system	Findings in HE
○ Glutamate (neuro-excitation)	– ↓ receptors – ↓ glutaminergic function
○ GABA/BZ (Neuro-inhibition)	– ↑endogenous BZs
○ Dopamine/Noradrenaline (motor/cognitive)	– ↓ false neurotransmitters
○ Serotonin (Arousal)	– ↑ serotonin turnover, synaptic defect

Abbreviations: BZ, benzodiazepine; GABA γ-aminobutyric acid

Clinical Tip: Sedation and HE

- Propofol safe in cirrhosis with no Δ cognition
- Midazolam worsens NCT (number connecting time), i.e. ↑ severity of HE score
- Fentanyl or midazolam created greater agitation
- Titrate sedation to point where patient's speech is slurred.

➢ Pathology

- 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

- Diagnosis
  - Clinical examination
    - Memory
    - Writing
    - Sleeping
    - Agitation
  - Scoring systems
    - PSET (portosystemic encephalopathy syndrome test)
    - Psychometric tests
  - Blood concentrations of NH_3
    - Arterial hyperammonemia in 90% of HE
    - 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 NH3 ≥ 200 mg/L predict brain edema and herniation of the brain stem
  - Critical flicker frequency test
  - MR-based techniques
  - EEG abnormalities of bilateral slow wave activity neither sensitive nor specific

- The finding of an elevated serum ammonia concentration is not specific for the diagnosis of hepatic encephalopathy. Give 15 causes of hyperammonemia

- Liver/GI tract
  - Acute liver failure
  - Cirrhosis

- Gastrointestinal bleeding

- Renal
  - Chronic kidney disease

- Inborn errors of metabolism
  - Proline metabolism disorders
  - Urea cycle disorders (e.g carbamyl phosphate synthetase I deficiency, ornithine transcarbamylase deficiency, argininosuccinate lyase deficiency, *N*-acetyl glutamate synthetase deficiency)
- Medications
  - Alcohol
  - Diuretics (e.g. acetazolamide)
  - Narcotics
  - Valproic acid

- Muscle exertion and ischemia

- Blood sampling
  - Tourniquet use
  - High body temperature
  - High protein diet

- Diet
  - Do not restrict dietary protein
  - May need to reduce salt intake to 2 g/day
  - May choose to ↑ intake of K^+-containing foods depending on diuretic use and serum K^+
  - Do not restrict water intake unless serum $Na^+ < 120$ mEq/L

- Cigarette smoking

Adapted from: *Sleisenger and Fordtran's Gastrointestinal and Liver Disease: Pathophysiology/ Diagnosis/ Management*. Ninth edition, 2010, Table 92-1.

- Clinical

There are now thought to be 5 (not 4) stages of HE,

- Give these 5 stages of HE.
  - Stage 0 – NO clinical findings, but abnormal psychometric tests may progress to higher stages of HE (aka MHE, minimal hepatic encephalopathy)
  - Stage 1 – Minor changes in
    - Trivial lack of awareness
    - Euphoria or anxiety
    - Shortened attention span
    - Impaired performance of addition
    - Sleep-wake disorder
    - Tremor
  - Stage 2 – Lethargy or apathy
    - Minimal disorientation of time or place
    - Subtle personality changes
    - Inappropriate behavior
    - Impaired performance of subtraction
  - Stage 3 – Somnolence to semi-stupor
    - Still responsive to verbal stimuli
    - Confusion
    - Gross disorientation
    - Somnolence
    - Incoherence
  - 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 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 the 3 upper motor neuron signs in stage 3 or 4 HE which can be demonstrated without the patient's corporation.
    - Hyperreflexia
    - Clonus
    - Hyperigidity

- Give the precipitating causes ("PAEDI") of Hepatic Encephalopathy (HE).

P ↑ Protein intake, GI bleed → ↑ protein load

A Metabolic alkalosis, alcohol

E Electrolytes, especially ↓ K^+ (hypokalemia alkalosis)

D Drugs
- Benzodiazepine
- Opioids
- Sedatives
- Dehydration

I Infection (including SBP)

Abbreviation: SBP, spontaneous bacterial peritonitis

Minimal Hepatic Encephalopathy (MHE)

- Give the clinical neurological deficits in MHE.
    - Affect/ emotion
    - Behaviour
    - Cognition/ memory/ attention
    - Note: Language and verbal skills are relatively spared in HE

- Give 4 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)

➢ Treatment

Management 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

Identify precipitating cause of hepatic encephalopathy

➢ GI tract
- Gastrointestinal hemorrhage
- Constipation / dietary protein overload
- Poor compliance with lactulose therapy
- Prior anesthesia

Bowel obstruction or ileus

➢ Liver
- Prior portal decompression procedure (e.g. TIPS)
- Superimposed hepatic injury
- Development of hepatocellular carcinoma
- Venous thrombosis

Initiate empiric treatment for hepatic encephalopathy

- Lactulose, oral dose is 1-30 ml twice daily (or higher doses until diarrhea occurs)
- Rifaximin, oral dose of 550 mg twice daily
- Metronidazole, oral dose of 250 mg four times daily
- Vancomycin, oral dose of 250 mg four times daily
- Neomycin, oral dose of 500 mg four times daily (use high doses with caution)
- Sodium benzoate, oral dose 5 g twice daily (not approved for use in the USA)
- Flumazenil (competitive GABA-benzodiazepine receptor antagonist),

(PVT, HAT)
- Dehydration
- Hypokalemia / alkalosis
- Uremia

intravenous injection of 1-3 mg (potentially effective, but very short duration of action)

- Lung
  - Hypoxia
  - Hypercapnia
  - Acidosis
- Kidney
  - Gross electrolyte changes
  - Uremia
- Infection
  - SBP
  - UTI
  - RTI
- Endocrine
  - Hypoglycemia
  - Pancreatic encephalopathy

Abbreviations: HAT, hepatic artery thrombosis; PVT, portal venous thrombosis; RTI, respiratory tract infection; SBP, spontaneous bacterial peritonitis; UTI, urinary tract infection

- Treat precipitants
  - 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 associated zinc deficiency
  - Increased diffusion across BBB – alkalosis
  - Constipation
  - 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%), ↑BS, alkalosis; ↓hypoxemia, thyroid, dehydration

- Drugs (30%)
  - Benzodiazapines
  - Analgesics
  - Interferon
  - Alcohol
  - NSAIDs
  - Acetaminophen
  - Excess use of diuretics (producing ↓ K^+)
- Surgery shunting, anesthetic, TIPS
- Liver decompensation, HCC, PVT
- Surgery

- Give the pathophysiological explanation why hypokalemia resulting from over-aggressive therapy for ascites with diuretic may precipitate the development of HE (hepatic encephalopathy).
  - Hypokalemia (low serum or extracellular K^+) causes renal intracellular K^+ to move into the extracellular space.
  - The loss of K^+ from the intracellular space of the kidney causes H^+ to move from the blood into the renal cells, causing hypokalemic alkalosis of blood
  - The intracellular acidosis causes ↑ synthesis of NH_3 in the proximal tubular cells.
  - The hyperammonemia contributes to the development of HE.

"We know what we are, but know not what we may be."

William Shakespeare

- Give 2 clinical examples in which the ratio of spironolactone 00 mg to furosemide 40 mg per day may need to be changed.
    - Development of hypokalemia may occur, e.g. in associated with severe alcohol hepatitis.
    - Development of hyperkalemia may occur, e.g.
        - In association with
            - Hypoperfusion
            - ATN (acute tubular necrosis), or
            - HRS (hepatorenal syndrome)

➢ Lactulose (beta-galactosidofructose), lacitol beta-galactosidosorbitol (traps NH_3) - enter colon, broken down by colonic bacteria to lactic acid, acetic acid 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, ↑ stool volume, loss of nitrogen compounds
    - Helps symptoms
    - No change in mortality rate

➢ Antibiotics

- ↓ proteolytic microbiotics → ↓ NH_3
- Rifaximin, oral dose of 550 mg twice daily
- Vancomycin, oral dose of 250 mg four times daily
- Neomycin, oral dose of 500 mg four times daily (use high doses with caution)

- Diet
  - High calorie, high protein diet
  - Short term (<72h) protein restriction may be considered in severe HE
  - No long-term protein restriction (causes muscle wasting)
- Modifiy glucose absorption
  - Acarbose
    - ↓ α-glucosidic
    - ↓ glucose absorption → ↑ SAC charolytic bacteria and ↓ proteolytic microbiotica
    - ↓ NH_3
  - LOLA (L-ornithine-L-aspartate) activate the urea cycle and ↑ NH_3 clearance
    - Improves grade 3 or 4 HE in ~ 25% of patients
- Neurotransmitters
  - Flumazenil (a competitive GABA-benzodiazepine receptor antagonist) or
  - Bromocriptine
- ICP monitoring for HE used in many centres (to monitor ICP)
  - Intracranial pressure (ICP) monitoring, transcranial Doppler, jugular venous oximetry
  - Manage lactic acidosis and sepsis
  - 45˚ elevation of head of bed
  - Moderate hypothermia to reduce
    - ICP and cerebral blood flow (CBF)
    - Arterial NH_3
    - Cerebral NH_3 uptake
- Manage circulatory effects
  - Fluid management, consider CVP monitoring
  - Perform short synacthen test
    - Give GCS if adrenal insufficiency is present
  - Inotropes
    - Terlipressin (a vasopressin analog)
    - Norepinephrine

- Albumin infusion

- ‘Biotics (pre-, pro- and synbiotics)
  - ↓ urea producing luminal bacteria
  - ↑ bacterial NH_3 utilization
  - ↓ pro-inflammatory response
  - ↓ gut permeability
  - ↓ bacterial translocation

- 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
  - ↑ lactobacillus spp., ↓ urease-containing bacteria, ↓ NH_3 production by replacing urease-positive bacteria
  - ↓ production of potentially toxic SCFA (proprionate, butyrate, violerate)
  - Removes shunted (non-detoxified blood)
- Driving license – psychometric testing to detect minimal hepatic encephalopathy

Adapted from: Fitz GJ. *Sleisenger & Fordtran’s Gastrointestinal and Liver Disease: Pathophysiology/Diagnosis/Management* 2006 pg. 1971-1972; Garcia Tsao, et al. *The American Journal of Gastroenterology* 2009; 104: 20; and Holstege A, et al. *Best Practice & Research Clinical Gastroenterology* 2007; 21(3): pg. 541.

- Prognosis

- Give the approximal survival rate and etiological factors for the 3 types of hepatic encephalopathy (HE) (acute liver failure, cirrhosis with precipitant, and chronic HE).

Type of HE	Approximate Survival Rate	Etiological factors
○ Acute liver failure	~ 20%	– Hemostasis – 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 (including TIPS) – ↑ Dietary protein intake – Intestinal bacteria

"Hope is the origin of all humanity."

Grandad

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".

AMEBIC LIVER ABSCESS

- When to suspect amebic liver abscess
  - ↑ AP, ↑ leukocytes without eosinophilia
  - Strong male predominance
- When to suspect poor prognosis
  - ↑ bilirubin
  - ↓ albumin
- Diagnosis
  - Serology positive in 95% (after only 1 week of infection)

- CT scan
  - Elevated right hemidiaphragm (50%)
  - Adhesions destroy the costophrenic angle
  - Solitary
  - Lesions
    - Large, round lesion
    - Usually right lobe of liver
    - Low attention (dark)
    - Enhancing rim of hepatic tissue
    - “anchovy paste” aspirate

- Give 3 reasons why percutaneous biopsy / aspiration of a suspected amebic liver abscess is generally **contraindicated**.
  - Right Lobe
    - Subcapsular peritonitis
  - Left lobe
    - Extension to
      - Peritoneum
      - Pleural space
      - Pericardium

- Give 3 reasons when it may be necessary to accept the above potential complications, and or aspirate 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.

