Best Practice Guidelines in Hepatopancreaticobiliary Disorders

Alan BR Thomson and David Hudson

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For no-charge textbooks in Gastroenterology, Hepatology, and General Internal Medicine

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THE WESTERN WAY

TABLE OF CONTENTS

CANMED OBJECTIVES

Medical Expert

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

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

Communicator

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

Collaborator

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

Manager

The participants are provided with assignments in advance of the three day GI Practice Review. There is much work for them to complete before as well as afterwards, so they learn to manage their time effectively, and to complete the assigned tasks proficiently and on time. They learn to work in teams to achieve answers from small group participation, and then to share this with other small group participants through effective delegation of work. Some of the material they must access demands that they use information technology effectively to access information that will help to facilitate the delineation of adequately broad differential diagnoses, as well as rational and cost-effective management plans.

Health Advocate

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

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

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

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

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

Carl W. Buechner, on teaching.

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

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

ACKNOWLEDGEMENTS

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

A warm and heartfelt thank you goes to **Dr. Naiyana Gujral** for her excellent assistance for helping to bring this project to a successful completion.

When Rebecca, Maxwell, Megan, Henry, Felix, Toby, Grady, Jasper, and Laila, ask about their Grandad, I will depend on James and Anne, Matthew and Allison, Jessica and Matt, and Benjamin and Kim to be understanding, generous, kind and forgiving. For what I was trying to say and to do was to make my professional life focused on the four Cs and an "H"; competence, caring, compassion, and composure, as well as humor - and to make my very private personal life dedicated to family – to you all.

DEDICATION

“To Jeannette Mineault -Thomson”

Dr. Alan Thomson

Dedicated to my wife, Jennifer, and our child, Noah, as well as the numerous residents, fellows, and staff physicians, including Dr. Alan Thomson, whose support and career guidance have been invaluable and much appreciated.

Dr. David Hudson

x

HEPATOBILIARY

Alajmi, Abdulaziz

Alazemi, Khaled

Almudaires, Abdulaziz

Alsager, Mohammed

Hindi Zaid

Howarth, Nisha

Hudson, David

Iablokov, Vadim

Lavalle, Christopher

Parthasarathy, Pavithra

Rahman, Hasib

LIVER FUNCTION

Functional Zonation of Hepatic Cells along the Sinusoids: Background

Ramachandran P, et al. Nat Rev Gastroenterol & Hepatol 2020; 17: 457-472.

- Single-cell RNA sequencing (scRNAsq) with spatial mapping and bioinformatic support have demonstrated molecular patterns of metabolic zonation along the hepatocyte sinusoids in hepatocyte, endothelial cells, and stellate cells.
  - Distinct populations of these cells form a "…spatial distinct fibrotic niche"
    - Monocytic macrophages in the fibrotic niche activate mesenchymal cells to form scar tissue

❖ Zonation of cells

- Pathway enrichment analysis of zonated genes show that the periportal hepatocytes are responsible for
  - Oxidation
  - Fatty acid metabolism
  - Mid-zonal hepatocytes are responsible for cytochrome P450 metabolism of xenobiotics
- Along the sinusoid the self-renewing hepatocyte have similar properties
  - Telomerase
  - ↑ ribonuclear protein
    - Maintains telomer structure / integrity
    - Prevents chromosomal
      - Fusion
      - Degeneration
    - Corrects chromosomal partitioning
- Source of new hepatocytes forming the liver
  - Hepatic progenitor cells (HPCs) of biliary origin
    - HPC from within the canals of Hering → expand ducts in hepatic parenchyma ("ductular reactions) → differentiate into hepatocytes in hepatic parenchyma
- Monocyte phagocytic system (MPS)
  - Monocytes
  - Dendritic cells
  - Macrophages
    - Kupffer cells within the hepatic sinusoids)
    - Functions
      - Scavenge gut-derived pathogens/RBCs
      - Severe tissue damage
      - Maintain immune tolerance
      - Regulate lipid/iron metabolism

} ▪ Only important in process of injury / resection-stimulated hepatic proliferation

Zonation of cells across the liver sinusoid

- Blood flows into the liver from the hepatic artery (HA) and portal vein (PV), and leaves the liver through the hepatic vein.
  - The PV and HA are located in the portal triads in close proximity to the bile ducts, which drain bile secreted by the hepatocytes.
  - Incoming blood, which is high in oxygen and nutrients flows from the portal zone, through radial sinusoids and into the central vein.
  - Blood oxygen and nutrients are depleted along the sinusoid creating a gradient.
- Concentric layers of hepatocytes are positioned between the portal triad and central vein.
- Non-parenchymal cells associated with the sinusoid include
  - Fenestrated liver sinusoidal endothelial cells (FLSECs)
  - Kupffer cells (KC)
  - Hepatic stellate cells (HSC) which reside in the space of Disse
- Single-cell RNA sequencing has revealed genes which differentiate
  - Portal zone / central zone hepatocytes
  - FLSECs and HSCs
- These markers such as E-Cadherin (portal zone hepatocytes), Cyp2e1 (central zone hepatocytes), NGFR (portal-associated HSC) and c-Kit (central zone LSEC) → use to identify zonation in the liver using immunohistochemistry
- Monocyte-derived macrophages (MDMs)
  - Inflammation causes circulating monocytes to home to liver → differentiate into macrophages → differentiate into Kupffer cells
- Dendritic cells (DCs)
  - Antigen-presenting innate immune cells
  - Subtypes
    - Plasmacytoid→ interferons, type 1
    - Conventional DCs (cDCs) → regulate CD4 T cell responses
- Ongoing studies of possible zonation of
  - Granulocytes
    - Basophils
    - Eosinophils
    - Mast cells
    - Neutrophils
  - T/B lymphoid cells, innate lymphoid cells (ILC), natural killer cells (NKCs)
- Liver sinusoidal endothelial cells (LSECs)
  - Zonation between triad and central vein
  - LSEC capillary zonation also present

  } ▪ Function to ↑ WBC migration

- Lymphatic vessels
  - Normally present only in periportal area
  - In cirrhosis, lymphatics extend to central vein

❖ Hepatic Fibrosis

- Mesenchymal cells (these show zona heterogeneity)
  - Hepatic stellate cells (HSCs)
    - Liver specific pericytes in the parenchyma peri-sinusoidal space
      - Vitamin A storage, metabolism
      - Form myofibroblasts → produce collagen, especially NSCs near central vein
  - Portal fibroblasts
    - In portal niche, providing structural support to BD, HA, PV
    - With injury → deposit extracellular matrix
  - Vascular smooth muscle cells
  - Mesothelial cells

- In health
  - Surface markers of mesenchymal cells along sinusoid
  - Cellular interaction in fibrotic niche

Scar-associated cells	Macrophage phenotypes	Mesenchymal activation	Angiogenesis	Expression of ligands
○ Macrophage		+	+	▪ Activation: AREG, TGFβ1 ▪ Proliferation: PDGFβ, TNFSF12 ▪ Survival: IL-1β
○ Mesenchymal cells	+		+	▪ PDGFRα+/β+
○ Endothelial cells	+			▪ NOTCH3 receptors: DLL4, JAG1/2

Abbreviations: BD, bile duct; cDCs, conventional dendritic cells; CV, central vein; DC, dendritic cells; HA, hepatic artery; HSCs, hepatic stellate cells; HV, hepatic vein; ILCs, innate lymphoid cells; LSECs, liver sinusoid endothelial cells; MDMs. Monocyte-derived macrophages; MPS, monocyte phagocytic system; NGFR, portal-associated HSC; NKC, natural killer cells; PV, hepatic vein; scRNAsq, single cell RNA sequencing

Evaluation of Abnormal Liver Chemistries: ACG (2017)

Kwo PY, et al. Am J Gastroenterol 2017: 112: 18-35.

❖ Summary Statements, Background

- Overview
  - Liver chemistries including alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (AP) and bilirubin (Bil) are markers of liver injury, not liver function, and should be referred to as liver chemistries, not liver function tests.
  - Albumin, bilirubin, and prothrombin time are markers of hepatocellular function that can be influenced by extrahepatic factors.
  - The laboratory measurements of ALT, AST, and AP are highly reproducible.
  - Elevations of AST and/or ALT, AP, and Bil suggest hepatocellular injury and are the abnormal liver chemistries that require assessment and potential evaluation.
  - ALT is a more specific marker of hepatic injury than AST.
  - An ↑AP of hepatic origin may be confirmed by ↑ gamma-glutamyl transferase (GGT), or fractionation of AP.

- When are liver chemistry tests normal?
  - A true healthy normal ALT level in prospectively studied populations without identifiable risk factors for liver disease ranges from 29 to 33 IU/l for males, and from 19 to 25 IU/L for females
    - Levels above this should be assessed.
  - ↑ ALT or AST above the upper limit of normal (ULN) in a population without identifiable risk factors is associated with ↑ liver-related mortality.
  - There is a linear relationship between ALT level and body mass index (BMI) that should be taken into consideration and assessed by physicians.
  - A normal ALT level does not necessarily exclude significant liver disease.
  - AST and ALT upper limit of normal (ULN) ranges can vary between different laboratory.
  - Clinicians may usually rely on local lab' ULN ranges for AP and Bil.
  - Clinical assessment of the patient with abnormal liver chemistries.
    - Clinical assessment of the patient with elevated liver tests should begin with a thorough history and physical examination.
    - History should include risk factors for underlying liver disease, associated medical conditions, use of alcohol, and use of medications including over the counter products and herbal supplements.
    - Physical examination should assess for stigmata of chronic liver disease, as well as signs or symptoms pointing to a specific liver disease etiology.

- Patterns of liver chemistry test elevations
  - Hepatocellular injury is defined as disproportionate elevation of AST and ALT levels as compared with the alkaline phosphatase level.
  - Cholestatic injury is defined as disproportionate elevation in alkaline phosphatase level as compared with AST and ALT levels.
  - Mixed pattern of injury is defined as elevation of both alkaline phosphatase and AST/ALT levels.
  - Isolated hyperbilirubinemia is defined as elevation of bilirubin with normal alkaline phosphatase and AST/ALT levels.
  - The R ratio is calculated by the formula R = (ALT value ÷ ALT ULN) ÷ (alkaline phosphatase value ÷ alkaline phosphatase ULN) with an R ratio of > 5 defines type of liver disease as hepatocellular injury, < 2 cholestatic injury, between 2-5 cholestatic injury, or mixed pattern.

❖ Abnormal ALT/AST values

Recommendation

- Perform the liver panel twice, or perform a “clarify test” to confirm that the chemistry is truly abnormal (Strong recommendation, very low level of evidence).
- ALT +/- AST < 5x ULN
  - History/further lab testing for HBV, HCV, HH, ArLD, NAFLD, WD, DILI, α1-AT deficiency
  - ALT +/- AST concentration 5x – 15x ULN, consider all of the above, plus acute HAV, HBV, HCV
  - ALT +/- AST > 15x ULN, or 1,000 IU/L, also consider acetaminophen toxicity, or shock liver / ischemic hepatopathy

  (All above are Strong recommendations, very low level of evidence)

- ↑ ALT or ↑ AST > ULN “without identifiable risk factor”
  - ↑ liver-related mortality, ↑ morbidity
  - US NHANES database studies
    - ↑ ALT
      - F > 19 U/L
      - M > 30 U/L

      → ↑ mortality
      - Liver-related, 11.2x
      - Diabetes-related, 3.3%
    - ↑ ALT
      - F > 30 U/L
      - M > 43 U/L

      → ↑ risk of coronary heart disease, even when excluding
      - ↑ alcohol use
      - ↑ BMI
      - Chronic viral hepatitis

➢ Causes of Abnormal Liver Enzyme Transaminitis

- Hepatic
  - Parenchymal liver diseases, especially
    - Infection
      - Acute/chronic viral hepatitis
      - Sepsis
    - Inflammation/immune
      - Autoimmune hepatitis
    - Iatrogenic
      - Drug/toxins/ total parenteral nutrition (TPN)
      - Acute/chronic viral hepatitis
      - Liver trauma/surgery
    - Infiltration
      - Malignant infiltration
    - Injury
      - Trauma/surgery
    - Ischemic/vascular (thromb
      - Hepatic artery/vein
      - Portal splenic vein
      - Shock
- Non-hepatic
  - Muscle damage
    - Skeletal
    - Cardiac trauma/damage
  - RBC hemolysis
  - Heart stroke
  - Endocrine
    - Thyroid disease
    - Adrenal insufficiency

❖ Abnormal Alkaline Phosphatase (AP)

- Bile duct
  - Bile duct damage / obstruction
    - Idiopathic
      - Vanishing bile duct syndrome (VBDS)
    - Infection
      - HIV infection
      - Viral hepatitis
      - AIDS cholangiopathy
      - Abscess
      - Tuberculosis
      - Liver flukes
    - Ischemia
    - Intra-/extrahepatic cholangiopathy
- Liver
  - Inflammation/immune
    - Primary biliary cholangitis (PBC)
    - Primary sclerosing cholangitis (PSC)
    - Sarcoidosis
    - Liver transplant (LT) rejection
  - Iatrogenic
    - Drugs (DILI)
    - Alcohol

- Infiltration
  - 1º/2º tumour
  - Amyloid
  - Lymphoma
  - RBC
    - Ischemia
    - Shock
    - Sickle cell crisis
- Injury
  - Admission to intensive care unit (ICU)
  - Shock
- Ischemia
  - Heart failure
- Inherited

- Pregnancy
- Bone
  - Osteomalacia
  - Paget disease
  - 1º/2º malignancy
- Placenta

❖ GGT

- Give the non-hepatic causes of ↑ GGT.
  - Heart
    - Myocardial infarction
  - Lung
    - Emphysema
  - Kidney
    - Renal failure
  - GI
    - Pancreatic disease
  - Drugs
    - Barbiturates
    - Phenytoin

❖ Viral hepatitis

- HCV infection
  - High risk for HCV infection
    - Parenteral exposure
      - Intravenous (IV)
      - Intranasal (IN)
      - Blood transfusions before routine HCV screening (US, 1992)
      - Needle stick exposures
      - Tattoos/body piercings