Liver Parasites

Buzzwords

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

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

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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

Treatment alert

- Metronidazole
  - To treat amebic liver abscess
- Paromomycin
  - To prevent luminal colonization and reinfection

BENIGN HEPATIC TUMORS

Hepatic Adenoma

- Associated with OCAs, anabolic steroids
- May perforate → hemoperitonium
- May undergo malignant transformation
- May regress as the offending drug is stopped
- Pathology
  - 90% single, 10% multiple
  - Circumscribed, but not encapsulated
  - Vascular channels of various sizes
  - Thrombi in vascular channels
  - Mast cells within hemangiomas
  - Sclerosis
  - May be associated with glycogenesis
  - May be associated with focal nodular hyperplasia (FNH)
  - Adenoma
    - Non diagnostic
    - Pre contrast: Hypo or isodense
    - Irregular enhancement
    - Delayed peripheral arterial enhancement during venous phase
    - Irregular enhancement with delayed washout
    - ↓ uptake compared to surrounding liver
  - Adenoma - heterogeneous, hemorrhage, fat, necrosis, impaired arteriole (no bile duct) “feeding” lesion

Angiosarcoma

- Aggressive tumor
- Examples of causative drugs
  - Anabolic steroids
  - Thorotrast

Cavernous hemangioma

- 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

- Caused by
  - Congenital malformation, or
  - Hamartomatous change
  - Enlarges under influence of estrogens / pregnancy
  - May be associated with focal nodular hyperplasia (FNH)
- 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)

- In the context of a giant (> 5 cm) hepatic cavernous hemangioma, give the meaning of KMS (Kasabach-Merritt Syndrome).
  - KMS is against hepatic hemangioma plus DIC (disseminated intravascular coagulopathy)

You are sensible and don't want to perform a percutaneous biopsy in a patient with a large hypoechoic liver lesion on abdominal ultrasound / suggestive of a cavernous hemangioma.

- Give the findings of diagnostic imaging tests which suggest that a hepatic mass is a cavernous hemangioma.
  - Hemangioma – nodular, no washout at periphery; RBC scan, triphasic CT scan (arterial phase); MRI
  - 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

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),
  - Common congenital malformation of the liver vasculature, with hyperplasia of hepatocytes around the vascular abnormality, leading to a central scan

- Demography
  - Focal Nodular Hyperplasia (FNH) is 2nd only to hemangiomas as a cause of a benign tumor of the liver.
  - More common in females

- May be associated with
  - Adenomas
  - Cavernous hemangiomas (20%)
  - HHT (hereditary hemorrhagic telangiectasia)
  - Epithelial hemangioendothelioma
  - Peliosis
  - Not caused by OCA (oral contraceptive agents), but may enlarge under the influence of OCA

- Pathology
  - Usually single (multiple in 30%)
  - Malformed blood vessels no central arterial scar
  - Static / very slow growth
  - Bile duct proliferation

- Diagnostic Imaging
  - Ultrasound
    - Variable appearance
    - Well-defined borders
  - Contract-enhanced CT
    - Single lesion
    - Subcapsular
    - Hypodense or isodense
    - Hypodense central scar
    - Hypodense delayed imaging
    - Arterial phase
      - Homogenous enhancement
    - Enhancement of mass during arterial phase
    - Fibrous septa
    - Centre
      - No enhancement
      - Central stellate scar
      - Hemorrhage / necrosis
  - MRI
    - T1 low signal
    - T2 hyperintense signal with central scar
    - Homogenous arterial enhancement
    - Hypodense central scar
    - Contrast accumulates in scar on delayed T1
    - Equal or ↑ uptake compared to surrounding liver

- For hepatic hemangioma focal nodular hyperplasia and adenoma, give the diagnostic features on 4 types of diagnostic imaging.

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

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

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

- Give the diagnostic imaging characteristics on CT/MRI/PET scan/nuclear medicine of hemangioma, 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 scan), 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); renal, thyroid, sarcomas, melanomas, neuroendocrine (islet, carcinoid, pheochromocytoma)

Adapted from: Hussain SM, and Semelka RC. *Magn Reson Imaging Clin N Am* 2005;13(2):255-75.

➢ Differential

- Give an approach to distinguish between focal nodular hyperplasia (FNH) and hepatic adenoma (HA).

Characteristic	FNH	Adenoma
○ Gender	Female	Female
○ Hormone therapy	No	+++
○ Symptoms	Rare	Occasional
○ Multiple	About 30%	12-30%
○ Pathological associations	Hemangiomas	Glycogenoses, androgens, peliosis
○ Central arterial scar	Yes	No
○ Growth	Static*	If stimulated (estrogens, OCA)
○ Treatment	Conservative	Resection if symptomatic
○ Malignant potential	-	+

*the telangiectatic subtype of FNH is associated with estrogen use

- 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	-	+
○ Diagnostic imaging		
- Central scar	+	+
- Calcification	-	+
- ↓ Intensity (dark, hypointense) on T2-images of MRI	-	+
- Progressive enlargement	-	+
○ Pathology		
- Large, granular cells	-	+
- Pale bodies	-	+
- Bands of fibrosis	-	+
- Bile duct proliferation	+	-
- Malformed blood vessels in central scar	+	-

- Treated
  - Surgical resection — Depends +

Nodular Regenerative Hyperplasia (NRH)

- Injury to the hepatic vasculature from autoimmune disorders, myeloproliferative syndromes and from antineoplastic medications results in remodeling of surrounding liver tissue into a nodule which contains liver tissue and no fibrosis

- The nodules of regenerative liver tissue may compress adjacent hepatic vasculature, leading to
  - Non-cirrhotic portal hypertension, and
  - Compress bile ducts, leading to jaundice
  - Regenerative nodules
  - Around portal triads without fibrosis
- MRI is the best diagnostic imaging test to distinguish HCC from NRH or a large cirrhotic nodule

Abbreviation: NRH, nodular regenerative hyperplasia

- Associated conditions
  - Hematological
    - Hypercoagulable states
    - Myelopreliferative disorders
    - Lymphoproliferative disorders
  - Drugs
    - Azathioprine
    - Chemotherapeutic agents
  - Treatment
    - Stop offending drug
    - Treat associated hematological drugs

"Teaching is the art of acting.

I don't teach Gastro', I teach about myself."

Grandad

SO YOU WANT TO BE A HEPATOLOGIST!

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

- 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.

Specific patient with ascites despite salt restriction plus complaint in taking of 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.

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

➢ Mass <1 cm	○ Diagnosis ○ Follow up	○ Low likelihood of being HCC, therefore no specific diagnostic tests ○ Repeat imaging study every 3 months ○ If no growth in 1-2 years, no HCC; continue screening every 6 months ○ If growth, treat as HCC		
➢ Mass 1-2 cm	○ Diagnosis	○ 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 ○ Follow up after biopsy	○ One dynamic imaging study (US, CT scan, or MRI) ○ Biopsy confirms HCC ○ Non diagnostic biopsy	○ Typical vascular pattern ○ Atypical vascular pattern ○ Treat as HCC ○ Repeat imaging study every 3 months: ○ If no growth in 1-2 years- no HCC ○ If growth, treat as HCC	○ Treat as HCC ○ Biopsy of mass

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

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

HEPATOCELLULAR CANCER (HCC)

- Demography
  - 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 with the part 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

Asians	11
Hispanics	6.8
African Americans	4.2
Caucasians	2.6

➢ Risk factors

- Give 15 risk factors for developing HCC.
  - Patient
    - Africans > 20 years (HBV^+)
    - Asian males> 40 years (HBV^+)
    - Asian females >50 years (HBV^+)
    - HBV viral load > 10^5 copies/mL (20,000 IU/mL)
    - Family history of HCC
    - Obesity (male)
    - Diabetes mellitus
    - Intake of
      - Alcohol
      - Tobacco
      - Aflatoxins
    - Tobacco, marijuana smoking
    - Oral contraceptive agents (OCAs)
    - Some persons with HCC have no known risk factors

- Hepatitis B carriers
  - Asian males >40
  - Asian females >50
  - Family history of HCC
  - African >20 years
  - All cirrhosis
- Non hepatitis B cirrhosis
  - Hepatitis C
  - Alcoholic cirrhosis
  - Hereditary hemochromatosis
  - Primary biliary cirrhosis
  - Possibly: alpha 1 antitrypsin; NASH; autoimmune hepatitis (AIH)

Adapted from: El-serag H.B. *2009 ACG Annual Postgraduate Course*: 39-43.

- Give 10 **risk factors for developing HCC** in persons with HBV infection.

➢ Patient

- Race, region of the world, gender (including association between HCC and HBV infection)
  - Race (African > Asian men > Asian women)
  - Asian or African race

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

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

- Age > 45 yr
  - Young age of acquisition of HBV infection
- Alcoholism
  - ↑ risk of HCC by alcohol itself when taking > 60 g/day, and ↑ further (2x) for alcohol plus HBV or HCV
- Smoking cigarette

➢ Liver

- First degree relative with HCC
- Presence of cirrhosis of any etiology

- 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

(clearance of HBV [i.e. HBsg-pos → HbsAg-neg] dose not preclude development of cirrhosis or HCC; just reduces the risk)

- HBsAg-pos; HBeAg-neg (inactive carriers) 324
- HBsAg-pos, plus HBeAg-pos 1169
  - 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

Abbreviation: SIR, standardized incidence ratio

  - 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

➢ ↑ AFP (alpha-fetoprotein > 2 mcg/L)

➢ Diabetes/metabolic syndrome

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

Abbreviation: RR, relative risk

➢ Screening

- o Risk stratification, including HBV and HCV
- o 96 months AFP (alpha-fetoprotein) and abdominal ultrasound over 5 years improves survival from HCC in HBV-positive patients in China (42-5). Most of the detected HCC in the screened group were detected at an early stage; with 3 year survival rates after HCC resection of 53% in the screened group versus none in the non-screened group
- o Improved survival from HCC screening depends of course on the availability of effective therapy for the early detected lesions
- o HCC screening in persons awaiting liver transplantation is cost-effective

Abbreviation: AFP, alpha-fetoprotein; HCC, hepatocellular cancer

- Without cirrhosis
  - Chronic HBV infection (even without cirrhosis)
  - Chronic HCV infection
    - Japan
    - All others, HCV cirrhosis
    - HCV stage 3 fibrosis
  - NAFLD (non-alcoholic fatty liver disease); includes non-cirrhotic NAFLD
  - Autoimmune hepatitis
  - Toxins
    - Alcohol
  - Hepatic adenoma
  - Hemochromatosis

- Give **3 precursor lesions** of HCC (hepatocellular cancer) in the patient with hereditary hemochromatosis.

  - Males with iron overload and advanced fibrosis
  - Dysplastic lesions
  - Proliferative lesions
  - Increased number of iron free foci (IFF, >50% at risk to develop HCC)

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

  - 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

- 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

SO YOU WANT TO BE A HEPATOLOGIST!

You are aware of the many factors which increase the risk of developing HCC. Let us consider the effects of treating the HBV infection, and of using statins or drinking coffee.

- Give the pharmacological conditions under which the statement is not correct that treatment of chronic HBV using interferon or nucleos(t)ide derivatives reduces the risk of HCC by about 60%.
    - The reported 60% reduction in the incidence of HCC is not enjoyed by chronic HBV patients who develop nucleos(t)ide resistance.
- Give the effect of statins on the development of HCC, even in HBV infected persons who have a normal cholesterol concentration.
    - As the cumulative daily dose of statins is increased, there is a decline in the risk of HCC.
- Give the deleterious effect of drinking 2 or more cups of coffee a day on the development of HCC.
    - None! In fact, this amount of coffee reduces the risk of the development of HCC by 43%, both in persons with or without associated liver disease.

HCC in HCV

- 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
  - Degree of hepatic fibrosis
  - Associated iron overload (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 4 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.

➢ 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

<u>Paraneoplastic syndromes in HCC</u>

- Give 10 paraneoplastic syndromes associated with hepatocellular carcinoma.

  - CNS
  - Neuropathy

o MSK	– Carcinoid syndrome – Hypertrophic osteoarthropathy – Osteoporosis – Polymyositis – Thrombophlebitis migrans
o Endocrine	– Sexual changes- isosexual precocity, gynecomastia, feminization – Hypoglycemia – Pre-IGF II (insulin-like growth factor) – PTHrP (parathyroid hormone related peptide) – Hypercalcemia – Thyrotoxicosis
o CVS	– Systemic arterial hypertension
o Skin	– Porphyria
o GI	– Watery diarrhea syndrome
o Hematology	– Polycythemia (erythrocytosis) – Erythropoietin (or erythropoietin-like substance)

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

- Diagnostic imaging (DI)
  - 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 4 non-histological diagnostic criteria for HCC (hepatocellular cancer).
  - Hepatic mass on ultrasound in cirrhotic
  - Focal lesion > 2 cm with evidence of cirrhosis (if < 2 cm, on 2 imaging modalities: CT angiogram
  - Arterial hypervascularization and venous washout; MRI (contrast enhanced ultrasound; MRI – triphasic (hyper T_2, 150-T_1)
  - Sulphur colloid scan – old (Kupffer cells positive in FNH)
  - AFP > 200 ng/ml (normal AFP does not rule out HCC)
  - Non-cirrhotic HBV, HCV (Japan), hemochromatosis, αAT deficiency

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

  - Diagnosis usually in a cirrhotic and made, without a liver biopsy
  - A non-invasive diagnosis of HCC in a cirrhotic
    - 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

  - Ultrasound
    - Algorithm for mass / nodule in cirrhotic liver on abdominal ultrasound (US) in persons at risk for HCC

Size, diameter	Follow-up
< 1 cm	US every 4 months for 1 year, then every 6 months long-term
> 1 cm	4-phase CT / dynamic contrast enhanced MRI

- Give the imaging criteria applied for confirming HCC in patients with cirrhosis and a nodule detected by 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**

➢ 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

	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.

- CT
  - Arterial enhancement (hypervascular, supplied by hepatic artery) and washout, for HCC, sensitivity is 90% and specificity is 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

- Give 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 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)

➢ 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)

CLINICAL TIP
When the HCC enlarges these diagnostic imaging may change.
- 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 vein

"Sometimes you have to burn the bridge behind you"

James Calvin

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

➢ Treatment

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

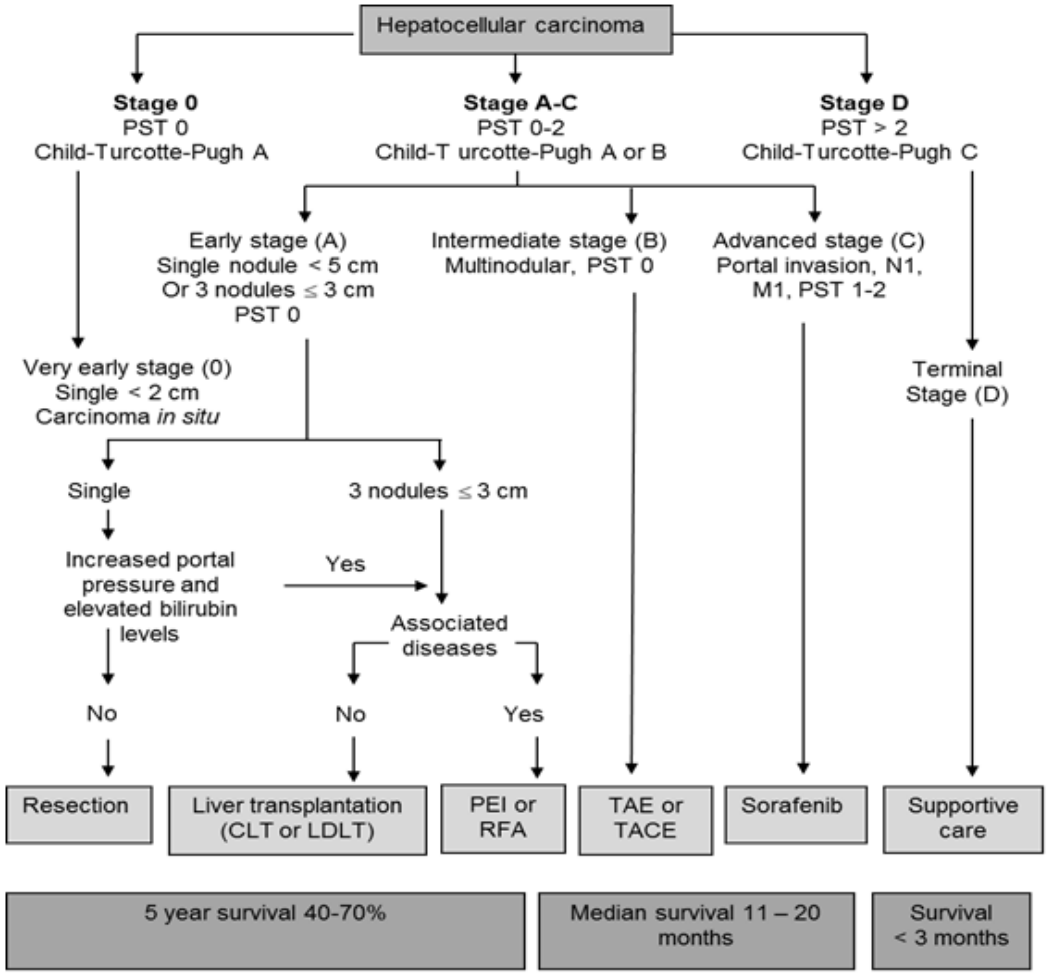
➢ CTP A, PS-O	○ Single HCC <2cm	○ HVPG <10mm Hg and bilirubin < 1.5 mg/dL ○ Varices/collaterals or HVPG ○ >10 mm Hg or bilirubin >1.5mg/dl	○ Surgical resection ○ Live transplant evaluation ○ RFA/PEI
➢ CTP A-B, PS, 0-2	○ Single HCC 2-5 cm	○ HVPG <10mm Hg and bilirubin <1.5 mg/dL ○ Varices/collaterals 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.

- Staging

Algorithm for staging and treating patients diagnosed as having hepatocellular carcinoma, based on the Barcelona Clinic Liver Cancer guidelines.



Abbreviations: CLT, cadaveric liver transplantation; LDLT, live donor liver transplantation; PEI, percutaneous ethanol injection; PST, performance status test; RFA, radiofrequency ablation; TACE; transarterial chemoembolization; TAE, transarterial embolization.

Printed with permission: Cabibbo et al. *Nature Clinical Practice Gastroenterology and Hepatology* 2009;6(3): 159-69; Bruix J, Sherman M. Hepatology. 2011; 53(3): 1020-2.

- Several Staging systems available to stratify HCC, eg.
  - Barcelona
  - Milano / Mazzoferro

    - TNM / AJCC
    - AHPBP
  - Tumor
    - No single system covers all HCC patients
  - To stratify the patient
    - MELD (Model for end-stage liver disease)
    - Childs-Pugh staging (C-P)
  - Tumor
    - Number and size of nodules
    - Presence/absence of macrovascular invasion
    - Presence/absence of extrahepatic spread
  - Patient
    - Child-Turcotte-Pugh status

Abbreviation: ECOG, Eastern Cooperative Oncology Group.

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.

- Compare and contrast the prevention and treatment of HCC in persons with HBV and HCV infection.

	HBV	HCV
○ New infection	– Neonatal vaccination	▪ General infection control
○ Existing infection	– Antiviral therapy (suppression) – Nucleos (t) ide analogues, or interferon	▪ Antiviral eradication) ▪ Protease inhibitor (PI), or ▪ Interferon plus ribavirin

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.

Useful background: The **Okuda staging system** of HCC.

Criterion	Cut-off
○ Tumour size	>50% (largest cross-sectional area of tumour to largest cross-sectional area of liver) = positive <50% = negative
○ Ascites	Clinically detectable = positive Undetectable = negative
○ Serum albumin	< 3g/dL = positive > 3g/dL = negative
○ Serum bilirubin	< 3g/dL = positive > 3g/dL = negative
○ Stage	
– I	No positive criterion
– II	positive criteria
– III	Three positive criteria

Printed with permission: Nguyen MH, and Keeffe EB. *Best Practice & Research Clinical Gastroenterology* 2005;19(1):164.

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	Complete response
< 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

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- 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
< 2	100%
< 3	70% to 80%
> 3	50% to 60%

- Local recurrence

< 3	10% to 33%
> 3	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 5 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: 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 5 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 the unfortunate adverse effect of 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
  - The benefit is small, with an extent of median survival by ~7 month (4.6 month to 11.6 month).
  - Suggested combinations (Stuart KE, UpToDate, 2012)
    - 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 IFNa.
    - 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 4 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 5 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)

- 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-year. 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%

SO YOU WANT TO BE A HEPATOLOGIST!

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.
  - Size

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.

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.

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, such as
    - 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

- Laboratory
  - 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.)
- Abdominal ultrasound
  - Sensitivity, > 60%, specificity, > 90%
- 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

➢ Prevention

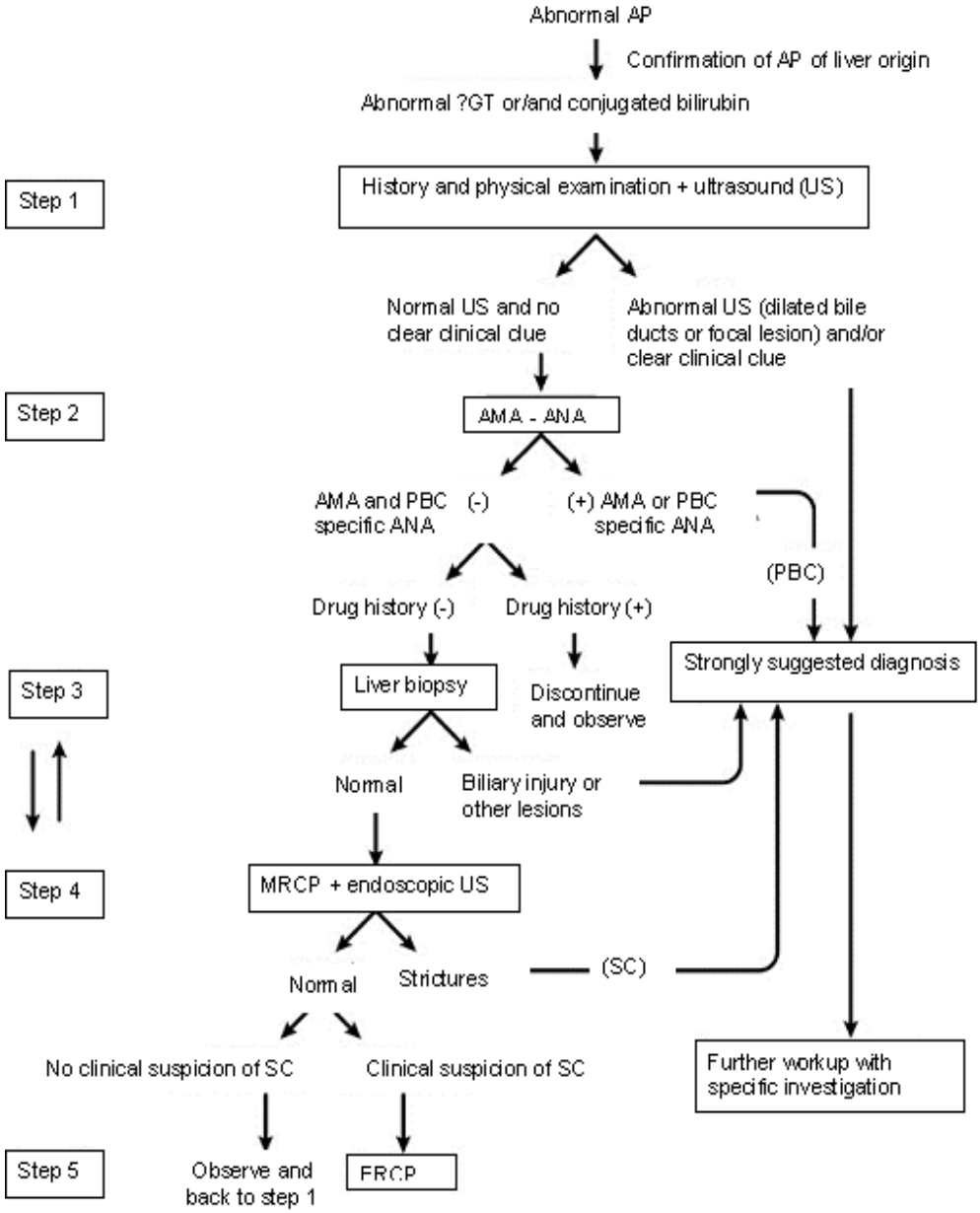
- Give 5 steps to reduce the incidence of HCC.
  - Prevent and treat HBV and HCV, including
    - Immunization programs for HBV
    - Safe injection practices
    - Surveillance programs for HCC
  - Change lifestyle
    - Alcohol
    - Smoking
    - Obesity
    - Diabetes
  - Avoid
    - Alpha toxin
    - High intake of red meat/saturated fats
    - Betal nuts
  - Improve quality of drinking water

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).