- Testing
  - Screen
    - HCV antibody
  - Because of HCV antibody testing having high (30%) false positives in some persons.
    - Follow HCV-positive antibody test with very sensitive HCV RNA CRP assay (please see http://www.hcvguidelines.org/full-report/hcv-testing-and-linkage-care)
  - Who to test for HCV?
    - Persons with
      - Risk factors for HCV infection
      - Acute/chronic liver disease
      - Individuals born within 1945-1965 birth cohort should be considered for universal HCV antibody testing independent of abnormalities in AST/ALT level
      - May be normal in the presence of chronic infection including abnormal liver disease (Centre for Disease Control [CDC], and United States Preventive Services Task Force [USPSTF])

Recommendations

- Test for acute HCV with anti-HCV and HCV RNA by nucleic acid testing.
- Test for chronic HCV with anti-HCV and if positive → confirm with HCV RNA.
- Access the patient for risk factors (Strong recommendation, very low level of evidence)
- Acute HCV infection
  - Unusual
  - Asymptomatic
  - No jaundice
- Post-exposure
  - HCV antibody usually becomes positive at wk 6-8 after HCV exposure

- HBV Infection
  - Mode of transmission
    - Endemic vertical/horizontal
      - Africa/Asia
    - Parenteral/sexual
      - "Western" countries
  - Risks of HBV infection
    - Birth in areas with prevalence > 2% (endemic hyperendemic)
    - Men who have sex with men (MSM)
    - Persons who inject drugs (PWID)
    - Renal dialysis patients
    - Pregnant women
    - HIV infection
    - Contacts
      - Family
      - Household
      - Sexual

- Testing
  - HBeAb
    - Exposure
    - HBV acute infection
    - IgM Hbc antibody
  - HBsAg
    - HBV infection
  - HBsAb
    - Immunity (natural/vaccination)
    - +/- HBV DNA HBV infection, viremia
  - HBe Ag/Ab
  - HB genotype
    - HBV viral load
  - Test for fibrosis
    - Liver biopsy
    - Non-biopsy e.g., FibroScan®

Recommendation

- Test for acute HBV with HBV with HBsAg and IgM anti-HBe
- Test for chronic HBV with HBsAg
- Those at risk of HBV (Strong recommendation, very low level of evidence)

❖ Non-Alcoholic Fatty Liver Disease (NAFLD)

- AST usually < 300 IU/L
  - May be normal simple steatosis, but ↑ 2x ULN suggests NASH
    - Indirect measures may suggest NASH/fibrosis, but "…liver biopsy is required to establish a diagnosis of NASH"

Recommendations

- Persons with ↑ BMI plus other features of metabolic syndrome (diabetes, hypertension, hyperlipidemia) with transaminitis should have abdominal ultrasound (AUS) for NAFLD (Strong recommendation, Very low level of evidence).
- The degree of steatosis may be quantified by
  - MRI
  - Elastography, plus controlled attenuation parameter measurement
- Liver biopsy
  - Required to diagnose NASH

❖ Alcoholic-related Liver Disease (ArLD)

- Give ways to distinguish ALD from NAFLD.
  - Clinical
    - History of alcohol intake
      - Males, > 210 g per wk
      - Female, > 140 g per wk
    - Physical findings, e.g.
      - Parotid gland enlargement, Dupuytren contracture

- Laboratory
  - AST, ALT < 300 IU/L but AST:ALT ratio > 2:1 (90%) (ratio of 3:1 makes ALD more likely)
- Suggestive of ALD
  - ↑ GGT (not helpful by itself, ↑ in > 50%)
  - ↓ folate
  - ↑ IgA

Recommendation

- Women who consume > 140 g per wk of alcohol, or men who consume > 210 g per wk and who have AST > ALT should be considered at risk for alcohol-related liver disease, and should be counselled for alcohol cessation (Strong recommendation, very low level of evidence)

❖ Autoimmune Hepatitis (AIH)

- More common in females than in men (4:1)
- Laboratory tests

Antibodies
Anti-nuclear (ANA)
Anti-smooth muscle (ASM)
Anti-liver kidney microsome (ALKM)
Anti-soluble liver antigen (ASLA)
↑ IgG

- Liver biopsy required to diagnose AIH (to include the results of the liver biopsy as part of the scoring system to determine whether diagnosis of AIH is possible, or probable.

Recommendation

- Persons with transaminitis, especially if they have another autoimmune condition, should have testing for AIH: anti-nuclear antibody (ANA), anti-smooth muscle antibody (ASMA), and immunoglobulin (IgG) (Strong recommendation, very low level of evidence).

❖ Hereditary hemochromatosis (HH)

- Prevalence C282Y homozygous mutation is ~400/10^5 rates
  - Patient may be C282Y homozygous
    - Do **not** develop the HH phenotype
    - Have another cause for abnormal iron tests, or another cause of liver disease
- Abnormal AST/ALT, family of HH
  - Transferrin solution > 45%, ferritin > 1000 µg/d → perform genetic testing, consider liver biopsy
- Liver biopsy
  - Stage fibrosis
  - Quantify iron absorption
  - Determine fibrosis/location of hepatic iron (parenchyma likely HH; Kupffer cells, likely non-HH)

Recommendation

- Persons with abnormal liver chemistries not due to acute hepatitis should have testing for serum iron, transferrin saturation (TS) and serum ferritin concentration.
- Perform testing for HFE mutation if TS ≥ 45% +/- ↑ ferritin (Strong recommendation, very low level of evidence)

❖ Wilson disease

- ↑ ALT/AST, family history, personal history of neuropsychological problems → serum ceruloplasmin, 24 h urine copper, slit-lamp examination for Kayser-Fleischer rings → generates testing for ATP7B mutation
- Liver biopsy confirms diagnosis
  - Stage fibrosis
  - Quantity copper deposition

Recommendations

- Patient with transaminitis, especially < 55 yr old, perform serum ceruloplasmin to screen for Wilson disease
  - If ↓ ceruloplasmin, perform 24 h urine copper plus slit lamp examination for "pathognomic" Kayser disease Fleischer rings (Strong recommendation, very low level of evidence)

❖ Alpha-1 anti-trypsin deficiency

- Suspect in patient with
  - Family history
  - Personal history of lung disease
    - Panacinar emphysema
    - Chronic obstruction lung disease (COPD), especially in a non-smoker
- Testing
  - ↓ alpha-1 anti-trypsin
  - Genotype
    - PiZZ mutation
    - PiMZ mutation
      - Lesser but significant risk of chronic liver disease, especially if associated steatosis, or HBV/HCV

Recommendation

- In patients with persistently increased and unexplained transaminitis [and non-smoking emphysema/COPD], perform screening for α-antitrypsin deficiency with α1-antitrypsin phenotype (Strong recommendation, very low level of evidence)

❖ Drug-induced liver injury (DILI)

- Many drugs give changes in ALT/AST, but particularity the following classes of “anti-drugs”
  - Biotics (anti-biotics)
  - Epileptics
  - Non-steroidal (anti) inflammatory
  - Retroviral
  - Tuberculosis
  - Tumour / anti-cancer (chemotherapy)

Recommendation

- In patients with abnormal liver chemistries, ask about prescribed and over-the-counter (OTC) medications, non-prescribed complementary or alternative medicines (CAMs) or dietary / herbal supplements, for possible dieting (Strong recommendation, very low level of evidence).
- Most commonly, acetaminophen
  - ALT/AST may be > 1000 IU/L

❖ Cholestatic Liver Disease

Recommendation

- ↑ alkaline phosphatase (AP), ↑ gamma glutamyl transferase (GGT)
  - If ↑AP → perform GGT to determine if ↑AP likely due to liver disease
- Do **not** use GGT as a screening test for liver disease without other liver chemistries being abnormal (because of low specificity of GGT (Strong recommendation, very low level of evidence)

- Primary biliary cholangitis (PBC)
  - Chronic damage to intralobular bile ducts
  - ↑ AP/GGT +/- ↑ bilirubin
  - Anti-mitochondrial antibody positive
  - ↑ IgM

Recommendation

- In patients with ↑AP (due to hepatic cause): ↑ total bilirubin, perform testing for anti-mitochondrial antibody testing for PBC (Strong recommendation, very low level of evidence).

❖ Primary Sclerosing Cholangitis (PSC)

- Laboratory
  - ↑ ANCA (anti-neutrophil cytoplasmic antibody)
  - ↑ IgG4
- Histopathology
  - Intrahepatic duct
    - Thick
    - Inflamed
    - Dilated
  - Fibrosis
    - Periductal fibrosis, concentric: “onion skin”
- Diagnostic imaging
  - MRCP
    - Multiple strictures of extra-/intrahepatic bile ducts

❖ Other Cholestatic Conditions: suspect from association

○ PSC but no ulcerative colitis	− HIV/AIDS cholangiography
○ Neuropsychiatric symptoms	− Wilson disease
○ Bronze skin, diabetes, cardiomyopathy	− HFE-hemochromatosis (HH)
○ Hematological malignancy plus chemotherapy	− Sinusoidal obstruction syndrome (SOS; aka veno-occlusive disease [VOD])
○ Post-operative / hypercoagulable condition	− Thrombosis (HV, PV, SV)

❖ Hyperbilirubinemia

- Serum level of total bilirubin
  - ↑ serum level of total bilirubin → fractional into direct / indirect bilirubin

- Indirect (unconjugated)
  - RBC hemolysis
    - ↓ haptoglobin
    - ↑ reticulocytes
    - ↑ lactic dehydrogenase (LDH)
  - Liver
    - ↓ bilirubin
      - Uptake
      - Conjugation

Clinical Gem

- Give the exception to the general rule that chronic hemolysis generally does not cause total bilirubin > 5 mg/dL.
  - Presence of hemolysis plus
    - Acute hemolysis (rather than chronic)
    - Kidney/liver disease co-existing

- Direct (conjugated) hyperbilirubinemia
  - Causes
    - Hepatic parenchymal disease
    - Bile ducts
      - Obstruction
  - Total bilirubin may be > 30 g/dL, especially from
    - Hepatic parenchymal disease
      - Alcohol hepatitis, cirrhosis
      - Cirrhosis, advanced
      - Renal failure
      - Sepsis
      - Post-operative, isolated direct hyperbilirubinemia
    - Inherited direct hyperbilirubinemia (50%)
      - Dubin-Johnson syndrome
        - ↓ multidrug resistance (MDR) gene
      - Rotor syndrome
        - ↓ hepatocyte storage of bilirubin

SO YOU WANT TO BE A GASTROENTEROLOGIST!

- Give the reason why in the patients with alcohol-related liver disease (ArLD) there is ↓ALT compared with AST, resulting with a ratio of AST to ALT > 2:1.
  - In ArLD, there may be pyridoxine deficiency which results in ↓ALT but not ↓AST, resulting in the reversal of this ratio.

- Liver biopsy (please also see RCP/ROR Guidelines, 2020)

- Give liver conditions for which liver biopsy may be considered.
  - Autoimmune hepatitis (AIH)
  - Drug-induced liver disease (DILI)
  - HFE-associated iron overload (HH [hereditary hemochromatosis])
  - Non-alcoholic steatohepatitis (NASH)
  - Wilson disease (WD)

Recommendations

- Indications for liver biopsy “when serological testing / imaging fails to provide diagnosis”
- Proposes
  - Diagnose
  - Stage
  - Determine extent of fibrosis
  - Guide treatment

  (Strong recommendation, very low level of evidence)

Abbreviations: AGA, American Gastrointestinal Associations; AIDS, acquired immunodeficiency syndrome; AIH, autoimmune hepatitis; ALKM, anti-liver kidney microsome (antibody); ALT, alanine aminotransferase; ANA, anti-nuclear antibody; AP, alkaline phosphatase; ArLD, alcohol-related liver disease; ASLA, anti-soluble liver antigen; ASM, anti-smooth muscle (antibody); AST, aspartate aminotransferase; Bil, bilirubin; BMI, body mass index; CAM, complementary alternative medicines; CDC, Center for Disease Control; DILI, drug induced liver injury; F, female; GGT, gamma-glutamyl transferase; HAV, hepatitis A virus; HBc, hepatitis B core antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; HEV, hepatitis E virus; HH, hereditary hemochromatosis; HV, hepatic vein; ICU, intensive care unit; IgM, immunoglobulin M; INR, international normalized ratio; M, male; MDR, multidrug resistant (gene); MR, magnetic resonance; NAFLD, non-alcoholic fatty liver disease; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis; PV, portal vein; RBC, red blood cells; RNA, ribonucleic acid; SV, splenic vein; ULN, upper limit of normal; US, United States; USPSTF, United States Preventive Service Task Force; WD, Wilson disease; wk, week; α1-AT, alpha 1 antitrypsin

Abnormal Liver Blood Tests: Guidelines: BSG (2017)

Newsome PN, et al. Gut 2018;67(1):6-19.