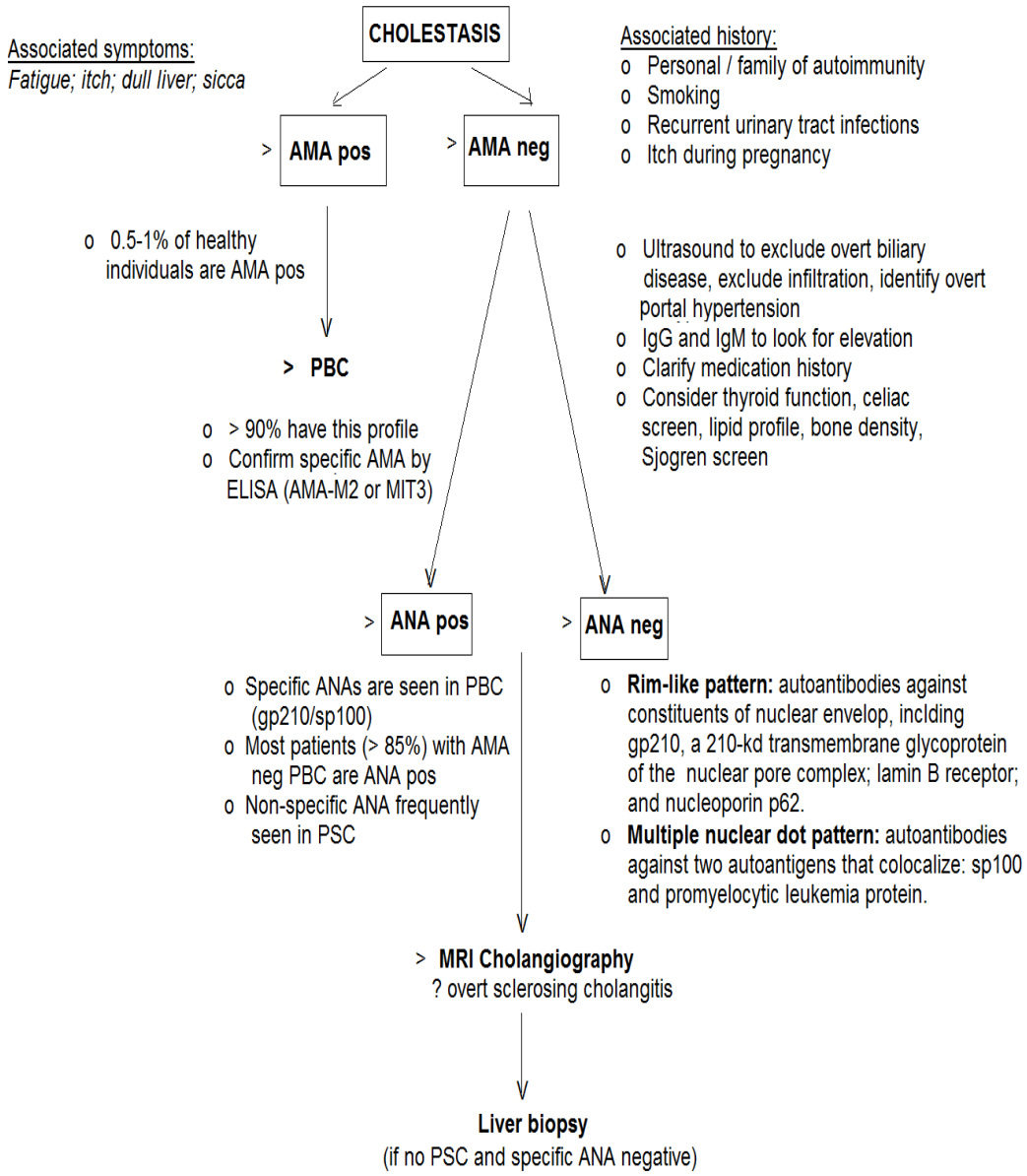
CHOLESTATIC LIVER DISEASE

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.

- Laboratory
  - Suggested flow chart for investigating cholestatic patients



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

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 immunoabsorbent) 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

➢ Pathology

- 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
  - 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

"When you are transparent, there is no place to hide."

James Calvin

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).

- 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

- 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.

Tricks 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.

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 12 examples of chronic benign biliary disorders involving the intrahepatic, extrahepatic, and combined intra- and extrahepatic ducts (big duct abnormalities), which may mimic PBC.
  - ○ Congenital
    - Alagille syndrome (and nonsyndromatic)
    - Cystic fibrosis
    - Duct plate abnormalities
    - Choledochal cysts
  - ○ Infectious
    - Cytomegalovirus
    - Biliary sepsis
    - Parasites
    - HIV (intrahepatic), AIDS cholangiopathy (extrahepatic)

- Infiltrative
  - Cholangiocarcinoma
  - Histiocytosis X
  - Lymphoma
  - Mastocytosis
- Ischemic
  - Thrombosis of hepatic artery
  - Paroxysmal nocturnal 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

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

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

Finding	PBC	AIH
○ Gender	F>M	F>M
○ Priominent 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

o 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)
o Nutrition	- Fat soluble vitamins
o 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

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.

- 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 7 beneficial outcomes for the use of UDCA in PBC.

Probability of Developing Cirrhosis When UDCA used for PBC

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

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

- Liver transplantation (LT)
  - 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.

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 ▪ Cholangitis ▪ Drug-induced liver injury (DILI) ▪ Acute cellular rejection ▪ Biliary obstruction ▪ Graft-vs.-Host Disease (GVHD)

➢ Exclusion of differential diagnostic considerations

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

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

PRIMARY SCLEROSING CHOLANGITIS (PSC)

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

- Demography
  - Incidence – 1/105 per year
  - Prevalence – 10/105
  - The prevalence of PSC is 20.9 and 6.3 per 100,000 men and women, respectively.

- 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
      - Hepatic allograft rejection
      - Hepatic graft-versus-host disease (after bone marrow transplantation)
      - Cystic fibrosis
      - Overlap with PBC
      - May be difficult to distinguish from AIH (PSC may have lymphocytic interface hepatitis)

    - Bile ducts
      - Cholangiocarcinoma
      - Choledocholithiasis
      - Stricture

        - Biliary parasites
        - Recurrent pyogenic cholangitis
        - Fungal infection
        - Cholangitis
    - Pancreas
        - Chronic pancreatitis
        - IgG4-associated cholangitis (IAC), with or without IgG4-associated pancreatitis
- Post-liver transplantation (fibro-intimal hyperplasia)
- Systemic diseases with fibrosis
    - Retroperitoneal fibrosis
    - Riedel thyroiditis
    - Mediastinal Fibrosis
    - Pseudotumour of the orbit
    - Inflammatory pseudotumour
    - Peyronie's disease
    - Chronic sclerosing sialadenitis
- Autoimmune or collagen vascular disorders
    - Systemic lupus erythematosus
    - Systemic sclerosis
    - Type I diabetes mellitus
    - Rheumatoid arthritis
    - Sjögren's syndrome
    - Autoimmune hemolytic anemia
- Kidney
    - Membranous nephropathy
    - Rapidly progressive glomerulonephritis

- Infections
  - Biliary TB
  - HIV (CD4+ T lymphocytes < 100 / mm3)
    - AIDS cholangiopathy
    - Cryptosporidium
    - Microsporidium
    - CMV
- Inflammation
  - Sarcoidosis
  - Hypereosinophilic syndrome
- Immunodeficiency diseases
  - Congenital immunodeficiency
  - Combined immunodeficiency
  - Dysgammaglobulinemia
    - X-linked agammaglobulinemia
  - Acquired immunodeficiency
    - Selective immunoglobulin A deficiency
    - Acquired immunodeficiency syndrome (HIV/AIDS)
    - Angioimmunoblastic lymphadenopathy
- Congenital abnormalities
  - Caroli 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

o 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.

➢ Pathology

o 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 20% large-duct PSC 10% cholangiocarcinoma

o 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)

- Laboratory

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

Antibody	Prevalence
Anti-neutrophil cytoplasmic antibody	50%–80%

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

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 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.

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 negative
      - Negative Lewis antigen status
    - False positive
      - Choledochalithiasis
      - 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)

➢ 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	- Intrahepatic ducts smoothly tapered and narrow
○ Diffuse segmental strictures	▪ Lymphocytic interface may be hard to distinguish from AIH (autoimmune hepatitis)
○ Dominant strictures	▪ Diffusely thickened, fibrotic wall
○ Intrahepatic duct "pruning" (↓ arborisation) → "beading"	▪ 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

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

➢ IBD and PSC vs IBD without PSC

- Give 10 characteristics of inflammatory bowel disease (IBD) associated with primary sclerosing cholangitis (PSC).
  - More R-sided colitis and rectal sparing

- More CRC, puchitis, backwash ileitis
- Rectal sparing
- Extensive colitis
- Right-sided predominance of inflammatory activity
- Often mild or quiescent course
- Clinical course of PSC + IBD
  - Independent
  - Colectomy does not affect PSC
- ↑ risk of colorectal neoplasia
- ↑ risk of pouchitis in patients undergoing proctocolectomy with IPAA
- Backwash ileitis
- ↑ risk of peristomal varices in patients undergoing proctocolectomy with ileostomy
- After liver transplantation for PSC
  - UC may still develop
  - HGD / CRC may develop
    - HGD may already have been present
    - HGD may develop following diagnosis of UC
- UC → panproctocolectomy → PSC may develop de novo
- PSC → liver transplantation → UC may develop de novo, or PSC may recur
  - Note: That's why annual colonoscopies may still be needed in PSC patients who do not (yet) have UC.
- Perform annual colonoscopy in UC + PSC

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

Adapted from: Chapman R, et al. American Association for the Study of Liver Diseases. Diagnosis and management of primary sclerosing cholangitis. Hepatology. 2010;51(2):660-78.

- The high mortality in PSC (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 8 **biliary tract complications** in PSC.
    - Gallbladder tumors (in 41%)
        - Current guidelines recommend an annual screening ultrasound for gallbladder cancer in patients with PSC, and a cholecystectomy once a gallbladder polyp is detected regardless of size.
    - Gallbladder polyps → cancer
        - Gallbladder polyps < 8 mm on ultrasound have a low likelihood of being malignant in non-PSC persons.
    - Cholelithiasis (in~ 25%)
    - Choledocholithiasis in ~25%)
    - Cholangitis
    - Multiple strictures
    - Single / strictures
    - “dominant” stricture (> 1.5 cm)
        - Intrahepatic > 10 mm in length
        - Extrahepatic, > 15 mm)
    - Cholangiocarcinoma (in ~ 10%)
    - Cirrhosis, and its complications
    - Cholecystectomy
        - Use the Child-Pugh score to risk-stratify patients with PSC who undergo a cholecystectomy.
        - Primary sclerosis cholangitis (PSC) with or without cirrhosis have a high morbidity rate following a cholecystectomy that is comparable to patients with cirrhosis from other causes.

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

- Prognosis
  - This high mortality in PBC (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.

	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

- 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:	▪ Solitary anastomotic stricture
- Intrahepatic and/or extrahepatic strictures*	▪ Ischemic strictures
- Beading and irregularity of bile ducts	▪ Bacterial or fungal cholangitis with strictures
○ Compatible Histopathology	▪ Chronic ductopenic rejection
- Fibrous cholangitis and/or	▪ ABO incompatibility between donor and recipient
- Fibro-obliterative lesions with or without ductopenia, fibrosis or cirrhosis	▪ CMV infection
- Interface hepatitis	▪ 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.

"The man who follows the crowd will usually get no further than the crowd. The man who walks alone is likely to find himself in places no one has ever been."

Alan Ashley-Pitt

PREGNANCY AND THE LIVER

- Incidence
  - 1/200
    - 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

- For 8 liver enzymes/ tests of liver function, give which increase, decrease, or remain unchanged in normal pregnancy.

- Unchanged
  - AST, ALT
  - INR
  - Bilirubin
  - GGT

- 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 4 physiological mechanisms which contribute to the altered metabolism of some drugs during pregnancy.
  - ↑ maternal blood volume (50%)
  - ↓ maternal serum albumin concentration (20%)
  - Progesterone → proliferation of SER
  - Estrogen → proliferation of RER
  - ↑ cytochrome P-450 gene products
  - Increased maternal nitric oxide (NO) release during pregnancy causes maternal vasodilation, ↓ systemic vascular resistance, mean arterial blood pressure, reduced responsiveness to vasoconstrictors, resulting in maternal cardiac output rising 30-50%, sixth activation of the rennin-angiotensin system, and increased GFR as well as renal blood flow.

- 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	Not recommended	-
Methotrexate	X	**Contraindicated**	
Metronidazole	B		
Octreotide*	B		+
Penicillamine	**D**	**Significant embryopathy**	-
Ribavarin	**X**	**Contraindicated**	**+**
Thalidomide (IBD)	**X**	**Contraindicate**	
Trientine	C	Alternative to penicillamine	-
Ursodiol (UDCA)	B	Low risk	+

* Octreotide is useful to stop the bleeding from esophageal varices (EV) in males and in non-pregnant females, but in the setting of a pregnant woman with bleeding EV, infusion of octreotide may result in ischemia of the uterus, and the induction of premature labor, so do not use.

Note: Avoid the “X” medications for 6 months before conception.

Printed with permission: Katz PO. 2008 ACG What’s New in Pharmacology Course: pg. 50.

- Give 3 medications used in gastroenterology and hepatology which have an FDA (food and drug administration, USA) "X" category of fetal risk.
    - Ribavirin (HCV)
    - Thalidomide
    - Methotrexate (IBD
    - Cyclosporine

- 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.

"Resonate with the residents."

James Calvin

A trick question

- What is the effect of pregnancy on the prevalence of cholelithiasis, and the incidence of acute cholecystitis?
    - Cholelithiasis ↑
    - Acute cholecystitis – no change from non-pregnant state

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

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
o Nausea/vomiting	Yes	Variable
o Abdominal pain	Variable	Variable
o Pre-eclampsia	No	No
o Cholestasis	Mild to marked	Marked
o AST/ALT elevation	High	Low
o Coagulopathy	Rare and late (acute fulminant)	No
o Hepatic failure	Rare	No
o U/S	Nonspecific	Dilated bile ducts, stones
o Management of mother and child	Support HBV – Lamivudine for mother, mT3 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.

BILE METABOLISM

- Give 5 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

<u>Cholestasis</u>

- Give 4 factors associated with increased risk of recurrent cholestasis of pregnancy.
    - Further pregnancies
    - Use of OCAs
    - Cholecystectomy for increased risk of cholelithiasis, cholecystitis, pancreatitis
    - Use of progesterone during subsequent pregnancy
    - Use of estrogens
    - 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

LIVER DISORDERS SEEN ONLY IN PREGNANCY

- Give the trimester of onset and treatment of 4 liver diseases unique to pregnancy.

Liver disease	Onset	Treatment
○ Hyperemesis gravidarum	T1	- Supportive care, rehydration
○ Intrahepatic cholestasis of pregnancy (ICP)	T2-3	- Ursodeoxycholic acid (UDCA)or cholestyramine - Preterm delivery if fetal compromised
○ Pre-eclampsia and eclampsia	T2-3	- Antihypertensive drugs, magnesium sulfate
○ HELLP syndrome	T3	- Induction of delivery
○ Acute fatty liver of pregnancy	T3	- Consider early induction of delivery

Abbreviations: 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 4 mechanisms for the development of hyperemesis gravidarium (HG), and 4 associated conditions.

➢ Mechanisms

- Gastroparesis – estrogen, progesterone
- Obesity (estrogen)
- Gastric infection –H. pylori
- Hormone changes
  - HCG
  - Estrogen
  - Progesterone
  - Thyroid hormones
  - Leptin

➢ Associations

- Female fetus
- Multiple gestation
- Trophoblastic disease
- Trisomy 21 (Down syndrome)
- Hydrops fetalis
- Personal/ family history

Abbreviation: HCG, human chorionic gonadotropin

- **T2 – Second Trimester**

<u>Intrahepatic cholestasis of pregnancy (ICP)</u>

- Demography
  - Present in 2% of pregnancies in America, 6% in Chile and Scandinavia
  - 10-15% of first degree relatives of women with ICP also develop ICP
  - 3rd trimester

- Pathophysiology
  - Usual cholestatic effects of estrogen in pregnancy, plus
  - Genetic predisposition (imitations in canalicular transporters for bile acids, phospholipids and cholesterol [amino phospholipid flippase], as well as FXR, the nuclear regulator of bile acid synthesis)

- Risk factors
  - Previous ICP (50% recurrence)
  - Multiple pregnancies
  - Multiple gestations
  - Descent
    - Chilean
    - Scandinavian

- Clinical
  - Usual presentation is painless jaundice and pruritus, possibly due to elevated serum bile acid concentrations
  - Generalized pruritus of skin especially on palms & soles but no rash
  - Second or third trimester (T2, T3)
  - Fetal complications
    - Usually occur after 32 weeks and include
      - Intrauterine growth retardation
      - Fetal distress
      - Premature labour

        - Stillbirth (fetal death rates in ICP are two-fold increased, usually occur between 37-40 weeks, are associated with much higher concentrations of serum bile acids, and may be sudden and intrauterine
    - For this reason the fetus should be delivered early [36-37 weeks of pregnancy]
    - The newborn may have meconium ileus
    - When serum bile acids > 40 µmol / L, ↑ risk of complications
    - Increase risk for
        - Prematurity
        - still birth
        - spontaneous preterm labour and delivery,
        - fetal compromise,
        - fetal cardiac dysrhythmias
        - meconium stained amniotic fluid, and intrauterine fetal death
- Maternal complications
    - Vitamin K deficiency
    - Coagulopathy postpartum hemorrhage
    - Pruritus and abnormal laboratory tests resolve with delivery
    - Recurs 40-60%)with subsequent gestations
    - Increased risk for cesarean delivery due to fetal compromise
    - Can recur with subsequent use of oral contraceptives (OCAs) and hormonal fluctuations
    - Recurrence of ICP (~50%)
    - ↑ risk of need for Cesarean section delivery
    - ↑ risk of
        - Cholelithiasis
        - Cholestasis with use of OCAs
        - Cholecystitis
        - Pancreatitis

- Give the clinical presentation and outcomes from intrahepatic cholestasis of pregnancy (ICP).
    - Second or third trimester (T2, T3)
    - Generalized pruritus with no rash

- Marked increases in serum alkaline phosphatase, bilirubin, and serum bile acid levels
- Normal or slight increases in GGT levels
- Mild increases in serum aminotransferase levels

Printed with permission: Schutt VA, and Minuk GY. Best Practice & Research Clinical Gastroenterology 2007; 21(5): pg. 778.

- Laboratory
  - Cholestasis: serum bile acids > 10 □mol/ L
  - Jaundice in 20%
  - ALT/ AST may be □ 20x
  - Pruritus & LE/ LFTs fluctuate
  - Marked increases in serum alkaline phosphatase, bilirubin, and serum bile acid levels
  - Normal or slight increases in GGT levels
- Pathology
  - Liver biopsy is not necessary, but would show intrahepatic cholestasis, centralobular, with bile plugs in 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	- Increase risk for ▪ Prematurity ▪ still birth ▪ spontaneous preterm labour and delivery,

- Can recur with subsequent use of oral contraceptives (OCAs) and hormonal fluctuations
- fetal compromise,
- fetal cardiac dysrhythmias,
- meconium stained amniotic fluid, and intrauterine fetal death

➢ Treatment

- Give the medical treatment options in cholestatic disorders during pregnancy

Indication/drug	Fetal risk (FDA category)	Use and safety
➢ Immune-mediated disorders		
o UDCA	B	Low risk
o Prednisolone	C	Low risk: increased risk of cleft palate, adrenal insufficiency
o Azathioprine	**D**	Low risk
Indication/drug	Fetal risk (FDA category)	Use and safety
➢ Bacterial cholangitis		
o Ampicillin	B	Low risk
➢ Sedation and analgesia		
o Fentanyl	C	Use in low doses
o Meperidine	B	Use in low doses
o Midazolam	**D**	Use in low doses
o 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. EASL Clinical Practice Guidelines: Management of cholestatic liver diseases. J Hepatol 2009; 51(2), Table 7: 237–267.

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. Management of the Patient with Suspected Cholestatic Liver Disease

- Give 4 benefits of UDCA in the management of cholestasis of pregnancy
  - ↓ concentration of bile acids in maternal serum and amniotic fluid
  - ↑ transport of bile acids in placenta
  - ↓ cholestatic potential of progesterone during pregnancy
  - ↓ pruritus
  - ↓ fetal distress, premature delivery, stillbirth

- 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 8 different types of drugs used for the **treatment of pruritus** in patients with cholestatic liver disease.
  - Decrease degree of cholestasis: UDCA
  - Non-absorbable anion exchange resins: cholestyramine
  - Changes in opioidergic neurotransmission : naloxone, natrexone
  - Hepatic enzyme (cP452) inducers: rifampicin, metronidazole, phenobarbital
  - Cannabinoid agonist
  - Serotonin antagonists: ondansetron
  - Changes in threshold to experience nociception: dronabinol
  - Antidepressants (SSRIs)
  - Sedation (antihistamines)

- Invasive procedures: plasmapheresis, MARS (extracorporeal albumin dialysis), biliary drainage
- IV propofol
- Gabaergic changes: gabapentin
- UV light
- Liver transplantation – removes cause of cholestasis

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

- **T3 – Third Trimester**

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
- Third trimester
- Early ("expeditious") delivery
- Caution: the mother may deteriorate after delivery of baby, and require LT

SO YOU WANT TO BE A GASTROENTEROLOGIST!

Using the presence of elevated serum values of AFP (alpha-fetoprotein) is **not** widely recommended as a screening test for hepatocellular cancer (HCC).

- In the setting of a pregnant woman with cirrhosis or chronic HBV infection who has been found to have an increased serum AFP, what are the differential possibilities besides HCC?
  - Mother
    - Physiological (↑ AFP in normal pregnancies)
    - Hydatidiform mole
  - Fetus
    - Down syndrome
    - Neural tube defects

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

	ICP	AFLP	HELLP
○ Mother			
- % Pregnancies	0.1-1.0	0.005-0.01	0.2-0.6
- Time of onset in pregnancy	T3	Second half of pregnancy, or postpartum	Second half of pregnancy, or postpartum
- Trimester	(2 or) 3	3 or postpartum	3 or postpartum
- Maternal mortality (%)	0	7-18	1-25
- Presence of preeclampsia	No	50%	Yes
- Typical clinical features	Pruritus Elevated serum ALT/AST fasting bile acids	Liver failure with mild jaundice, coagulopathy, encephalopathy, hypoglycemia, DIC	Hemolysis Elevated serum liver tests Thrombocytopenia (often <50,000/μL)
- Nausea/ vomiting	Rare	Yes (80%)	Yes
- Abdominal pain	Rare	Yes (60%)	Yes (100%)
○ Laboratory			
- Cholestasis	Marked	Modest and late	Mild or absent
- ALT	Mild to 10-20-fold ↑	5-15-fold, ↑ variable	Mild to 10-20-fold ↑
- 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
	ICP	AFLP	HELLP
○ 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 is low risk after first T1, and is 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.

HEMOLYSIS, ELEVATED LFTS, LOW PLATELETS (HELLP)

The HELLP (hemolysis, elevated liver enzymes, low platelet) syndrome is a form of pre-eclampsia liver disease.