- Demography
  - In persons < 65 yr, the standard mortality rate is increasing due mostly to
    - Alcohol-related liver disease (ArLD)
    - Non-alcoholic liver disease (NAFLD)
    - Hepatitis B/C viral infection (HBV/HCV)
    - Autoimmune hepatitis (AIH)

- Clinical
  - Caution
    - Liver disease may be asymptomatic until late in the patient's illness

- Laboratory
  - The standard screen for the etiology abnormal liver blood tests include:
    - HBsAg
    - HCV antibody (HCV RNR on PCR if HCV-antibody positive)
    - Serum immunoglobulins
    - Anti-mitochondrial, smooth muscle/nuclear antibodies
  - Liver enzymes (ALT, AST, AP) and liver function tests (albumin, bilirubin, INR, platelet count) do **not** necessarily become abnormal early in the liver disease, and do **not** necessarily reflect the extent of liver disease

Recommendation

- In the patient with liver disease suspected from history/physical examination, perform
  - Liver enzymes (LEs, alkaline phosphatase [AP], gamma glutamyl transferase [GGT], ALT and AST)
  - Complete blood count (CBC), unless already done in past 12 mon (level 2 b, grade B)
- ↓ platelet numbers reflect the presence of fibrosis
- It is uncertain whether it is best to define a liver blood test as being abnormal as
  - "…a value outside the standard reference interval", or as the number of times the value exceeds the upper limits of normal (ULN).
- INR value reflects extent of liver disease, and not coagulation status in patients with liver disease.
  - Liver injury is > 70% when there is ↑ INR
    - Remember that ↑ INR may occur in cholestatic liver disease
- Albumin functions
  - Binds bilirubin, drugs, fatty acids
  - Maintains oncotic pressure
  - Metabolism (e.g., lipids)
  - Antioxidant

- Platelet number (thrombocytopenia)
  - ↓ production
    - Alcohol
    - Drugs
    - Iron overload
    - Viral infections
  - ↑ sequestration
    - Portal hypertension/hypersplenism
  - ↑ destruction
    - Bacterial translocation
    - Fibrinolysis
    - Sheer stress
    - Immune-mediated damage e.g., antiphospholipid immunoglobulin
- ↑ AP in isolation
  - May be bone origin e.g.,
    - Vitamin D deficiency
    - Paget disease
    - Metastases to bone
    - Rarely may be ↑ in pregnancy
- GGT
  - Present in
    - Liver, pancreas, intestine
    - Kidney
    - Prostate
  - Has low specificity for liver disease
  - Do **not** use by itself for screening (use if ↑ AP)
    - Good prediction of liver-related mortality
- Addition of GGT to liver blood test panel ↑ likelihood of an adult having abnormal liver blood tests from around 15% and 30%.
- ALT is more liver-specific than AST, which is also present in
  - Muscle
    - Skeletal
    - Cardiac
    - Smooth
  - AST may however be more sensitive than ALT for detection of liver injury in
    - Alcohol-related liver disease (ArLD)
    - Autoimmune hepatitis (AIH)
- If ratio AST > ALT (x1.5), suspect
  - Non-alcoholic liver disease (NAFLD)
  - Alcohol related liver disease (ArLD)
  - Advanced fibrosis of liver

Recommendations

- Further evidence is required to establish the most cost-effective approach to identify patients with ArLD and NAFLD at risk of having advanced liver fibrosis.
- Interpret abnormal liver blood tests in the context of the
  - Current medical condition / medical history
  - Past liver tests

  (Level 5, grade D)
- Extent
  - The clinical significance of an abnormal blood test (outside the laboratory reference range) should be interpreted from the
    - Clinical context
    - Previous results, past-medical history, the current medical condition (Level5, grade D)
    - If known duration of the abnormal liver blood tests (level 2 b, grade B)
    - The extent of liver blood test abnormality does not necessarily reflect clinical significance (Level 5, grade A)

- Duration
  - When abnormal liver blood tests are reported over time, 84% remain abnormal in 1 mon, and 75% at 2 yr.

❖ Non-alcoholic fatty liver disease (NAFLD)

- In the patient with suspected fatty liver
  - Perform abdominal ultrasound (AUS)
    - An echo bright liver indicates ↑ liver lipid
- Follow the abdominal ultrasound (AUS) with liver biochemistry tests, and a scoring system

		Abnormal		
		< 65 yr	> 65 yr	
First-line	NAFLD fibrosis score (NFS)	< -1.455	< 0.12	
	Fibrosis-4 (FIB-4)	< 1.3	< 2.0	
Second-line	Serum enhanced liver fibrosis (ELF) if			
	NFS	1.455 to 0.675		Indeterminant values, therefore do ELF
	FIB-4	< 3 – 3.25		
	or			
	FibroScan® or acoustic radiation force impulse)			

  - Suggest values for referral to specialist
    - NFS > 0.475
    - FIB-4 > 3.25
    - ELF > 9.5, or
    - FibroScan® > 7.8 Pa

- In patients in whom alcohol is suspected to be the main injurious factor, the extent of consumption influences early decision-making.
  - For those drinking at harmful levels (≥35 units/wk women and ≥50 units/wk men)
    - An assessment of liver fibrosis is the critical next step.

- Please note the recent Canadian recommendation on "safe" alcohol intake as no more than two drinks a day and no more than two per wk.

- For other patients, administration of the AUDIT C questionnaire plus brief intervention is recommended initially.
- For patients who continue to drink at hazardous levels
  - For the higher-risk category according to liver fibrosis evaluation.
- This is particularly important for those with a GGT of >100 U/L.
- Cut-off points for ARFI vary according to manufacturer and thus should be tailored to the device used.
- The Steatosis Activity and Fibrosis (SAF) score is superior to NAS, especially in the intermediate scores (supported by European guidelines)

Abbreviations: ARFI, acoustic radiation force impulse; ELF, enhanced liver fibrosis; GGT, γ-glutamyl transferase; HCC, hepatocellular carcinoma.

➢ Non-invasive algorithms for gauging liver fibrosis in patients with NAFLD

NAFLD fibrosis score	−1.675 + 0.037 × age (yr) + 0.094 × BMI (kg/m^2) + 1.13 × IFG/diabetes (yes=1, no=0) + 0.99 × AST/ALT ratio – 0.013 × platelet (×109/L) – 0.66 × albumin (g/dL) www.nafldscore.com
Fibrosis-4 (Fib-4)	(age × AST) / (platelets × (√ALT)) https://gps.camdenccg.nhs.uk/fib-4-calculator

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; IFG, impaired fasting glucose; NAFLD, non-alcoholic fatty liver disease.

Printed with permission: Newsome PN, et al. Gut 2018; 67(1): 6-19. (Table 3).

Parameter	NFS	FIB-4
Age	+	+
BMI	+	
ALT	+	+
AST	+	+
Platelets	+	+
Glucose (fasting)	+	
Albumin	+	

- AUS for Screening for AAFLD
    - The abdominal ultrasound (AUS) becomes echobright indicating fatty liver disease when the hepatocytes a > 30% steatotic
        - If NAFLD suspected but US negative, consider
            - LE testing
            - Follow-up US/LEs testing including CGT
            - Careful assessment for ↑ intake of alcohol
    - Stratify all patients with NAFLD for their risk of fibrosis
        - First line
            - NFS or FIB-4 (level 2bm grade B)
            - Calculation facilitations for Fib-4 and NFS should be incorporated in all primary care computer systems (level 5, grade D)
        - Second line
            - ELF, or FibroScan®/ARF electrography (level 2 b, grade B)
            - Encourage use of these recommendations by primary, secondary, and tertiary care physicians

❖ Alcohol related Liver Disease (ArLD)

- Alcoholism
- The relationship between alcohol intake and the risk of alcohol-related cirrhosis is exponential, not linear.
    - ↑ relative risk increasing from ~3 to 20 units of alcohol per wk, to a RR of 30 for 80 U/wk
    - The value of the RR increases when BMI > 35
- When a physician suspects possible alcohol abuse in their patient (harmful, at-risk drinkers), perform an AUDIT assessment
    - An AUDIT score > 19 represents “alcohol dependence” (first use AUDIT-c, followed by 10-item AUDIT if AUDIT-c is positive)

Recommendations

- Refer patient for alcohol-dependency when AUDIT score > 19 (level 3b, grade C)
- In addition to the clinical assessment / Audit score
    - Weekly (units per wk) intake of alcohol
        - Men ≥ 50
        - Women ≥ 35

        } → Perform FibroScan® / ARFI elastography
- Performing biochemical testing is also appropriate, but the above recommendations prevail even when AST/ALT, GGT are normal, because
    - LEs may be normal in the presence of alcohol use in excess and the at-risk patient.

- Harmful drinkers should have clinical assessments
  - If evidence of cirrhosis / portal hypertension e.g., FibroScan® > 16 kDa, refer for specialist care (level 2b, grade B)
- Adults with abnormal liver blood tests (even with a negative extended liver etiology screening and no risk factor for NAFLD)
  - Refer to a gastroenterologist with an interest in liver disease / hepatologist for further evaluation (level 4, grade C)

Abbreviations: ALT, alanine aminotransferase; AP, alkaline phosphatase; ARFI, acoustic radiation force impulse; ArLD, alcohol-related liver disease; AST, aspartate aminotransferase; BMI, body mass index; BSG, British Society of Gastroenterology; CBC, complete blood count; ELF, enhanced liver fibrosis; GGT, gamma glutamyl transferase; HBV, hepatitis B virus; HCC, hepatocellular cancer; HCV, hepatitis C virus; INR, International Normalized Ratio; LEs, liver enzymes; LFTs, liver function tests; NAFLD, non-alcoholic fatty liver disease; NFS, NAFLD fibrosis score; PCR, polymerase chain reaction; RR, relative risk; US, ultrasound; yr, year

MCQ GEMS

- Causes of ALT > 1000 IU/L
  - Liver
    - Acute viral hepatitis
    - Autoimmune hepatitis (AIH)
    - Drug-induced liver injury (DILI)
    - Wilson disease (WD)
  - Bile duct
    - Obstruction
  - Vascular
    - Budd-Chiari syndrome (HV obstruction)
    - HA obstruction
    - Ischemic hepatitis
  - Common Infectious Complications of Liver Transplantation

AD	Adenovirus
CMV	Cytomegalovirus
EBV	Epstein Barr Virus
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
VZV	Varicella Zoster Virus

Assessment of Hepatic Fibrosis in Patients with NAFLD: Elastography

Tapper EB and Loomba R. Nat Rev Gastroenterol Hepatol 2018; 15: 274-282.

- Liver stiffness marker (LSMs)
  - Biochemical
  - Imaging
    - Acoustic resonance radiation force impulse (ARFI)
    - Magnetic resonance elastography (MRE)
    - Shear-wave elastography (SWE)
    - Vibration-controlled transient elastography (VCTE; only VCTE may be used at point-of-care)
  - Cut-off values are established for each device, and for each hepatic condition
    - Confounders which affect elasticity of the liver
      - Blood
      - Fluid
      - Infiltration/steatosis
      - Post-prandial hyperemia
      - Heart failure
      - Inflammatory cells
    - Range of indeterminant results with confidence intervals +/- 10% to 20%
      - The question to be answered: optimize false positive and false negative values
    - The continuous values generated from these LSMs is dichotomized into cut-off for the presence or absence of advanced fibrosis

Elastography and the Evaluation of Hepatic Fibrosis: Guidelines (AGA)

Lim JK, et al. Gastroenterol 2017; 152(6):1536-1543

➢ Basic concepts

- "the assessment of liver fibrosis represents a central component in the evaluation of chronic liver fibrosis"
- A surrogate measure of fibrosis is needed because of the complications of liver biopsy when used to assess the histological extent of fibrosis:
  - Morbidity
    - Pain, 30%
    - Bleeding, severe, < 1%
    - Tumour seeding
  - Mortality
    - ~0.33%
  - Sampling error
    - Intra-/inter-observer

❖ Vibration-controlled transient elastography (VCTE)

- Acceptable variability
- Probe placed in 9th to 11th right intercept/space
  - Probes
    - M 25-65 mm
    - XL 35-75 mm
  - Obtain
    - Validated measurement
    - With quartile median value of stiffness < 30%

- ↓ accuracy of readings
  - Intake of food, within 2-3 h
  - Heart failure
  - Acute hepatitis
  - Alcohol abuse
  - Cholestasis, extrahepatic
  - The cut-off for abnormal VCTE varies by the underlying cause of fibrosis, e.g., alcohol-related chronic liver disease, HCV-associated chronic liver disease

- Non-invasive tools for liver fibrosis
  - Performance characteristics, HCV infection

Test	Sensitivity (95% CI)	Specificity (95% CI)
APRI*	0.77 (0.73-0.81)	0.74-0.81
FIB-4**	0.87 (0.74-0.94)	0.91 (0.89-0.92)
VCTE	0.89 (0.84-0.92)	0.91 0.89-0.92)

*Aspartate Aminotransferase to platelet ratio

**"Caution should be exercised in the relevance of any fibrosis assessment tool in ruling in or ruling out cirrhosis"

➢ HCV infection

Recommendations

- In patients with chronic HCV infection, diagnose cirrhosis with VCTE rather than with propriety non-invasive serum tests, e.g., APRI or FIB-4 (GRADE: Strong recommendation, moderate quality evidence)
- In order to minimize a false-negative value, or to miss the diagnosis of cirrhosis, the cut-off for liver stiffness was 12 K kPa, with pooled-sensitivity, 0.86 (95% CI, 0.83-0.88) and specificity, 0.91 (95% CI: 0.89-0.92)
  - Misclassification, < 5%
  - Overclassification (false positive), < 10%

  } ▪ If patient classified as having fibrosis → perform HCC screening
- In patients with chronic HCV, use the VCTE cut-off of 12.5 kPa to establish the presence of cirrhosis (Conditional recommendation, low-quality evidence)
- In patients with HCV infection, use VCTE not MRE to detect cirrhosis (GRADE: Conditional recommendation, very-low quality evidence)
- Performance characteristics of VTE vs. MRE to detect cirrhosis

	Sensitivity (95% CI)	Specificity (95% CI)
− MRE	0.89 (0.84-0.92)	0.91 (0.89-0.92)
− VCTE	0.94 (0.87-0.97)	0.81 (0.61-0.98)

- Rule out advanced liver fibrosis in previously non-cirrhosis patients with HCV who achieve a sustained virological response with anti-HCV therapy using a post-treatment VCTE of < 9.5 kPa (GRADE: Conditional recommendation, very-low quality evidence)

- HBV infection: cut-off to diagnose HBV chronic infection with VCTE
  - Perform characteristics

Test	Sensitivity (95% CI)	Specificity (95% CI)
− VCTE	0.86 (0.79-0.81)	0.85 (0.78-0.89)
− APRI	0.66 (0.47-0.85)	0.74 (0.56-0.84)
− FIB-4	0.87 (0.79-0.92)	0.65 (0.51-0.73)

  - VCTE
    = FIB-4 to **rule in** cirrhosis
    >FIB-4 to **exclude** cirrhosis

Recommendation

- In patients with chronic HBV infection use VCTE rather than other propriety non-invasive serum tests (e.g., or FIB-4) to diagnose cirrhosis (GRADE: Conditional recommendation, low-quality evidence)

- HBV infection: cut off to diagnose cirrhosis by VCTE in patients with cirrhosis

Recommendation

- In patients with chronic HBV, use the VCTE cut-off of 11 kPa to diagnose cirrhosis

- Non-alcoholic liver disease (NAFLD)
  - Performance characteristics NAFLD

Test	Sensitivity (95% CI)	Specificity (95% CI)
− VCTE	0.90 (0.82-0.95)	0.87 (0.85-0.89)
− APRI	0.78 (0.71-0.97)	0.71 (0.030-0.93)
− FIB-4	0.74 (0.54-0.87)	0.71 (0.64-0.76)

    - The above tests were determined to be "…subject to unacceptable bias due to intrinsic limitations of available studies"

Recommendation

- In patients with NAFLD, **no** recommendation is made regarding use of VCTE to diagnose cirrhosis.

➢ NAFLD: VCTE vs. MRE to detect NAFLD-associated cirrhosis

Risk of Cirrhosis	Sensitivity (95% CI)	Specificity (95% CI)	
≤ 5% low-risk	− Poor performance of both VCTE and MRE		
> 30% high-risk*			
− VCTE	0.84 (0.60-0.97)	0.89 (0.84-0.93)	▪ High false positive
− MRE	0.83 (0.59-0.96)	0.72 (0.65-0.75)	

*Examples of high-risk factors for NAFLD-associated cirrhosis

- ↑ age
- ↑ BMI (body mass index, i.e., obesity)
- Diabetes mellitus
- ↑ LEs (liver enzymes

Recommendations

- In adults with diagnosed NAFLD cirrhosis
  - Low risk: VCTE = MRE
  - High-risk: MRE superior to VCTE (GRADE: Conditional recommendation, low quality evidence)

➢ Chronic Alcohol-related Liver Disease (ArLD)

Test	Sensitivity (95% CI)	Specificity (95% CI)
○ VCTE	0.95 (0.87-0.98)	0.71 (0.56-0.82)

- Chronic ArLD (VCTE cut off, 12 kPa)

Risk Cohort	Prevalence of Advanced Fibrosis	Prevalence of Cirrhosis	
		FPT	FNT
− Lower	5%	28%	0.2%
− Higher	Obesity/coinfection; HBV, HIV	1.5%	20%

Abbreviations: FNT, first negative test; FPT, false-positive test; HBV, hepatic B infection; HIV, human immunodeficiency infection; VCTE, vibration-controlled transient elastography

Recommendation

- In patients with ArLD, use the VCTE cut off 12.5 kDa to detect cirrhosis.
  - Note that this cut off value for VCTE is **not** applicable to patients with acute alcoholic hepatitis (AAA)

- Remember
  - Patients who are falsely labelled with a diagnosis of cirrhosis may still have advanced fibrosis (F3).
  - Persons with ArLD and F3 have risk of HCC, as also with other chronic liver diseases, and they benefit with HCC screening by abdominal ultrasound (AUS).
  - Use this cut off value of 12.5 kDa for selection of patients to screen for esophageal varices.

➢ Suspected compensated cirrhosis: ruling out high risk esophageal varices (EV) with VCTE

- Platelet count and risk of having EV in patients with newly diagnosed compensated cirrhosis, with no obvious features of portal hypertension.

Platelet count	Risk of EV
> 150,000	Low, 5%
< 150,000	High, 20%

- EV, VCTE cut-off 19.5 kPa

Test	Sensitivity (95% CI)
VCTE for EV	0.89 (0.84-0.92)

- EV misclassified

	Rule out FN	
– Low risk	0.6%	▪ Falsely reassured
– High risk	2.2%	

- Cut-off for VTE for diagnosis of high-risk esophageal varices

	VTE, kPa
– American Gastroenterology Association (AGA)	19.5
– Baveno VI Consensus Workshop	20

Recommendation

- In patients with suspected compensated cirrhosis and VCTE ≥ 19.5 kDa, perform EGD (esophagogastroduodenoscopy) to identify esophageal varices at high risk of bleeding (GRADE: Conditional recommendation, low-quality evidence).

- Elective non-hepatic pre-operative Care: Chronic liver disease and need to rule out clinically significant portal hypertension (PHT)
  - In patients with chronic liver disease, their risk of EV may be estimated from VCTE to determine if EGD should be perform before pre-operative care for elective non-hepatic.
    - Using VCTE cut off 17.0 kDa, performance characteristics for clinically significant portal hypertension

Sensitivity (95% CI)	Specificity (95%CI)
0.83 (0.80-0.87)	0.52 (0.47-0.57)

- Probability of clinically significant PHT

Prevalence	Misclassification of PHT
0.5%, very low	0.1%
5%, low	0.8%
40%, high	7%

Recommendation

- In patients with suspected chronic liver disease who are for elective non-hepatic surgery, perform pre-operative VCTE, with cut-off 17.0 kDa to detect having clinically signification portal hypertension, and to thereby "…uniform pre-operative care (GRADE: Conditional recommendation, low-quality evidence).

- Summary
  - VCTE superior to APRI/FIB-4 to diagnose cirrhosis in patients with HCV, HBV, NAFLD, ArLD, and
    - VCTE is superior to MRE in HCV, but not in NAFLD
  - Cut-off values of VCTE varies, depending upon diagnosis and complication being assessed.

Diagnosis	pKa
+ArLD	12.5
+ chronic HCV,	
▪ Untreated	12.5
▪ Treated	9.5
+ HBV	11.0
+ NAFLD	-

    - Complications: to rule out
      - High-risk esophageal varices (need for EGD to diagnose), ≥ 19.5
      - Clinically significant portal hypertension (need for pre-op EGD), ≥ 17

Abbreviations AGA, American Gastrointestinal Association; ArLD, alcohol-related liver disease; BMI, body mass index; CI, confidence interval; EV, esophageal varices; F, fibrosis; HBV, hepatitis B virus; HCV, hepatitis C virus; LEs, liver enzymes; MRE, magnetic resonance elastography; NAFLD, non-alcoholic liver disease; VCTE, vibration-controlled transient elastography

Use of Liver Biopsy in Clinical Practice Guidelines: British Society of Gastroenterology (BSG), **Royal College of Pathology** (RCP), **Royal College of Radiology** (RCR)

Neuberger J, et al. Gut 2020; 69: 1382-1403.

- Complications (percutaneous liver biopsy [PCLB])
  - Bleeding
    - Risk factors
      - Age
      - Coagulation status
      - Comorbidities
      - Indication for liver biopsy
      - Lesion, diffuse or focal (targeted biopsy)
  - Perforation
  - Infection
  - Death (<1/1000 biopsies)

- Coagulation status
  - Abnormal
    - Coagulation
    - Thrombolysis

    } ▪ "Rebalanced" → prothrombotic state in persons with chronic liver disease
  - Do **not** use fresh frozen plasma to ↓ bleeding risk
  - Safety targets
    - Diffuse lesions (non-lesional biopsies, INR > 1.4)
    - Lesional (mass) biopsy, INR < 2.0 (percutaneous)

- Indications

- Histopathological
  - Diagnosis
    - Identification
    - Severity
    - Prognosis/progression
    - Response to treatment
  - Other indications
    - Culture/microbiology
    - Biochemistry (e.g., context of copper, iron)

Recommendations

- All healthcare professionals included in requesting, obtaining and interpreting the liver biopsy need to be aware of the indication(s) for the biopsy (Strength of recommendation STRONG; quality of evidence WEAK).
- Multidisciplinary/multiprofessional discussions must occur and be recorded in the patient's clinical notes, especially if the biopsy is done outside guidelines or protocols (Strength of recommendation STRONG; quality of evidence WEAK).

❖ Biliary tree

- Obstruction (extrahepatic biliary obstruction [EBO])
  - Serious complications (e.g., biliary peritonitis) 2 to 4%

Recommendation

- Perform liver biopsy in patients with EBO only if the diagnosis is in doubt after appropriate diagnostic imaging (e.g., MRCP, ERCP)
- If the patient with EBO requires the biopsy after appropriate imaging, use the transjugular approach (transjugular liver biopsy; TJLB) to ↓ risk of leakage from biliary tree.
- Bacterial cholangitis
  - ↑ risk of bacteremia (14%) after percutaneous liver biopsy in patient with presumed bacterial cholangitis → peritonitis / septic shock
    - "Cholangitis is a relative contraindication to liver biopsy"
- Amyloidosis
  - When biopsy done in patient with known amyloidosis
    - ↑ risk of death, 5%
  - Suspected amyloidosis
    - Hepatomegaly
    - ↑ monoclonal immunoglobulins, serum and urine
    - ↑ light chains in urine
- Liver biopsy is absolutely needed for patient with suspected/proven amyloidosis
  - Use transjugular route (TJLB)
- Focal lesion, cystic component
  - These lesions may communicate with the biliary tree → ↑ risk of biliary infection
  - After diagnostic imaging
    - If biopsy of a focal hepatic lesion is still necessary
    - Treat risk factors e.g.,
      - Biliary infection/obstruction
      - Optimize patient / ↓ ascitic fluid
      - Patient sedation, if appropriate / necessary for performing a liver biopsy
    - Use fine needle aspiration (FNA)
    - Attempt to biopsy the solid component of the focal lesion without passing through the cystic component
  - "…biopsy justified when the risks are outweighed by the benefit"
- Ascites
  - In the patient with large-volume ascites
    - Drain/mobilize ascitic fluid before performing PCLB under ultrasound / CT guidance, or
    - Generally speaking, do **not** perform liver biopsy in the presences of large volume ascites, even under ultrasound guidance
- Obesity
  - In patient with obesity, use PCLB under ultrasound guidance or TJLB

- Pregnancy
  - In the pregnant patient with new onset liver disease in which the biopsy cannot be deferred until after delivery (e.g., an unusual life-threatening situation)
    - Consider the benefit of the biopsy vs. the risks to the mother and baby, such as small ↑ risk of premature birth.

Recommendations: Procedure

- Patient with stable liver disease, INR 1.5 to 2.0
  - Proceed with PCLB
  - There may be ↑ risk of patient has portal hypertension on cirrhosis

  (Strength of recommendation MODERATE; evidence MODERATE).
- Do **not** use fresh frozen plasma (FFP) before PCLB, unless INR > 2.0 (Strength of recommendation STRONG; evidence MODERATE).
- Hospital policies must be in place to ensure that any person performing the liver biopsy is "… suitable experienced [competent] to undertake liver biopsies independently (i.e., with competent physician in attendance) (Strength of recommendation STRONG; evidence HIGH).
- Percutaneous liver biopsy (PCLB)
  - Best procedure for
    - Non-high-risk indication / patient
    - Diffuse parenchymal liver disease (i.e., non-focal) suspected

- Procedure
  - Informed consent
    - Spoken and written in simple, non-medical language, and including risks, benefits and options

- Guided biopsies
  - Perform liver biopsy under ultrasound guidance
    - If this is not possible, ensure there has been a liver ultrasound within past 3 mon
  - Needle
    - Diffuse lesion (16 G)
    - Targeted solid lesion (18 G)

    } ▪ Full core, automated cutting-type

    - Indicated if the biopsy is targeted to a focal lesion, or non-targeted for diffuse parenchymal liver disease (Strength of recommendation STRONG; evidence HIGH).
  - Length > 20 mm
  - 2 passes may be necessary
  - For persons who have had PCLB for non-localized lesions
    - Have patient lie on their right side after PCLB (possible ↓ risk of bleeding)

Recommendations

- Communication between clinical/pathologist is essential to improve diagnosis.
  - The biopsy report should include clinical indication and diagnostic summary (Strength of recommendation STRONG; quality of evidence HIGH).
  - There should be access for the opinion of a second histopathologist, if required/appropriate (Strength of recommendation STRONG; quality of evidence HIGH).
- Monitor patient (pain, blood pressure, pulse rate) q30min for ≥ 3 h after PCLB (low risk patient, monitor longer if patient is high risk) (Strength of recommendation STRONG; evidence WEAK).
- Patients who have LB for indication of suspicion of hepatic malignancy, and who are at ↑ risk of bleeding:
  - Liver biopsy may be safely done as a day case procedure if
    - There are no ↑ risk factors, and
    - The patient can be looked after when they have left hospital, can seek appropriate advice, and access appropriate medical help if needed

    (Strength of recommendation STRONG; evidence WEAK).

- Diffuse non-focal disease suspected

Recommendations

- Imaging guidance is recommended during procedure – ultrasound, CT, MRI guidance (high degree of accuracy)
- If guidance not possible, ensure patient has had liver imaging within past 3 mon (Strength of recommendation; STRONG; evidence WEAK).
- Use guidance biopsy when suspected
  - Focal lesion which requires targeted biopsy
  - Anatomical changes, if
    - Previous liver lobe resection
    - Split liver graft
- PCLB with ultrasound guidance has lower complication rates than without guidance for core biopsy (14G, 15G, 20G)

Clinical Pearl

- In patient with platelet count < 50x 10^9 /L, biopsy liver using TJLB rather than PCLB.

- Biopsy needle
    - Complications
        - Bleeding
            - Tru-cut® needle, 3/1000
            - Menghini-type needle, 1/1000
        - Inadequate biopsies
            - BioPince®16 G needle, 2%
            - Achieve® 18 G needle, 48%

Recommendation

- Use automated cutting type needles
    - "…familiarity with the device should also be taken into consideration when choosing the needle (Strength of recommendation MODERATE; evidence WEAK).