> Danger sign!
>
> A woman in the second trimester of pregnancy with RUQ (right upper quadrant) pain, nausea and vomiting, should be suspected of having HELLP always consider this possibility, rather than focusing just on gallbladder disease.

- Demography
  - Pre-eclampsia occurs in 5-10% of pregnancies, and accounts for 20% of maternal deaths (Van Dyke 09)
  - Preeclampsia occurs in about 4% of pregnancies, and HELLP occurs with about 12% of women with severe eclampsia
  - Pre-eclampsia and the HELLP syndrome usually occur in the 3rd trimester, but in 28% HELLP occurs in the early post-partum period.

- Pathophysiology
  - Pathophysiology relates to the fetal and maternal sides of the placenta
  - Even if there are no signs of preeclampsia at the time of delivery, about 30% of cases of HELLP will develop after delivery
  - On the maternal side,
    - There is increased release of anti-angiogenic and decreased release of pro-angiogenic factors
    - This leads to maternal vessel vasoconstriction
    - Increased sensitivity to vasoconstrictors, damage to the endothelium of the maternal blood vessels and deposition of fibrin.
    - This in turn leads to ischemic infarcts, including acute hepatic necrosis in 10-20% of pre-eclamptic women.
  - In HELLP, there are:

- The usual laboratory findings of hemolysis (H).
- The elevated liver tests (EL) include a wide range of changes in ALT/ AST, further increased in alkaline phosphatase, and jaundice in 5-40% depending on the extent of patchy ischemic necrosis and fibrin deposition, and hemolysis.
- The thrombocytopenia (LP) may be associated with low fibrinogen, increased fibrin degradation products and renal dysfunction.

  - Fetal hypoxia may develop quickly, with sudden intrauterine death, so early delivery of the fetus is recommended. Fetal mortality is 3-23%, and maternal mortality is up to 3.5%.

LCHAD

- LCHAD and Liver DIsease in Pregnancy
  - 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).
  - ↓ 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

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.

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

- Give the role of deficiency of the mitochondrial fatty acid oxidation enzyme LCHAD (long-chain 3-hydroxyacyl-coenzyme A dehydrogenase) in AFLD.
  - ↓ ability of fetus to oxidize long-chain fatty acids (LCFA), sometimes from a mutation causing ↓ LCHAD activity.
  - LCFA from fetus are transferred from fetus to placenta to mother.
  - If the mother is heterogeneous for LCHAD, she will accumulate LCFA as microvesicular fat, and will develop
    - Hepatic steatosis
    - HE (hepatic encephalopathy)
    - ALF (acute liver failure)

- If the newborn child has LCHAD deficiency, she / he has ↑ risk of fatal, fasting non-ketotic hypoglycemia over next several months – must check the newborn for their LCHAD levels.

- 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)

CLINICAL GEM: BEWARE

- After AFLP, microvesicular steatosis may progress!

- Pathology
  - The usual patchy hepatic necrosis may lead to confluent necrosis, hepatic hematoma, and even hepatic rupture requiring surgical intervention or hepatic artery embolization.
  - Fibrin deposit in sinusoids → focal ischemic necrosis → periportal hemorrhage subcapsular hematoma hepatic rupture.
  - Maternal and fetal mortality from a free rupture is 50-100%.

- Laboratory
  - The extent of laboratory abnormalities does not reflect the severity of HELLP
  - Lab' abnormalities
    - Hemolysis (from microangiopathic hemolytic anemia) unconjugated hyperbilirubinemia
      - ↑ LDH
      - ↓ 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).

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

- Differential

- Treatment
  - Urgent delivery is required; test the mother and infant for LCHAD mutations

Abbreviations: AFLP, acute fatty liver of pregnancy; LCHAD, long chain 3-hydroxyacyl-CoA-dehydrogenase

LIVER DISEASES OCCURING in PREGNANCY WHICH ARE NOT UNIQUE TO PREGNANCY

- Give the cautions to be considered when treating the following liver conditions during pregnancy.

  - **HAV infection**
    - Hepatitis A has low risk in pregnancy
  - **HBV infection**
    - Hepatitis B has low risk in pregnancy for mother (high risk of vertical transmission to neonate)
    - Lamivudine is low risk in pregnancy
    - Interferon and ribavirin are contraindicated in pregnancy (use lamivudine, tenofovir if necessary)
    - Adefovir and entecavir have no data in human pregnancy
    - Hepatitis B vaccine has low risk in pregnancy
    - Vertical transmission from mother to child is the commonest route for HBV infection, and depending upon the viral load, may be 80-90%.
    - Babies born to HBV positive mothers should receive HBIG and HB vaccine at birth, and further vaccine at one and six months of age. at 18 months of age, the child born to the HCV positive mother should have HCV RNA testing.
  - **HCV infection**
    - 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 infection**
    - HDV may be transmitted at the same time as HBV. In contrast, only 5-8%.
  - **HEV infection**
    - HEV hepatitis in pregnant women is associated with a high rate of fulminant hepatic failure, and maternal as well as fetal death. Transmission of HEV is vertical, and the HEV vaccine will soon be available.
    - HEV – often fatal in Africa and Asia
      - Underlying chronic liver disease
    - Rare to become pregnant

- Prognosis variable
- Stillbirths increased
- High bilirubin → kernicterus

- **HSV infection**
  - The risk of herpes simplex hepatitis is increased during pregnancy, and may present with markedly elevated transaminases or with fulminant hepatic failure.
- Autoimmune Hepatitis
  - 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.

- If the patient with WD were 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 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

PANCREAS

PANCREATITIS

Acute Pancreatitis

- Clinical

	Organ failure	Morbidity	Mortality
o Mild	-	-	Low
o Moderate	-	+	Low
o Severe / fulminant	+	+	25% to 30%

- Pathological
  - o Mild — Edematous / interstitial
  - o Severe — Necrotizing
- Diagnostic imaging
  - o Early prognostic assessment of severity of pancreatitis (within first 24 hr)
- Risk stratification
  - o BISAP (Bed Side Index for Severity of Acute Pancreatitis) score
    - \> 60 years
    - Glasgow Coma score < 15
    - BUN (blood urea nitrogen) > 25 mg/dL
    - Pleural effusion on imaging
    - SIRS
    - 1 point for each of above
    - Approximate hospital mortality, by number of points
      3, 5%
      4, 13%
      5, 23%
    - Predicts organ failure after 48 hr
  - o HAPS (Harmless Acute Pancreatitis Score)
    - No abdominal rebound tenderness +/- guarding
    - Hematocrit, normal
    - Serum creatinine normal
    - Indicates mild (non-severe course)

        - Specificity 96%
        - PPV (positive predictive value), 98%
    - Other early predictors
        - ↑ serum creatinine at 48 hr, PPV for pancreatic necrosis, 93%
        - ↑ BUN OR (odds ratio for death)

	OR
BUN at admission > 20 mg/dL	4.6
↑ BUN within 24 hr	4.3

- In the patient with acute pancreatitis, give the significance of the presence of the clinical signs Chvostek, or Trousseau.
    - These signs suggest neuromuscular instability / irritability, possibly due to hypocalcemia +/- hypomagnesemia, which unless corrected by replacement therapy, may result in seizures
- Give the mechanisms of hyperglycemia in acute pancreatitis.
    - ↓ release in insulin
    - ↓ utilization of glucose
    - ↑ gluconeogenesis
    - Poorly monitored use of PN / TPN (parenteral nutrition; total parenteral nutrition)

➢ Treatment

- IV fluids
    - Re-establish or maintain microcirculation
    - Lactated Ringer's solution better than 0.9% NaCl ("normal saline")
    - In the first to 4th hr, 500 to 1000 ml per hr, with careful monitoring for fluid overload
    - Maintain IV fluids at 250 ml to 300 ml per hr to keep urine output (UO) > 0.5 ml per Kg per hour (unless ATN [acute tubular necrosis] has developed)
- Determination of cause
    - Alcohol
    - Gallstones
    - Drugs

- ↑ TG (> 1000 mg/dL)
- ↑ Ca^{2+}
- Post ERCP

- Caution: for mild (interstitial) pancreatitis, do not choose
  - EN / TPN
  - Antibiotics
  - Necrosectomy
- Frequent monitoring
  - Vitals
    - Vital signs
    - Hematocrit
    - BUN (blood urea nitrogen)
  - Labs
    - CRP
    - Lactate
    - Lytes
    - Blood sugar
    - Calcium, magnesium
    - Creatinine, BUN
  - Watch out for fluid overload: ↑ JVP, S3, hypoxia
- Urine output
- Admission to ICU for
  - Hypoxemia to keep O_2 saturation > 95%
  - Hypotension
  - Renal insufficiency
  - Severe hepatobiliary dysfunction
- Pain control
  - Hydromorphone IV; or fentanyl IV bolus, infusion or PCA (patient-controlled analgesia)

CLINICAL PEARL

There is no evidence that morphine must be avoided for analgesia in acute pancreatitis, but there is a good reason not to use meperidine.

- Give the reason why meperidine is **not** the analgesia of choice in acute pancreatitis.
  - Large amounts of analgesia are usually needed in acute pancreatitis
  - Meperidine has a short half-life, and is rapidly metabolized to normeperidine
  - Normeperidine may accumulate and cause seizures

  - DVT prophylaxis
  - Nutrition
    - po
      - With pain improving with no vomiting and no ileus
    - Early
      - Enteral feeding for SIRS or
      - Organ dysfunction, using nasogastric or nasojejunal tube
      - 25 kcal/ Kg (increased as tolerated)

- Give evidence-based reasons why **enteral nutrition** is superior to parenteral nutrition in patients with acute pancreatitis.

  - Enteral nutrition results in less
    - MOF (multiple organ failure)
    - Systemic infections
    - Need for surgery
    - Death
  - Sliding scale insulin and insulin for hyperglycemia
    - Correcting hyperglycemia may ↓ risk of pancreatic infections
  - Management of pancreatic infection
    - Controversial evidence for prophylactic antibiotics to ↓ risk of infected necrosis

- When there is pancreatic
  - ~ 33% develop infected necrosis
  - See CT criteria for pancreatic necrosis
- For > 30% of pancreas (necrotic induced with necrotizing pancreatitis), using CT criteria, use antibiotics which are active against
  - Escherichia coli
  - Pseudomonas
  - Klebsiella
  - Enterococcus
- Suspect necrosis is infected when
  - Vital signs not stable
  - Signs of sepsis
- Perform CT-guided percutaneous aspiration of area of necrosis
  - Sterile
    - No antibiotics
  - Infected
    - Antibiotics
- 75% of pancreatic infections are monomicrobial
- Suggestion
  - Imipenem 500 mg tid IV, for7 days to 10 days
  - Imepenem achieves 34% ↓ risk of infected necrosis
  - Meropenem use also reduced sepsis and mortality
  - Change antibiotic choice when results of culture and sensitivity of percutaneous CT-guided aspiration become available

SO YOU WANT TO BE A GASTROENTEROLOGIST!