- Optimal size of biopsy
    - In order to have visualization of complete portal tracts (CPTs), the biopsy must be ≥ 20 mm, long and the thickness obtained by a 16 G needle.
        - It is necessary for the histopathologist to have sufficient tissue to visualize 6 portal tracts
            - It is ideal to have ≥ 11 portal tracts per tissue section

- Number of needle passes
    - The number of passes does not ↑ severity of complications
        - If one pass does not provide adequate material, repeat the biopsy pass a second time (but no more than two times)
    - In order to obtain the necessary CPTs, it may be necessary to make two passes because
        - Short biopsies underestimate
            - Fibrosis stage
            - Inflammation grade
        - Make 2 passes / central biopsy
        - < 10 mm to 20 mm in length, and the purpose of the biopsy is to establish
            - Fibrosis stage
            - Biliary tract disease

Recommendations

- Perform one pass for the biopsy "… unless the diagnostic yield is likely to produce insufficient material for a full histological examination (< 10 mm, or 10 mm to 20 mm, for indication of assessment of fibrosis stage, or to investigate biliary tract disease.
- For suspected diffuse parenchymal (non-focal) liver disease
    - Use full core biopsy needles ≥ 18G (as long as the operator is experienced / competent with the use of this needle).

- Antibiotics

Recommendation

  - Do **not** use antibiotic prophylaxis before PCLB, except if
    - Previous history of post-biopsy infection, or
    - Overt biliary infection/sepsis

    (Strength of recommendation MODERATE; evidence WEAK)

- Plugged liver biopsy
  - Use of coaxial introducer needle plus ultrasound guidance
    - Inner trocar removed, then introduce cutting needle
      - This allows multiple passes of the needle, but only one trocar puncture of the liver capsule
      - Many materials have been tried, e.g., blood products, cyanoacrylate glue, fibrin, frozen plasma gelatin sponge
  - Complications: morbidity
    - 7 d mortality from
      - PCLB, all case death 2/1000 biopsies
      - PCLB, cancer investigation 12/1000
      - Directly from PCLB 1/10,000 (often in patients with cirrhosis/cancer)
    - Bleeding
      - Major 6/1000 biopsies
      - ↑ risk with
        - > 50 yr
        - Concurrent diagnosis/comorbidities
        - Coagulopathy:

INR	
1.2 to 1.5	3.3%
> 1.5	7.1%

} ↑ rate of bleeding

        - Hemoperitoneum $32/10^5$
        - Hemothorax $22/10^5$
        - Hemobilia $6/10^5$
    - Puncture
      - Lung puncture $14/10^5$
      - Gallbladder $12/10^5$
      - Kidney $3/10^5$
      - Colon $2/10^5$

➢ Transvenous Liver Biopsy

Recommendation

  - Use a transvenous approach such as TJLB is if platelet count < 50 x 10^9 /L (Strength of recommendation STRONG; evidence MODERATE).

- Transvenous liver biopsy
  - Transjugular liver biopsy (TJLB)
    - Long length, 18/19 G automated cutting-type biopsy needle
    - Use when PCLB contraindicated
    - Complications
      - Minor, 6.5%
      - Major, 0.56%
      - Mortality
        - Bleeding, 0.06%
        - Cardiac arrhythmias, 0.03%
    - TJLB is considered to be safer than PCLB when clotting process is abnormal
    - Multiple needle passes may be done safely
  - Complication rate may be high for TJLB performed after bone marrow transplantation

Recommendation

- Perform TJLB if the indication is suspected non-lesional / diffuse parenchymal liver disease, plus if INR > 1.4 (Strength of recommendation MODERATE; evidence MODERATE).
- For TJLB, at least 2 biopsies should be taken (Strength of recommendation STRONG; quality of evidence HIGH).
- Transfemoral liver biopsy
  - Alternate to transjugular liver biopsy

- Endoscopic ultrasound guided liver biopsy (EUS-LB)
  - Percutaneous EUS-guided liver biopsy for non-targeted and targeted lesions

Biological Outcome	EUS	PCLB
- Number of portal tracts on biopsy	13	5
- Sufficient tissue for diagnosis	100%	93%

  - Features
    - ↑ resolution
    - ↑ detection of smaller lesions missed on CT/MRI
    - Ideal for both focal and non-focal lesions
  - Adverse effects

	EUS-LB	PCLB
- Any/all adverse event	2.3%	9.8%
- FND needle vs. core biopsy needle	0.9%	2.7%

- Laparoscopic liver biopsy (LLB)
  - Use for patients with coagulopathy when TJLB not available
    - May be performed with standard laparoscopy or mini-laparoscopy
    - Superior to PCLB
      - With Menghini needle for non-focal disease
      - For diagnosis of cirrhosis
  - Complications
    - Delayed bleeding (abdominal wall or site of biopsy in liver), 0.7%
      - ↑ risk

	Odds Ratio
- ↓ platelets	0.1
- INR (> 1.5)	8.9
- Portal hypertension (PHT)	2.1
- Cirrhosis	1.9

    - Abdominal adhesions from previous abdominal surgery
    - Intestinal perforation, 0.3%
    - Death, 0.07%

Recommendations

- Community physicians must have ready access to have their patients seen and evaluated for suitability and performance of liver biopsy (Strength of recommendation STRONG; evidence WEAK).
- In patients with chronic liver disease who require LB and have experienced a previous procedure-related bleeding which was not related to portal hypertension,
  - Consult a hematologist with an interest in hemostasis (Strength of recommendation STRONG; evidence WEAK).

❖ Anticoagulation and Antiplatelet Drugs

- Testing Coagulation Status in Patient with Liver Disease
  - Rebalance in hemostasis in liver disease
    - ↓ procoagulants
      - Factor VIII / von Willebrand Factor, relative to
    - ↓↓ anticoagulants, including vitamin K dependent INR sensitive fibrinogen and factors II, V, VII, X
    - ↓ platelets
  - This rebalance may lead to a procoagulant state, as seen with ↑ risk of thromboembolic disease in patients with cirrhosis
    - Including hepatic vein (HV), portal (PV), splenic vein (SV), and deep vein thrombosis (DVT)

- In patients with compensated liver disease (CLD)
  - The INR is
    - A good predictor of abnormal hepatic synthetic function, but
    - A bad predictor of coagulation status (risk of bleeding), because both the pro-/anti-coagulant proteins fall in liver disease → rebalance
      - INR is usually not an independent risk factor for bleeding in CLD
      - For assessment of coagulation status of patient with chronic liver disease, consult a hematologist with an expertise in coagulation disorders, with access to clot viscoelastic assay assessment.
  - Vitamin K deficiency may occur in patients with chronic liver disease, as the result of
    - Malnutrition
    - Malabsorption/cholestatic liver disease
    - Use of antibiotics

Recommendations

- Give vitamin K before LB to correct possible deficiency (Strength of recommendation STRONG; evidence WEAK).
- In patients with chronic liver disease/cirrhosis who require invasive procedure but INR > 1.8 +/- platelets < 50 x 10^9 /L
  - Use viscoelastic assays to provide a thromboelastogram-guided transfusion strategy
    - ↓ use of blood predicts → ↓ bleeding, ↓ unnecessary prophylactic transfusions
    - No ↓ major bleeding or death
- Note that the viscoelastic assays have not yet been proven "…to reliably predict bleeding in patients with liver disease"
- Testing coagulation status in persons with chronic liver disease
  - Generation of thrombin
  - Viscoelastic hemostatic assays

  } ▪ These tests of "global hemostasis" are **not** recommended at this time (Strength of recommendation LOW; evidence WEAK)

- Antiplatelet agents
  - The anti-platelet P2Y inhibitors (e.g., clopidogrel) have an antiplatelet effect which lasts 7-10 d
    - Stop these drugs 7 d before those elective procedures which have an ↑ risk of bleeding
      - If not possible to stop P2Y12 inhibitor this far in advance, then stop as soon as possible before intervention
      - A platelet transfusion may be required prior to surgery/invasive procedure
      - It may also be reasonable to perform TJLB (transjugular) rather than percutaneous liver biopsy (PCLB).
  - Aspirin
    - Stop 7 d before invasive procedure/surgery
      - If performing a liver biopsy is urgent (rare) then "…aspirin can be continued at the discretion of the clinician"

- Anti-coagulants
- Aspirin plus P2Y12 inhibitor (Clopidogrel) (direct oral anticoagulants [DOCAs])
  - Delay liver biopsy, or delay ASA for 7 d, but continue Clopidogrel
  - Consult with appropriate specialist, e.g., cardiologist, for patient with cardiac stent
- Dipyridamole
  - Stop just on the day of liver biopsy
- Low-molecular weight heparin (LMWH)
  - Prophylactic dose
  - > prophylactic dose

  } Stop before procedure
  - 12 h
  - 24 h
- Direct oral anti-coagulants (DOAC)

Drug	Time to stop before liver biopsy
Clopidogrel	7 d
Aspirin (ASA)	3-7 d
DOAC	2 d
LMWH, high dose	1 d (24 h)
LMWH, low dose	12 h

A Comment

- "…pausing aspirin may not [always] be necessary and should be at the discretion of the operator [the person performing the liver biopsy] if urgent"

- Stop warfarin 5 days before LB and use bridging LMWH, if appropriate.
- Stop DOAC 2 days before LB, or longer before if the patient is taking dabigatran, and depending upon renal function (Cr_s)

Recommendations

- Stop aspirin 3 d before PCLB "where time allows", but the decision will depend upon
  - The indications for aspirin, and
  - The urgency of biopsy

  (Strength of recommendation MODERATE; evidence WEAK)

- Maintain local monitoring of serious complications e.g.
  - Bleeding requiring blood transfusion
  - Bile leaks
  - Pain requiring hospitalization
  - Death due to liver biopsy

  (Strength of recommendation STRONG; evidence WEAK)
- Perform periodic audits of practice, outcomes, quality improvement.
- If liver biopsy (LB) is used for a research purpose, local/national/professional guidelines with respect to the taking of the LB must be stringently respected, including
  - Informing the patient that the biopsy is done partly or only for research purposes (Strength of recommendation STRONG; evidence HIGH).)
  - Consent must be obtained, and local/national guidelines must be followed (Strength of recommendation STRONG; evidence HIGH).
- Informed consent must be communicated verbally as well as in writing, and in a media/language which can be understood by the patient (Strength of recommendation STRONG; quality of evidence HIGH).
- Informed consent given to patient must include risks and benefits of the procedure (Strength of recommendation STRONG; quality of evidence HIGH), must be readily understandable (Strength of recommendation MODERATE; quality of evidence WEAK).

Suggestions

- It is suggested that the research which is proposed for consideration by the members of the human ethics committee be scientifically sound and of quality to meet the standards of excellence required for national/international journals and professional/scientific organizations.
- The ethics committee must have in place ethical and legal precautions for persons who are in any way impaired to provide free and non-pressured consent, including persons help “at his Majesty’s request” (in prison).
- The ethics committee must be made aware of every and all benefits coming to the investigation, included financial benefit to the investigator, and the information must be provided to the patient or their legal guidelines.
- The committee must have in place a policy with regards to the acquisition of biopsy tissue taken from persons on life support, who are brain/cardiac dead.
- Note added by author
  - The same holds true if LB to be obtained after death of the patient

Abbreviations: ASA, aspirin; CT, computed tomography; d, days; DAA, direct acting anticoagulant; DVT, deep vein thrombosis; ERCP, endoscopic retrograde cholangiopancreatography; EUS, endoscopic ultrasound; EUS-LB, endoscopic ultrasound guided liver biopsy; EVB, esophageal variceal bleeding; FFP, fresh frozen plasma; FNA, fine needle aspiration; G, gauge of biopsy needle; HE, hepatic encephalopathy; h, hour; HRS, hepatorenal syndrome; HV, hepatic vein; INR, international normalized ratio; LB, liver biopsy; LLB, laparoscopic liver biopsy; LMWH, low molecular weight heparin; MRCP, magnetic resonance cholangiopancreatography; MRI, magnetic resonance imaging; PCLB, percutaneous liver biopsy; PV, portal vein; SBP, spontaneous bacterial peritonitis; SV, splenic vein; TJLB, transjugular liver biopsy; TPO-RAs, thrombopoietin receptor agonist; yoa, years of age

ALCOHOL-ASSOCIATED LIVER DISEASE (ALD)

Alcohol-associated Liver Disease (ALD): **Practice Guidance** (AASLD) **2019**

Crabb DW, et al. Hepatology 2020; 71(1):306-333.

- Previous Guideline (2010) Updates
  - Definitions
    - Alcohol use disorder (AUD)
    - Alcoholic hepatitis
  - Factors
    - Genetics
    - Environmental
  - Biomarkers
  - Screening
  - Treatment of alcoholic hepatitis
    - Corticosteroids
    - Liver transplantation

➢ Terminology

ALD, alcohol-related/-associated liver disease

AH, alcoholic hepatitis

AC, alcoholic-associated cirrhosis

AUD, Alcohol use disorder

ASH, steatohepatitis due to ALD

ALDF, fibrosis due to ALD

ALDC, alcoholic liver disease associated with cirrhosis

➢ Demography

- Prevalence
  - ALD
    - 2% of US population
  - AC
    - US Veterans, $327/10^5$
    - US insured, $100/10^5$
  - AH, ~$4/10^5$

➢ Natural history

- Factors influencing rate of progression from pre-stage to another (↑ risk of ALD)
  - Patient
    - Continued alcohol intake
    - Binge drinking / dose above threshold (> 14 g alcohol drink per day: women, 1; men. 2)
    - Associated liver disease, e.g.,
      - Hepatitis C infection
      - Hemochromatosis
      - Non-alcoholic fatty liver disease (NAFLD)
    - Female
    - Smoking
    - Obesity (↑ BMI)
    - Family history

      Polymorphisms

      - Genes: HSD17B13, MBOAT7, PNPLA3, TM6SF2
      - Twins, monozygotic
  - Diet

➢ Screening for AUD

- The "screening tests do **not** provide a diagnosis of AUD, but rather point to the most for a formal assessment"
- Suggestion
  - A one-question initial screen: How many times in the past year have you had 5 or more drinks in a day (for men) or 4 or more drinks in a day (for women)?" (National Institute of Alcohol Abuse and Alcoholism)
- If ≥ 1 episode meeting the above criteria
  - Do the Alcohol Use Disorders Inventory Test (AUDIT)
  - Examples of interpretation of AUDIT scores
    - > 8, harmful / hazardous use of alcohol
    - > 20, moderate / severe AUD (aka alcohol dependence)

Biomarkers (alcohol use)

- Caution
  - Should not be used on their own to confirm or refute alcohol use, but
  - Should be combined with other lab testing (including other alcohol biomarkers), physical examination and the clinical interview"
- Common liver tests
  - ↑ AST
  - ↑ bilirubin
  - ↑ gamma-glutamyl transferase (GGT)
  - Macrocytosis
- Carbohydrate-deficient transferrin (CDT)
  - ↑ with alcohol inhibition of glycosylation of transferrin
  - Often reported as % CDT 9cdt / total transferrin)
  - T1/2, 2-3 wk
- Urinary ethyl glucuronide (EtG) and ethyl sulfate (EtS)
  - Metabolites of alcohol by uridine diphosglucuronate-glucuronosyltransferase and diphosphoglucoronate sulfotransferase
  - Also useful to detect alcohol intake in persons with
    - Liver transplantation
    - Other liver conditions
- Phosphatidylethanol (PEth)
  - In the presence of alcohol, phosphatidylcholine is metabolized by phospholipase D
  - T1/2 10-14 d

➢ Treatment (AUD)

- Best option
  - "Integrated, multidisciplinary care remains the best option for management of advanced ALD and AUD"
  - Therapy
    - Individual, group, couple, family, network
    - Alcoholics anonymous
  - Psychologic
    - Cognitive behaviour therapy (CBT)
    - Motivational enhancement therapy (MET)
    - Contingency management
    - 12-step facilitation

- Pharmacotherapy (relapse prevention)
  - Disulfiram is FDA-approved to treat AUD, but is not recommended in patients with ALD, and is not included in the table below

Relapse Prevention Medications in Patients with Alcoholic Liver Disease (ALD)

Medication	Metabolism (M) and Excretion (E)	Mechanism of Action
○ Acamprosate*	− M: None − E: Renal	▪ NMDA receptor antagonist
○ Baclofen**	− M: Hepatic, limited − E: Renal	▪ GABA-B receptor agonist
○ Gabapentin**	− M: None − E: Renal 75%, fecal 25%	▪ Modulates GABA activity through action at presynaptic calcium channels
○ Naltrexone***	− M: Hepatic − E: Mostly renal, fecal 2%-3%	▪ Opioid receptor antagonist
○ Topiramate	− M: Not extensively metabolized − E: Renal	▪ GABA action augmentation, glutamate antagonism

*FDA-approved for AUD treatment. Disulfiram is not included on this list because it is not recommended for use in patients with ALD.
** only AUD pharmacotherapy tested in RCT in patients with AC plus AUD, may ↓ mentation
*** possible hepatotoxicity

Abbreviations: GABA, gamma-aminobutyric acid; NMDA, *N*-methyl-D-aspartate; NNT, number needed to treat; sq, subcutaneous; and t.i.d., 3 times per day

Adapted from: Crabb DW, et al. Hepatology 2020; 71(1):306-333 (Table 4)

Guidance Statements

- Patients without liver disease
  - Advice regarding safety levels of alcohol
    - Men ≤ 2
    - Women ≤ 1
- Patients with AUD / advanced ALD, refer to
  - ALD treatment profession
  - Multidisciplinary / integral management
  - Consider use of acamprosate
- Patient with ALD plus other liver diseases, but especially HBV/HCV, NAFLD/NASH, hemochromatosis
  - No alcohol: there is no safe level of alcohol

- Alcoholic Hepatitis

➢ Definition

Clinical Syndrome

- Clinical diagnosis of AH
  - Onset of jaundice within prior 8 wk
    - Ongoing consumption of > 40 (female) or 60 (male) g alcohol/day for ≥ 6 mon, with < 60 d of abstinence before the onset of jaundice
  - AST > 60, AST/ALT > 1.5, and both values < 400 IU/L
    - Serum total bilirubin > 3.0 mg/dL
- Potential confounding factors
  - Possible ischemic hepatitis (e.g., severe upper gastrointestinal bleed, hypotension, or cocaine use within 7 d) or metabolic liver disease (Wilson disease, alpha 1 antitrypsin deficiency)
  - Possible drug-induced liver disease (suspect drug within 30 d of onset of jaundice)
  - Uncertain alcohol use assessment (e.g., patient denies excessive alcohol use)
  - Presence of atypical laboratory tests (e.g., AST < 50 or > 400 IU/L, AST/ALT < 1.5), ANA > 1:160 or SMA > 1:80

Abbreviations: AH, alcoholic hepatitis; ALT, alanine aminotransferase; ANA, antinuclear antibody; AST, aspartate aminotransferase; and SMA, smooth muscle antibody.

➢ Subtypes

- Possible – Clinically diagnosed with potential confounding factors
- Probable – Clinically diagnosed without potential confounding factors
- Definite – Clinically diagnosed and biopsy proven

➢ Scoring systems

Characteristics of Lab-based Prognostic Scores in Alcoholic Hepatitis

Clinical Use		Bili	PT/INR	Cr/BUN	Age	Alb	WBC	Stratification	Remark
Initiate corticosteroids	MDF	+	+	-	-	-	-	Severe: ≥32	
	GAHS	+	+	+	+	-	+	Poor prognosis: ≥9	If ≥9 and MDF ≥32
Prognosis only	MELD	+	+	+	-	-	-	Severe: ≥21, but a continuous scale	
	ABIC	+	+	+	+	-	-	Low: <6.71	
Day 7 cessation or continuation of corticosteroids	Lille	+	+	+	+	+	-	≥0.45: Nonresponse <0.45: Response	

Abbreviations: ABIC, age-serum bilirubin, INR, serum creatinine; Alb, serum albumin; Bili, serum total bilirubin; Cr/BUN, creatinine/blood urea nitrogen; MDF, Maddrey discriminant function; MELD, Model for End Stage Liver Disease; PT/INR, prothrombin time/international normalized ratio; WBC, white blood cell count

Adapted from: Crabb DW, et al. Hepatology 2020; 71(1):306-333 (Table 7)

- Function
  - Corticosteroids
    - Start
      - MDF ≥ 32 (predictive only at 4 wk beware false positive), GAHS ≥ 9, plus MDF ≥ 30
      - Non-responsive (day 7) ≥ 0.45 (partial response, 0.46-0.56)
    - Stop
      - Lille
  - Prognosis
    - MELD Severe ≥ 21
    - ABIC Mild, < 6.71

    } Uncertain threshold for starting corticosteroids
  - ↑ prediction by combining models
    - MELD ≥ 21
    - Lille ≥ 0.45

    } MR at 2 mon, 24% (MR only with 1 test, 13%
- Biomarkers
  - Cytokeratin-18 (CK-18), circulating fragments
  - Mallory-Denk bodies, main constituents, M65/M30

  } AUROC, 0.84

Abbreviations: AUROC, area under the operating characteristic curve

- Other scoring systems (in development)
  - Gene expression patterns of 123 genes plus MELD (gs-MELD)
    - Differentiates good vs. poor risk of 90-d survival (AUROC, 0.86)
  - AHHS (alcoholic hepatitis histologic score)
    - Score histological features of inflammation, fibrosis, megamitochondria and bilirubinostasis
    - Differentiate low, moderate, high risk of 90-d survival (AUROC, 0.77)

➢ Histopathology

- Inflammation
  - Lobular
  - ↑ neutrophils
- Degeneration
  - Ballooning of hepatocytes
  - Mallory-Denk bodies

- Fibrosis
  - Pericellular
    - Changes may be found in patients with no symptoms, and only mildly abnormal biochemistry
    - Biopsy similar in NASH vs. ASH

➢ Guidance Statement

- Diagnose AH using the definition provided, take into account possible confounding factors, and classify as possible, probable and definite

Subtype	Clinical Diagnosis	Confounding Factors	Liver Biopsy
− Possible	+	+	
− Probable	+		Definite
− Definite	+		+

- Predictors of mortality in AH by way of lung/kidney diseases, and infection
  - Markers of infection
    - ↑ C-reactive protein (CRP)
    - ↑ DNA, bacterial.
    - ↑ lipopolysaccharide
    - ↑ Procalcitonin

    } Predict 90-d mortality
  - Systemic inflammatory response syndrome (SIRS)
  - Acute kidney injury (AKI) due to hepatorenal syndrome (HRS)

- Guidance Statements
  - Use MDF ≥ 32 / MELD > 20 to guide starting corticosteroids
  - Use “lab-based” prognostic scores
  - Recommend to abstinence from alcohol in survivors of AH (all patients with ALD should totally avoid alcohol)

➢ Prognosis

- AH, severe, 6 mon mortality rate, 70%
- First episode of AH
  - Mortality rate
    - 1 yr, 6%
    - 3 yr, 84%
  - Sustained alcohol intake
    - 1 yr, 10%
    - 3 yr, 17%

- Treatment
  - Alcohol
    - Abstinence (some patients may be best served by “harm reduction models”
  - Nutrition
    - Intensive conventional nutrition or enteral nutrition
    - ↑ calorie intake to > 21.5 kcal/kg per day (decreases 6 mon rates of infection / mortality from 66% to 33% ($p < 0.0001$)
    - Replace deficient vitamins / minerals, such as zinc
  - Corticosteroids (CS)
    - Recent metanalysis showed ↓ 28 d mortality rate (MR) of 36% (HR, 0.64; 95%CI, 0.48-0.86)
    - While CS → ↓ 28-d MR, but not at 90-d or 1 yr
    - Even very sick patients with AH may benefit from CS

- Contraindications to use corticosteroids in patients with AH
  - While some specialists may advise no use of CS in AH if there is an infection, ↑ serum creatinine (Crs) or gastrointestinal bleeding
    - Infection increases long but not short term mortality, so start CS in appropriate patients with AH while starting CS
    - If the acute ↑Crs can be managed by
      - Avoid nephrotoxic drugs / excess diuretics
      - Only treatment of hepatorenal syndrome
    - A retrospective study has shown that there is difference in survival (1, 3, and 6 mon) between AH patients with or without GI bleeding
  - N-acetylcysteine (NAC) plus corticosteroid
    - Acetylcysteine (NAC) plus corticosteroids
    - ↓ early
      - Infection
      - HRS
    - 1 mon MR ↓ from 24% with CS, vs. 8% with CS plus NAC ($P = 0.006$)
    - Network meta-analysis of 22 RCTs → combination of CS plus NAC superior to CS alone (RR, 0.28; 95%CI, 0.10-0.69)
  - Granulocyte-colony stimulating factor (GCSF)
    - GCSF plus pentoxifylline (PEN) vs, PEN alone (RTC) → greater ↓ 90-d /improved prognostic scores
      - Because it is disputed whether PEN by itself has any benefit, then in a sense it was a placebo, so future studies of the benefit of GCSF are encouraged
  - Other studies
    - Metadoxine
    - Fecal microbiota transplantation
    - Pentoxifylline

    } ▪ Pilot studies are suggestive of benefit

      - “The STOPAN trial and the higher-quality meta-analysis of individual patient data has failed to demonstrate and benefit of pentoxifylline”

Guidance Statement

- Give prednisolone 40 mg po per day to patients with severe AH, MDF ≥ 32, who do **not** have contraindications to its use
  - Add NAC to the prednisolone (↑ 30 d survival)
- Use the Lille score to identify patients who have not responded to CS and thus the CS should be stopped versus those who did respond to CS in the first 7-d and this the CS should be continued a further 3 wk (total of 88 d for CS)
- Do **not** use pentoxifylline
- Optimize nutritional status of patient
- If patent recovers, recommend total abstinence from use of alcohol

➢ Liver transplantation (LT)

- Timing
  - The consensus regarding the appropriateness and application of the 6-mon rule ("patient must be abstinent from alcohol for a minimal of 6 mon before listing for LT") has lessoned
  - "There is no single measure [such as a prognostic score or psychological assessment] that reliably predicts alcohol relapse after LT"
  - It is important to distinguish a minor relapse of alcohol intake post-LT, from a level of alcohol intake which risks the development of ALD in the transplanted liver
  - Patient with a severe relapse in alcohol intake (in women, > 20 g/d, in men, > 30 g/day) occurs in 18% of post-LT ALD patients
    - In this group of severe relapses, cirrhosis develops in the LT in 32%, over 5 yr post-LT (median time to cirrhosis, 1 yr)
    - Mortality rate, ~66%
- Prediction (US) if post-LT patients with sustained alcohol intake ("SALT" score)

	Points
Initial presentation > 10 drink/d	4
Multiple prior attempts at rehabitation	4
Previous legal issues related to alcohol	2
Previous use of illicit substances	

Negative predictive value (NPV) for future sustained alcohol use, SALT score < 5, (95%CI 89% - 98%)

Guidance Statement

- Do **not** base the selection for LT in patients with alcohol-associated cirrhosis on just a fixed interval of abstinence
- Refer patients with alcoholic-associated cirrhosis for LT if they are MELD-Na ≥ 21, or CPT class C
- Carefully consider LT in patients with severe AH who have
  - Failed medical therapy, and
  - "Favourable psychosocial profile"

Alcoholic Liver Disease (ALD)**: AGA Clinical Guideline (2018)**

Singal AK, et al. Am J Gastroenterol 2018; 113: 175-194

- Demography
  - Alcoholic liver disease (ALD) as a cause of cirrhosis-associated deaths, 48%
    - Variability due to
      - Patient age
      - Concomitant HBV/HCV infection
      - Obesity
      - Alcoholic steatohepatitis (ASH)
      - Smoking
      - Binge-drinking / long-term heavy alcohol intake
      - Development of HCC
  - Alcohol use disorder (AUD)
    - 1 person in 12 has AUD, as defined by consumption (drinks per day, “drink” increasing 4 g of alcohol
      - Males, > 3
      - Females, > 2

      or
    - Binge drinking (National Institute of Alcoholism and Alcohol Abuse [NIAAA])
      - Males, > 5
      - Female, > 4
  - Mortality rates
    - Cirrhosis, $12/10^5$
    - Alcohol-related cirrhosis, ~$6/10^5$