Pancreatic enzyme supplements may reduce the pain in some patients with chronic pancreatitis, such as those with early disease and only small duct involvement, non-alcoholic women without steatorrhea, with no known cause of the pancreatic disease (i.e. idiopathic)

- Give the mechanism of the analgesic effect of pancreatic enzyme supplementation.
    - CCF releasing factors (CCK-RF) in the intestinal lumen enhance the release of CCK
    - In the presence of pancreatic proteolytic enzymes, there is only breakdown of some CCK-RF, so there is a ↓ effect of CCK-RF, and this ↓ CCK
    - CCK stimulates pancreatic secretion of pancreatic enzymes, and this secretion against partially obstructed ducts may ↑ pain
    - When there is chronic pancreatitis and pancreatic insufficiency, there is ↓ breakdown of CCK-RF and ↑ CCK secretion with ↑ pain
    - When pancreatic enzyme supplements are taken, the digestion of CCK-R is partially restored, there is ↓ CCK secretion, ↓ pancreatic secretion, and↓ pain

- Give the mechanisms of the development of **hypoxemia** in acute pancreatitis.
    - ↓ ventilation
    - Atelectasis
    - Pleural infusion
    - Intrapulmonary shunt opening
    - ARDS (acute respiratory distress syndrome)
    - Risk stratification for necrotizing pancreatitis
    - In a patient with acute pancreatitis, suspect severe pancreatitis (necrosis), if the stem provides
        - History / signs

        - Fever, hypotension, tachycardia, dyspnea, oliguria
        - Abdominal guarding, rebound tenderness, ileus
        - Hemorrhage
        - Persisting /non-responsive pain
    - Abnormal blood tests
    - Abnormal CT scan (e.g., hematocrit or WBC, but not the level of the elevation of an

      Non-enhancing areas of large portions (> 50%) of pancreas

SPLENIC VEIN THROMBOSIS (SVT)

- SVT develops in ~ 20% of persons with acute pancreatitis
- Treatment
    - Underling pancreatitis
    - Anticoagulation if clot in SV extends to PV (portal vein) or SMV (superior mesenteric vein)
    - Complications of clot
        - PV hepatic decompensation
        - SMV intestinal ischemia

➢ Endoscopy

- ERCP, endoscopic papillotomy and insertion of plastic biliary stent for gallstone pancreatitis
    - Early ERCP for
    - Cholangitis
        - Persistent CBD stone abnormal or increasing Les (liver enzymes)
- EUS, MRCP to identify CBD stone

➢ Surgery

- Necrosectomy
    - Consider for
        - Sterile symptomatic necrosis
        - Infected pancreatic necrosis
- Cholescystectomy
    - Needed in all patients with gallstone pancreatitis, including those with biliary sludge
    - Cholecystectomy reduces the risk of

        - Cholescystitis
        - Cholangitis
    - Without cholecystectomy, the risk of the above complications is 25% to 30% in 6 wks to 18 wks
    - Timing of cholecystectomy
        - Mild pancreatitis
            - Within 1 week of recovery
    - Severe (necrotizing) pancreatitis
        - 3 wk of recovery
    - Suspected CBD stones
        - Pre-cholecystectomy ERCP, sphincterotomy, and stone extraction

The patient has experienced repeated episodes of severe abdominal pain radiating to the back, in associating with high levels of alcohol ingestion. On this occasion she/ he had similar pain and alcohol abuse, and the serum amylase or lipase is normal.

You are offered several plausible MCQ choices, as well as acute pancreatitis. Chronic pancreatitis is the answer – caution: normal serum amylase or lipase do not rule out chronic pancreatitis.

- Alcoholics have an ↑ risk of having gallstones in the patient with acute pancreatitis. Suspect biliary tract gallstones if
    - Bilirubin > 4 mg/dL
    - ALT, AST > 1000 U/mL
- But if the patient with acute pancreatitis has also been drinking recently, the ALT, AST may be > 1000 U/mL, and the bilirubin may be increased (true, often > 15 mg/dL).
- Treat complications
    - Hypocalcemia, hypomagnesemia
    - Hyperglycemia
    - Hypertriglyceridemia
    - Splenic vein thrombosis
    - Abdominal compartment syndrome (intraabdominal pressure > 21 mm Hg [measure pressure in urinary bladder])

ABDOMINAL COMPARTMENT SYNDROME

- Definition: Intra-abdominal hypertension > 21 mm Hg (measured as pressure in bladder)
- Causes of ↑ intra-abdominal pressure
  - Fluid
    - Excessive IV fluids → pancreatic / tissue edema
    - Ascites
  - Air
    - Ileus
    - Perforation
  - STissue
    - Peripancreatic inflammation
- Complications
  - Kidney
    - Liguria
  - Lung
    - Hypoventilation
    - Respiratory failure
  - Heart
    - ↑ JVP-CHF (congestive heart failure)
    - Hypotension, tachycardia
    - Peripheral edema
  - Abdomen
    - Ascites
    - Organ ischemia / necrosis
    - Lactic acidosis

CHRONIC PANCREATITIS

- Mechanisms

- Give 4 mechanisms of pain development in chronic pancreatitis.
  - Obstruction of pancreatic ducts
  - Stimulation or hyperstimulation of secretions into partially obstructed ducts
  - Inflammation
  - Ischemia and acidosis
  - Neuropathic pain

- Treatment
  - Food and fluids
    - Small, low fat meals
    - Hydration
  - No alcohol
  - No smoking (stopping smoking slows the progression of the chronic pancreatitis, and decreases the risk of the development of pancreatic ductular cancer
  - Treat underlying disorder
  - Analgesics
    - TCAs, e.g. amitriptyline 10 mg po tid
    - NSAIDs
    - Opiods
      - Continuous release
      - Patches
    - Anti-neuropathics e.g. pregabalin 75 mg po bid, increasing dose up to 300 mg bid as needed
  - Antioxidants
    - Selenium, ascorbic acid, beta-carotene, alpha-tocopherol and methionine
    - Antioxidant therapy rendered 32% of patients pain-free, versus 13% with placebo)
  - Pancreatic enzymes supplements

SO YOU WANT TO BE A GASTROENTEROLOGIST!

- Give the evidence for lactated Ringer solution (Ringer lactate) being superior to normal saline for initial and maintenance fluid resuscitation in acute pancreatitis.
  - Ringer lactate vs. saline gives
    - ↑ fall in CRP (C-reactive protein)
    - ↓ SIRS (systemic inflammatory response syndrome), 84% vs. 0%
- Give the clinical circumstance when the patient with acute pancreatitis must be given IV infusion with normal saline, and not with Ringer lactate.
  - Ringer lactate contains calcium (Ca^{2+}, 3 mEq/L), and must not be given to patient with hypercalcemia, which may develop in some persons with acute pancreatitis.

- Give 5 features of the patient with chronic pancreatitis which predict benefit to pain control with the use of pancreatic enzyme supplements poor benefit.

Yes	No
○ Ideopathic	- Late disease - Large duct disease - Men - Alcoholic - Steatorrhea

  - ○ Use of pancreatic enzyme supplements
    - Malabsorption
      - Symptoms
      - Correction of malnutrition
      - Reverse deficiencies
        - Fat soluble vitamins (A, D, E, K)
        - Vitamin B12
    - Even only 10% of normal daily pancreatic enzyme output may be sufficient to correct steatorrhea (~ 30,000 IU per day of lipase or 90,000 USP [United States Pharmacopeia units]
    - Take supplements throughout meal, from beginning to end
    - Enteric formulation delays acid-destruction of enzymes
  - ○ Endoscopic therapy
    - ↑ proportion of persons with pancreatic ductular lesions leading to ductular hypertension and tissue ischemia
      - Strictures, 47%
      - Stones, 18%
      - Strictures plus stones, 32%
    - Sphincterotomy ± stenting
      - ↓ ductal pressure
      - Pain relief in ~ 2/3 of patients
  - ○ ESWL (extracorporeal shock wave lithotripsy)
    - Pancreatic duct stones in ~ ½ of patients with chronic pancreatitis
    - Fragmentation of stones allows for spontaneous passage of stones, ↓ duct pressure and ↓ pain in 62% to 86% over 7 months to 44 months
  - ○ Radiation
    - Limited experience, but may ↓ pain
  - ○ Surgical approaches to chronic pancreatitis

- Decompression
  - Dilated main pancreatic duct (normal 3 mm head, 2 mm body, 1 mm tail) allowing for an anastomosis to drain the pressure into a loop of jejunum (> 10 mm)
  - Pain relief
    - Early, ~80%
    - > 2 yr, !60%
    - decompression surgery vs. endoscopic drainage; 75% vs. 32%
  - Need for second drainage procedure, surgery vs. endoscopy, 5% vs. 68%
  - % of patients treated by endoscopy who eventually require surgical drainage, 47%
- Resection
  - Variable amounts of resection needed to achieve pain relief
  - Diabetes may be prevented by autologous islet cell transplantation (AICT) (70% insulin-independent 2 years after AICT
  - Resection also interrupts pain nerves
- Denervation
  - Celiac ganglion and splanchnic nerves (afferent pain nerves pass through these)

"It is highly feasible to simplify complex issues."

Grandad

AUTOIMMUNE PANCREATITIS (AIP)

- Types
  - Primary IgG4 disease, or
  - Associated with other IgG4 disease, e.g. 9% to 36%

- Associations

- Give 8 conditions associated with autoimmune pancreatitis (AIP).
  - Bile ducts
    - PSC (have ↑ IgG4 in serum)
    - Autoimmune IgG4 cholangitis (AIC)
    - Autoimmune sclerosing cholangitis
  - Liver - Autoimmune hepatitis
  - Salivary glands - Sjogren syndrome
  - Small / large bowel - IBD (inflammatory bowel disease
  - Thyroid - Autoimmune thyroiditis
  - Kidney - IgG4 interstitial nephritis
  - Lung - Lung nodules
  - Miscellaneous
    - Mediastinal fibrosis
    - Retroperitoneal fibrosis
  - Pancreatic insufficiency
    - Exocrine or endocrine, in about 1/3

- Pathology
  - Typical pathological changes
    - Lymphoplasmacytic sclerosing pancreatitis
    - > 10 plasma cells which are IgG4-posiive
    - Periductular lymphoplasmacytic infiltrate
    - Obliterative phlebitis
    - Acinar fibrosis
    - Duct centric pancreatitis
    - Granulocytic epithelial lesion
  - Pancreatic mass (differentiate from pancreatic cancer)

- Single or multiple structures of pancreatic ducts
- Peripancreatic vascular complication (~23%)
- Pathological changes of associated conditions. e.g.
  - Autoimmune cholangitis (AIC)
  - Intra- and extrahepatic biliary duct strictures, in proximal ducts in ~ ½
  - Autoimmune sclerosing cholangitis

- Give 10 clinical and pathological features which distinguish between type 1 and 2 autoimmune pancreatitis (AIP).
  - Pathological types

Features	Type 1 AIP	Type 2 AIP
Older age	+	-
% ↑ IgG4 (≥ 280 mg/dL)	Low %	High %
Ideopathic ductal centric pancreatitis	-	+
Granulocytic epithelial lesion	-	+
Lymphoplastic sclerosing pancreatitis	+	-
> 10 IgG4-positive cells	+	-
Periductular lymhoplastic infiltrate	+	-
Obliterative phlebitis	+	-
Acinar fibrosis	+	-
Systemic involvement	+	-
Associated conditions	- Biliary tract - Kidney - Salivary glands - Retroperitoneum	IBD
High relapse rate	49%	0%

➢ Laboratory

- Give the performance characteristics of serum IgG4.
  - ↑ serum IgG4 > 2x ULN (upper limit of normal; normal is < 140 mg/dL, so > 280 mg/dL suggests IgG4-associated disease
  - ~10% of pancreatic cancers (PCa) are associated with ↑ IgG4 in serum
  - This figure falls to 1% of 280 mg/dL
  - Differentiation of IgG4 from AIP vs. pancreatic cancer, using varying cut-offs

	> 135 mg/dL	> 140 mg/dL	> 280 mg/dL
- Sensitivity	95%	76%	53%
- Specificity	97%	93%	99%

  - Note
    - ↑ CA 19-9 blood concentration is seen in only 9% of AIP and in 71% of pancreatic ductal cancer (PCa)
    - Anti-PBP (plasminogen-binding protein) peptide is positive in
      - AIH, 94%
      - PCa, 5%
      - ↑ IgG4 plasma cells on IHC (immunochemistry) of pancreatic tissue

SO YOU WANT TO BE A GASTROENTEROLOGIST!

The performance characteistics of the IgG4 distinguishing between AIP and other disorders depends upon the cut-off concentration of the IgG4 which is used. When the IgG4 concentration is > ULN (140 mg/dL) but less than 2x ULN (280 mg/dL), the sensitivity of the test for AIP falls, but most of the conditions involved will not be easily confused with AIP.