- Disease burden
  - The relationship between amount / duration of alcohol intake and development of ALD has numerous modifiers
    - Only about 10-20% of persons with ALD develop “clinically important ALD”
  - Mortality
  - Morbidity
    - Drinking accidents (31% of all drinking fatalities)
    - Violence (e.g., intimate partner abuse)
  - Prognosis
    - Decompensation (hepatic encephalopathy, esophageal variceal bleeding, ascites)
    - MR
      - 1 yr, 25%
      - 5 yr, 50%
    - MR with abstinence
      - 5 yr, 40% vs. 70%

- Modifiers / Cofactors for risk of alcoholic cirrhosis,
  - Demography
    - Female sex
      - ↑ risk due to ↑ body fat content
    - Obesity
    - HBV/HCV infection
    - Iron overload (hereditary hemochromatosis)
    - Smoking
  - Genetic, environmental behavioral

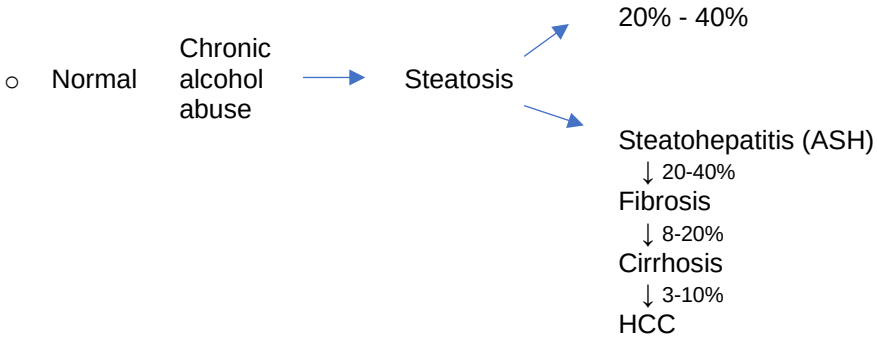
Recommendations

- No alcohol intake for persons with obesity / chronic HCV
  - Are at ↑ risk of ALD and should not consume alcohol (Conditional recommendation, very low level of evidence)
- No smoking in persons with ALD (Conditional recommendation, very low level of evidence)

- Genetics
  - Susceptibility
    - Modifiers of
      - Neurotransmission and amino butyric acid (GABA)
      - Alcohol metabolism
        - Alcohol dehydrogenase
        - Acetaldehyde dehydrogenase
  - Natural history
    - Endotoxin response
    - Inflammation, modifiers
    - Oxidative stress
  - Main determinant for risk / severity of ALD (disease progression)
    - Phospholipase domain containing protein 3 (PNPLA3)

- Spectrum
  - Even when there is decompensated liver disease, abstinence may lead to favourable regression to compensated cirrhosis

➢ Progression



- About 50% of patients with AUD / early liver disease already have advanced fibrosis (F3) or cirrhosis (F4)
- Persons with AUD who develop alcohol withdrawal syndrome (AWS) ↑ prevalence of ASH

- Alcohol Use Disorder (AUD)

➢ Assay patient's intake of alcohol

- History from family member
  - Time of day, frequency, type (binge), date of last drink)
- Physical examination from alcohol intake
  - Dupuytren contracture

- Alcoholic Hepatitis (AH)

➢ Clinical

- Usually presents with jaundice plus other liver-related complications
  - May occur at any stage of any liver disease, but
    - 80% of persons with severe AH (discriminant function [DF] ≥ 32; model for end-stage liver disease [MELD] score > 20 already have cirrhosis
- Laboratory tests
  - ↑ ALT or ↑ AST, ↑ ration of AST/ALT > 2, ↑ GGT, ↑ blood alcohol, RBC mean corpuscular volume, carbohydrate deficient transferrin
  - ↑ urinary ethyl glucuronide
- Screening tests
  - AUDIT screening test, original or short version of alcohol abuse and dependent test (AUDIT-C)

Condition	AUDIT Score
AUD	> 8
Alcohol dependence	> 20

Use the Alcohol Use Disorder Inventory Test (AUDIT, long or short form) to help identify the patient with alcohol obese and dependence

- Key comments and statements
  - In persons with harmful alcohol use +/- AUD
    - Perform liver function tests
    - Do **not** routinely do liver biopsy
    - To diagnose steatohepatitis / fibrosis
      - Consider doing non-invasive testing or liver biopsy

Recommendation

  - Tell persons who consume large amounts of alcohol (M > 3 drinks per day; F > 2/d) that they have ↑ risk for liver disease (Strong recommendation, low level of evidence)
  - Psychosocial factors
    - Patient Health Questionnaire (PHQ)
    - Have you had little interaction or pleasure in doing things
    - Have you been feeling down, depressed, or hopeless?
    - Generalized Anxiety Disorder (GAD)
    - Over the past 2 wk
      - Have you had a feeling of being nervous, anxious, or edge?
      - Not been able to stop or control worry
  - If PHQ or GAD score ≥ 3, the patient is at risk of AHD and needs “further intervention”

➢ Treatment

- Alcohol Use Disorders (AUD)
  - Abstain from alcohol
    - Pharmacological
      - Baclofen (γ amino butyric acid – β receptor agonist)
        - Safe in patients with AUD who already have ALD
        - Dose: 5 mg t.i.d. po, with slow ↑ dose q3-5 d until tolerance reached, but no more than 15 mg t.i.d.
      - Outcomes
        - ↓ risk of relapse of abstinence
        - Prevent/treat alcohol withdrawal syndrome (AWS)
    - Non-pharmacological
      - Cognitive behaviour therapy (CBT)
      - Motivational
        - Enhancement
        - Interviewing

        } Therapy
      - Psychoeducation

- For family physician/internists intervention: key components
  - Ask
    - About alcohol use
  - Assess
  - Assist
  - Advice
  - Average follow-up

  } Willingness to ↓/stop intake of alcohol

Recommendations

- In patients with ALT,
  - ↓ risk of relapse with baclofen (Conditional recommendation, low level of evidence)
  - Motivational interventions (Conditional recommendation, very low level of evidence)
- Key concept statement
  - "Complete abstinence from alcohol consumption is the cornerstone in the management of every spectrum of ALD"
- Approach the treatment of ALD with a multidisciplinary team, including alcohol addiction specialists

- Alcohol Withdrawal Syndrome (AWS)

➢ Definition

- Sudden reduction / cessation of alcohol intake in persons with alcohol dependence leading to characteristic symptoms as well as serious complications such as
  - Delerium, tremors, seizure, coma
  - Cardiac arrest / death (including sudden cardiac death)

➢ Symptoms

- CNS
  - Anxiety, irritability, headache
  - Tremors, hyperreflexia
- Cardiac
  - Hypertension, tachycardia, sudden cardiac death
- GI
  - Nausea/vomiting

➢ Treatment

- Determine severity; if moderate/severe
  - Admit to ICU
  - Monitor with Clinical Institute Withdrawal Assessment for Alcohol (CIWAA) score

- Benzodiazepines
  - Mild liver disease
    - Diazepam, chlordiazepoxide (long-acting, ↓ risk of delirium, seizures)
  - Severe liver disease
    - Lorazepam, oxazepam (short acting)
- Baclofen
  - Prevent / treat
  - Prevent alcohol relapse

Key Concepts and Statements

- Manage AWS using CIWAA protocol
- In patients with severe AWS
  - Use benzodiazepines
- Malnutrition
  - Calories
  - Protein
  - Vitamins / minerals
  - Manage
    - Obesity / diabetes if present
    - Smoking cessation
- Vaccination
  - HAV, HBV
  - Pneumococcus
  - Influenza
  - Covid
- Screening
  - Hepatocellular cancer
    - If F3 (advanced fibrosis), F1 (cirrhosis)
    - Heathy carrier of HBV infection

    } Doppler ultrasound of abdomen q1yr, +/- alpha-fetoprotein
  - Ascites
    - Low salt diet, diuretics, treat underlying liver disease
    - Paracentesis
      Diagnostic for spontaneous bacterial peritonitis (SBP)
      Therapeutic
      Hepatorenal syndrome: Albumin: day 1, 1.5 g/kg; day 3, 1 g/kg
  - Esophageal varices
    - When EGD when diagnosis made of F3/F4 fibrosis
    - Non-specific beta blockers or endoscopic band ligation for primary/secondary prophylaxis against bleeding
    - If bleeding from GI tract, give prophylactic antibiotic against SBP
  - Assess whether ≥ minimal HE present
    - Lactulose, antibiotics
    - Correct underlying risk factors

- Differential
  - Other CNS disease
  - Drug overdose
- Hepatic encephalopathy (HE)
- Thromboembolism
  - Anticoagulation

- Alcoholic Hepatitis

➢ Clinical

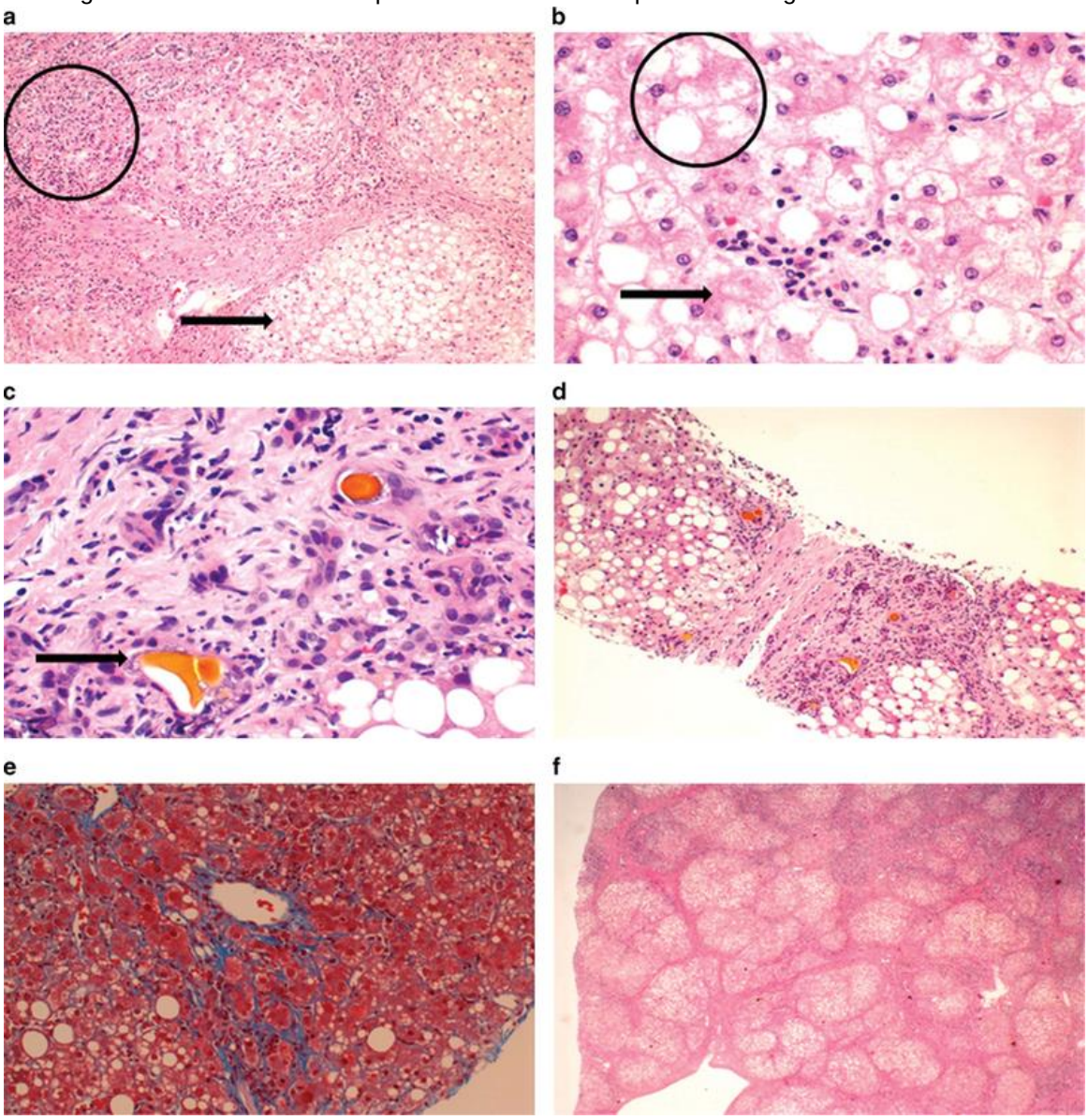
- Alcohol use, including date of last drink (see below re importance of diagnosis of AH with respect to onset of jaundice)
- Non-specific symptoms e.g., fatigue
- Jaundice
  - Recent or worsening of previous jaundice
  - In the setting of previous heavy alcohol intake up to ≥ 8 wk before jaundice
- Signs of
  - Alcohol intake
    - Dupuytren contracture
    - Rhinophyma
  - CLD
    - Jaundice
    - Palmar erythema
    - Spider angioma
  - Portal hypertension
    - Splenomegaly
    - Ascites
    - Hepatic encephalopathy)
  - AWS
    - CNS
    - CVS
    - GI symptoms
  - Systemic inflammation response syndrome (SIRS)
    - May be present even in the absence of infection
    - ≥ 20 of the following
      - HR > 100 bpm (beats per min)
      - RR > 12 breaths per mins
      - Temperature, > 38^{o}C or 36^{o}C
      - WBC, > 12,000 or < 4,000

Abbreviations: AWS, alcohol withdrawal syndrome; CLD, chronic liver disease; CVS, cardiovascular system; GI, gastrointestinal; HE, hepatic encephalopathy

- Laboratory
  - AST > 50, but < 400 IU/L
    - AST/ALT ratio > 1.5
  - Infection testing
    - WBC
    - Urinalysis
    - Ascites diagnostic paracentesis
    - Cultures blood, urine
    - Chest x-ray

- Subtypes
  - Clinical
    - "unclear" history of alcohol intake
    - Conditions other than AH possible → possible AH
    - No other causes of liver disease
    - Alcohol intake
      - Heavy, > 5 yr → probable AH
      - Until 4 wk before presentation
    - AST/ALT > 1.5, ↑ AST but < 400 IU/L
  - Clinical, laboratory evidence, plus compatible histopathology (cannot distinguish alcoholic steatohepatitis from non-alcoholic liver disease based only on histological changes)

Histologic features of alcoholic hepatitis and Alcoholic Hepatitis Histologic Score



(a) Circle represents lobular inflammation and arrow represents steatosis, (b) circle and arrow represent cell ballooning, (c) arrow represents cholestasis with bile canalicular and hepatocyte plugging, (d) steatosis and fibrosis, (e) chicken wire and pericellular fibrosis, (f) cirrhosis.