- Give 3 conditions which may be associated with ↑ IgG4 > 140, < 280 mg/dL.
  - Lung - Asthma
  - GI - Parasites
  - Skin - Atopic dermatitis
    - Pemphigus
      - Vulgaris
      - Foliaceus

➢ Diagnostic imaging

- Give 5 diagnostic imaging features suggestive of AIP.
  - Pancreas
    - Enlarged
    - No distal atrophy
  - Border, features
  - Rim-halo (hypoattenuation around the outside [rim] of pancreas)
    - Enhancement delayed
    - High density mass
  - Pancreatic duct
    - Narrowed main duct
    - No dilation
    - Irregular narrowing of intrahepatic ducts
    - No cut-off sign
    - Beaded (diffuse, irregular narrowing)
    - Focal stricture

- Give 3 diagnostic features on CT scanning in AIP which predict a favorable response to steroids.
  - Diffuse swelling of pancreas
  - Hypoattenuating halo around pancreas
  - No focal mass in pancreas
  - No strictures of ducts

➢ Diagnosis

- Give the Mayo Clinical HISORT Criteria for the diagnosis of AIP.
  - One more of the following:
    - ↑ IgG4 in serum
      - 10% of pancreatic associated with ↑ IgG4
      - In AIP, IgG4 falls with steroids
      - 9% of PSC associated with ↑ IgG4
    - Characteristic imaging on CT / MRCP / ERCP

- Extrapancreatic organ involvement
- Compatible histopathology of type 1 or type 2 AIP (see previous section)
- Response to steroids
  - Pancreatic, and
  - Extrahepatic manifestations

SO YOU WANT TO BE A GASTROENTEROLOGIST!

- Give 5 features on cholangiographic diagnostic imaging which help to distinguish PSC (primary sclerosing cholangitis) from AIC (autoimmune cholangitis).

	AIC	PSC
○ Stricture		+
- Band-like	-	+
- Beaded	-	+
- Pruned-tree-like	-	+
- Segment	+	-
- Long	+	-
- Prestenotic dilation	+	-
- Bifurcation	-	-
- Distal CBD	+	-
○ Diverticulum formation	-	+

  - ○ Note: In AIC, about half of patients have
    - Involvement of proximal intrahepatic or extrahepatic ducts
    - Intrahepatic strictures

SO YOU WANT TO BE A GASTROENTEROLOGIST!

- Give 4 features of cholangiographic diagnostic imaging which suggest a biliary duct malignancy, rather than benign disease such as AIP or PSC.
  - Length - > 10 mm
  - Contour - Irregular
    - Ragged
  - Filling defect - Fixed
  - Shouldering - Sudden transition above stricture for normal to abnormal tissue
  - Hilar region

➢ Treatment
- Dose prednisone 0.5 mg/kg po per day for 6 weeks, with a taper of 5 mg/week
- Response rates in IAP
  - Initial response, 50% to 87%
  - Relapse
    - 25% to 62%
    - After a median delay of ~ 6 months
    - More likely with higher IgG4, or extrapancreatic involvement
    - Give a repeat course of steroids, or repeat steroids while starting azathioprine
  - Response of relapse to azathioprine (AZA)
    - 46%
    - 2 mg/kg po per day
  - Need for maintenance, < 25%
  - Achieved and maintained remission for 4 months with AZA, 70%
- Response time
  - 2 weeks to 17 weeks
- Important benefits
  - With use of steroids, less likely development of

- Sclerosing cholangitis
- Stenosis of distal CBD
- Retroperitoneal fibrosis
- Within 6 months of stopping steroids in patients with a proximal stricture, 70% relapsed

PANCREATIC TUMORS

Pancreatic Pseudocysts

- Definition
  - A collection of pancreatic juice lined by fibrous and reactive granulation tissue, usually caused by pancreatitis or leakage of the pancreatic ducts, and usually communicated with the pancreatic ductal system
  - Small or large, single or multiple, inside or outside of the pancreas itself
- Pathophysiology
  - Acute or acute on chronic pancreatitis
    → Protein plugs, stones, strictures → ↑ obstruction → ↑ duct pressure → duct leakage → necrosis, liquefaction
- Clinical
  - Spontaneous resolution
  - Enlargement
    - Obstruct
      - Biliary tree
      - Duodenum
      - Blood vessels (e.g. splenic vein)
  - Perforation
  - Bleeding into pancreatic duct
    - Hemosuccus pancreatitis
      - Ascites
      - Pleural effusion
      - Pseudoaneurysm (seen in 10% of pseudocysts)
  - Infection
    - Infected necrosis
    - Abscess

- Diagnostic imaging
  - Use EUS to
    - Perform FNA
    - Identify ideal drainage site
    - Identify gastric varices, pseudoaneurysms
  - Diagnostic imaging, with percutaneous catheter drainage
    - Especially successful for pancreatic ducts normal, or
    - Strictures which do not communicate to duct

- Differential
  - Suspect that an encapsulated collection of fluid on diagnostic imaging is a pseudocyst rather than a cystic pancreatic cancer when
    - There is a history of
      - Pancreatitis
      - Pancreatic trauma
    - CT shows
      - Inflammatory changes
      - Simple cyst (i.e. no internal septae)
      - No echogenic mucin
      - No mass lesion

- Treatment
  - Endoscopic approach
    - Resolution 64% to 89%
    - Recurrence 6% to 18%
    - ECG (Endoscopic cyst gastrostomy), or ECD (cystduodenostomy)
    - Transmural approach for pseudocyst which is
      - Large (> 6 cm)
      - Single or multiple
      - Obstructed (non-communicating duct)
      - Close to wall of stomach or duodenum
    - Transmural puncture plus
      - Drainage
      - Lavage nasocystic
      - Stenting

- Note contraindication
  - Presence of a pseudoaneurysm (in specialized centres, endoscopic drainage of a pseudocyst complicated by a pseudoaneurysm has been successful and safely performed after angiographic embolization of the affected blood vessel)

- Surgical approach
  - Indicated for
    - Continued, significant abdominal pain, complications
    - Continued enlargement of cysts
    - Strictures or obstruction of ducts
  - Timing of surgery
    - Usually between 6 to 13 weeks
  - Procedures
    - Open or laparoscopic
    - Cystgastrotomy
    - Cysjejunostomy (direct, or Roux limb)
    - Resection
  - Use transpapillary stent for
    - Small (< 6 cm), single, communicating pseudocyst which is away from the wall of the stomach or duodenum
    - Severe ductal obstruction

"Happiness depends more on inward disposition of mind than on outward circumstances."

Benjamin Franklin

PANCREATIC DUCTULAR ADENOCARCINOMA

➢ Stages

- Give the 4 stages of pancreatic cancer.

Stage	Localization
I	o Pancreas
II	o Extension into – Duodenum – Bile duct – Peripancreatic tissue
III	o Extension into – Regional lymph nodes
IV	o Extension into – Stomach – Spleen – Colon – Large near-by vessels – Metastases

➢ Clinical

- In the context of pancreatic cancer, give the meaning of the Trousseau syndrome.

  o The Trousseau is vascular thrombosis in patient with pancreatic cancer

➢ Laboratory

  o While CA 19-9 may suggest this diagnosis, sensitivity is enhanced by adding diagnostic imaging

➢ Diagnostic imaging

  o Biliary stricture → brush cytology
  - Sensitivity 56%
  - Specificity 90% to 100%
  - PPV 59% to 100%
  - NPV 43% to 89%

- False positive results with strictures from
  - Inflammation
  - PSC
  - Sphincterotomy

	Overall	Non-operated
Sensitivity	91%	96%
Specificity	100%	100%

- Brush cytology + biopsy

	Sensitivity	Specificity
- Biopsy demonstrated HGD / adenocarcinoma	43% to 88%	> 90%
- Positive biopsy plus cytological LGD	100%	84%

Abbreviation: HGD, high grade dysplasia; LGD, low grade dysplasia; PSC, primary sclerosing cholangitis

- EUS + FNA

- Give the performance characteristics of EUS +FNA to establish a diagnosis of biliary tract malignancy.
  - Sensitivity 77%
  - Specificity 100%
  - PPV 100%
  - NPV 29%
  - Accuracy 79%

- Give the endoscopic treatment option for an obstructed biliary stent (tumor ingrowth or overgrowth, or debris)
  - Sweeping stent with balloon
  - Place a plastic or SEMS stent inside the original stent
  - Hilar cholangiocarcinoma, sensitivity
    - Brush cytology 40%
    - Brush biopsy 53%
    - Brush cytology plus biopsy 60%

- PSC plus cholangiocarcinoma
  - 10% of PSC develop cholangiocarcinoma over 6 years

➢ Treatment

- Pain control
  - Analgesics
  - Radiation therapy
  - Chemical celiac nerve block
  - Chemical splanchnicectomy
- Resectable
  - Resection
- Non-resectable
  - Radiation therapy
  - Radiation therapy plus 5-FU
  - Gemcitabine
- Palliation of biliary obstruction
  - Biliary stent
    - Percutaneous
    - Endoscopic
  - Surgical bypass

BILIARY DRAINAGE

<u>Pancreaticobiliary Obstruction and Endoscopic Stenting for Biliary Drainage</u>

- Preoperative
  - Plastic stent
  - SEM (self-expanding metal stent), using TTS (through-the-scope) delivery systems, +/- Argon plasma coagulation to trim / reposition stent
  - Preopertative endoscopic biliary drainage before pancreaticoduodenectomy
    - Reduced need for repeat surgery 4% vs. 15%, but
    - Increases the rate of serious complications 74% vs. 39%
- Palliation
  - Stents
    - Median stent patency
      - Plastic 126 days
      - Metal 273 days

        - Adverse outcomes
            - Plastic 39%
            - Metal 12%
    - Surgery
        - Bypass
        - Percutaneous drainage

- Regardless of estimated patient survival time, metal stents and not plastic stents should be used for cholangiocarcinomas and for proximal malignant biliary strictures (e.g. Klatskin tumor at hilar bifurcation)

- Obstruction of hilum
    - Use uncovered metal stents (SEMS)
    - Low rate of migration of stent
    - Difficult to remove
    - High rate of obstruction from ingrowth of tumor (diagnose tumor overgrowth with MRCP; sensitivity, 87%; specificity, 86%)
    - May also use plastic stents for both right and left hepatic duct systems
    - Note
        - Use uncovered rather than covered SEMS to rreduce migration of stent (15 vs. 7%)
        - Do not perform sphincterotomy before placement of covered SEMS in order to reduce migration (3% vs. 16%)
        - Do not use a covered metal stent for a biliary tract obstruction in a patient with a gallbladder, to avoid stent blockage of the cystic duct, leading to cholecystitis

"It can always be better."

Anonymous

Bile Leaks after Laparoscopic Cholecystectomy

- Significant bile leaks ~ 1%
- Detect on abdominal ultrasound
- If ultrasound is negative but clinical suspicion is high, perform cholescintigraphy (HIDA scan) or ERCP
  - ERCP gives identification of leaks ~ 95%
  - Other pathology detected, e.g.
    - Stones
    - Strictures
    - T-tube

➢ Endoscopic Management

- Place a transpapillary stent without biliary sphincterotomy, unless there is a retained CBD (common bile duct)
- If a biliary sphincterotomy needs to be performed for a retained CBD stone, the stone is removed and a covered SEMS is placed
- Multiple stents may be placed over serial sessions ("serial incremental biliary dilation"), or balloon dilation
- Remove the stent in 4 weeks, depending on patient's recovery
- If the biliary leak continues after stenting, repeat ERCP with balloon occlusion to determine if anomalous hepatic duct was cut at the time of laparoscopic cholecystectomy
- 83% response over ~ 4 year with endoscopic and surgical approaches
- If endoscopic approaches fails, surgical management is still possible
- Surgical drainage may be required
  - Often proximal hepatico-jejunostomy with Roux-en Y jejunal loop is performed
- Even if endoscopic treatment allows the damaged biliary leak to close, ~25% of patients may have a collection of bile (biloma) causing symptoms, and requiring percutaneous drainage, or surgical drainage if the collection of fluid is loculated

USEFUL WEBSITES

AASLD recommendations
http://www.aasld.org/PRACTICEGUIDELINES/Pages/default.aspx

IDSA recommendations http://www.idsociety.org/IDSA_Practice_Guidelines/

For further information re cytochrome P450 drug-drug interactions and the use of protease inhibitors boceprevir (BOC) and telaprevir (TVR), please refer to:
www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm
http//:222.drug-interactions.com
www.hep-druginteractions.org

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

Guidelines developed by WGO, World Gastroenterology Organization (www.worldgastroenterology.org/).

Online resource: www.giandhepatology.com

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