Printed with permission: Singal AK, et al. Am J Gastroenterol 2018; 113: 175-194 (Figure 4).

- Prognostic score
  - Maddrey discriminant Function (MDF) ≥ 32 predicts 30 d mortality rate of 20% to 50%
  - MELD score > 20 in AH predicts MR ~20%
  - Lille score < 0.45 at day 4 to 7 of patient with AH treated with corticosteroids suggest response and appropriateness

- Key concepts and statements
  - Suspect AH when
    - Clinical
      - Jaundice rapidly develops / worsens
        - Heavy alcohol intake until 4-8 wk before onset of jaundice
        - No other known liver disease
      - Serum bilirubin > 3 µg/dL
      - ↑ ALT, ↑ AST 1.5x ULN, but < 400 U/L
      - AST/ALT > 1.5
  - Evaluate classification of
    - Severity of AH from probable to definite AH by performing a liver biopsy by the transjugular approach
    - Useful when the diagnosis of AH is uncertain because of
      - Uncertain history of alcohol intake
      - Suspected / proven presence of another liver disease

- Treatment (the principle of this outline for AH apply to other subtypes of alcoholic liver disease)

Approach towards the diagnosis and management of alcoholic hepatitis

INITIAL EVALUATION FINDINGS SUPPORTING THE DIAGNOSIS OF AH

Clinical presentation	Laboratory markers
Prolonged heavy alcohol intake, recent-onset jaundice, malaise, ascites, edema pruritus, fever, confusion/lethargy/agitation, asterixis, tender hepatomegaly, splenomegaly, pedal edema	Abrupt rise in total bilirubin (> 3 mg/dL), AST > ALT (usually > 2x upper limit), GGT > 100 U/mL, Albumin < 3 g/L, INR > 1.5, in some patients leukocyte count > 12,000/mm3

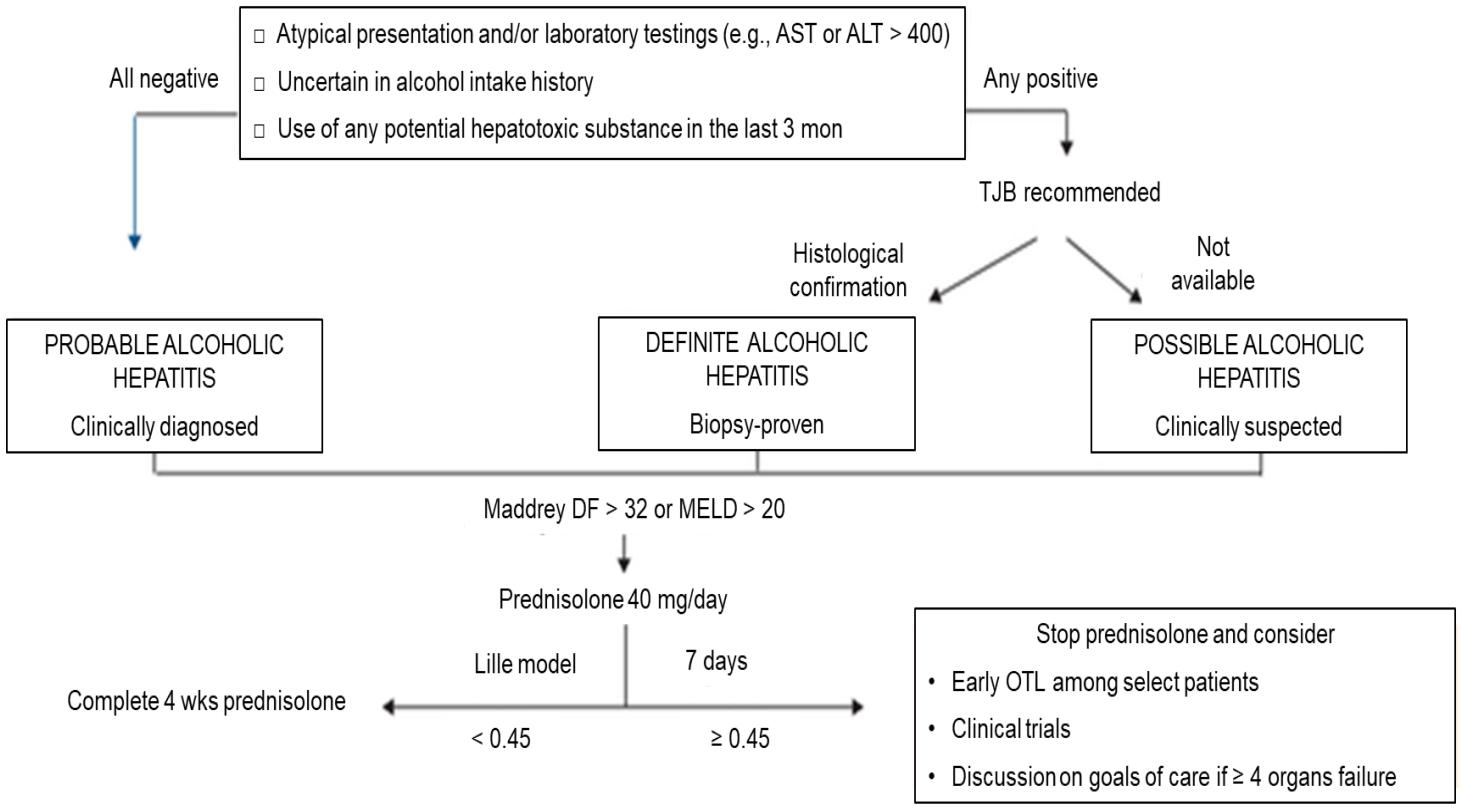
TREAT ALCOHOL ABUSE AND LIVER-RELATED COMPLICATIONS

Hepatic encephalopathy	Alcohol management	Infection	Renal insufficiency
• Assess for precipitant: GI bleed, infection, medication non-compliance • Treat underlying precipitant, add Lactulose, Rifaximin, Zinc	• Consult addiction specialist • Moderate WDS: Baclofen • Severe WDS: Benzodiazepine	• Rule-out pneumonia, cellulitis, SBP, UTI, meningitis • Pan-culture, Chest X-ray • Broad-spectrum antibiotics if indicated	• Early-detection and close monitoring • Volume expansion with albumin • Consider norepinephrine + albumin if progressive HRS-1

RULE OUT OTHER CAUSES OF JAUNDICE

Mechanical obstruction	Drug-induced liver injury	Viral hepatitis	Autoimmune hepatitis	Ischemic hepatitis
• Rule out HCC / biliary obstruction / Budd-Chiari • Perform doppler abdominal US and if indicated, MRI	• Review detailed history of medication, supplements, pharmacy records • http://livertox.nih.gov	• Rule out acute Hepatitis A, B, C or E, especially if first episode, or high clinical suspicion	• Rule out severe autoimmune hepatitis if first episode, and/or clinical suspicion (ANA, ASMA, IgG)	• Presence of hypotension, septic shock, massive bleeding or recent cocaine use

ROLE FOR TRANSJUGULAR LIVER BIOPSY?



Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; INR, International Normalized Ratio

Printed with permission: Singal AK, et al. Am J Gastroenterol 2018; 113: 175-194 (Figure 3).

- Nutrition
  - Daily calorie intake ≥ 35 kcal/kg
    - Calories
    - Protein, 1.2 to 1.5 g/kg
  - Vitamins, minerals
    - Replenish depleted stores
    - May require ↑ thiamine and B vitamins
  - Hydration
    - Restriction for hyponatremia only if Nas+ < 120 mmol/L
    - IV hydration, if necessary, use albumin for volume replacement
  - Level of care
    - Indications for ICU care
      - CNS
        - Hepatic encephalopathy stage III/IV
        - Severe AWS
      - Lung
        - Respiratory failure
        - Ventilation
        - SIRS
      - CVS
        - Hemodynamic instability

      - Depends upon disease severity, as assessed by
        - SOFA, CLIF SOFA score,
        - NACSELD ACLF score
      - ≥ 2 extra-hepatic organ failures
      - ≥ 2 infections
      - ↑ MELD

Abbreviations: NACSELD ALF, North America Consortium for Study of End Stage Liver Disease – Acute on Chronic Liver Failure

  - Infection
    - Sepsis surveillance with broad spectrum antibiotics
      - No penicillin allergy piperacillin-tazobactam (“pip-tazo”)
      - Penicillin allergy: vancomycin plus meropenem
    - Infections are common in patients with ALD
      - ~50% are culture negative
      - Have a low threshold for diagnosis / initiation of antibiotics
      - In patients with ascites, perform diagnostic paracentesis to rule out spontaneous bacterial peritonitis (SBP)
  - Ulcer prophylaxis
    - Prophylactic PPI for ICU patients in ICU
  - Bleeding
    - Target RBC transfusion to maintain hemoglobin concentration to 7 g/L (9 g/dL if patient has predisposition to cardiac ischemia)
  - Acute lobular necrosis
    - Sepsis-induced
      - Antibiotic therapy, renal replacement therapy
    - Hepatorenal syndrome
      - Octreotide, albumin, vasoconstrictor to maintain mean arterial pressure > 65 mm Hg

- Lungs
  - Where indicated, ventilation with low total volume

Recommendations

- Give patients with sever AH
  - Appropriate / adequate nutritional supplement (Conditional recommendation, very low level of evidence)
  - Corticosteroids (as long as no contraindications) (Strong recommendation, moderate level of evidence)
  - Do **not** use pentoxifylline in severe AH (Conditional recommendation, low level of evidence)

Key Concepts / Statements

- AH is considered to be severe when
  - MDF ≥ 32
  - MELD ≥ 20
- Diagnose and treat SIRS to ↓ risk of
  - Acute kidney injury (AKI)
  - Multi-organ failure
- ↓ risk of renal damage
  - Drugs: avoid
    - Nephrotoxic drugs
    - High doses of diuretics
  - Maintain normal circulation blood volume
    - IV albumin
    - IV 0.9% saline
- Assess response to CS with the Lille score on day 7
  - If < 0.45, continue CS for a total of 4 wk
- If non-response to CS and not eligible for early liver transplantation
  - Arrange for palliative care
- Continue “comprehensive” screening for infection
- Corticosteroids (CS)
  - po prednisolone, 40 mg
  - IV methylprednisolone 32 mg/d
    - ↓ MR from 34% to 20% half the patient at 30-d, but not at 60/90 d
    - Some studies have shown a 48% ↓ risk of mortality
  - After 4-7 d of CS, calculate Lille score (LS) to determine of patient has responded to CS
    - If LS < 0.45, continue CS for 3 more wks (total time for CS, 4 wk)

- CS ↑ risk of infection which is already ↑ in patients with AH
  - Use of prophylactic antibodies ↑ survival of patients with AH who are on CS
  - Anticipating that patients with AH have ↑ risk of infection (bacterial, fungal) and
  - That it may be difficult to diagnose the infections, consider using a level of bacterial DNA > 18.5 pg/mL as an indication to begin using
  - Prophylactic antibiotics
- N-acetylcysteine added to CS → ↓ survival at 3 mon, but not at 3 or 6 mon
- Despite the benefit of the above therapies, if the patient with AH and in the ICU has ≥ 4 failed organs, survival beyond 3 to 6 mon is "unlikely"

- Liver Transplantation (LT)

➢ Assessment Pre-LT

- Liver transplantation causes the ALD, but not the AUD
- Standard of care for patients without alcohol-related issues
- Recidivism
  - Most likely in first 2 yr after LT
  - Risk factors
    - Duration of abstinence
    - Amount of consumption
    - Young patient lack of social support
    - Failed rehabilitation
    - Family history
- Alcohol-associated comorbidities
  - CNS / psyche
    - Dementia
    - Encephalopathy, Wernicke
    - Neuropathy, peripheral
    - Seizures
    - Psychological comorbidities
    - Drug abuse
    - Smoking
  - CVS
    - Cardiomyopathy
    - Hypertension, systemic
    - Colorectal cancer
  - GI
    - Pancreatic, chronic
  - GU
    - Chronic renal disease
  - Blood
    - Anemia
    - Folate / B12 deficiency
  - MSK
    - Deconditioning / frailty
    - Osteoporosis
    - Sarcopenia

- Post-LT
  - Rates of recidivism ~50% in 5 yr, but
    - Severe recurrence, 18%
    - Death from alcoholic cirrhotic ALT, 5%
    - Even with recidivism, the overall survival rates for survival after LT for ALD are good

Post-LT, yr	Survival
1	84-89%
3	78-83%
5	73-79%
10	58-73%

(survival in persons with recidivism and recurrent alcoholic cirrhosis 59%)

- Causes for post-LT morbidity / mortality
  - Post-LT recurrent alcoholic cirrhosis (5%)
  - In cancer, de novo (↑ risk, 2-3x) (20-40%)
    - Head/neck
    - Esophagus
    - Lung
    - Pharynx
  - Infection, especially fungal

Recommendations

- Consider LT for highly selected patients with severe AH (Strong recommendation, moderate level of evidence)

Key Concepts and Statements

- Consider possible LT while developing a treatment plan for the patient with end-stage ALD.
- The decision to have a patient with ALD assessed for LT is made on the basis of many factors, not just the duration of their total abstinence from alcohol.
- Patients with ALD who are too sick to complete rehabitation therapy for the AWD may be considered for LT, and the rehabitation completed post-LT.
- All patients coming for LT must be assessed for all types of substance abuse including alcohol, smoking illicit drugs.
- Recidivism is assessed in terms of the amount and type of alcohol use.
- Immunosuppression post-LT must be adjusted to the lowest possible dose to prevent organ rejection.
  - Use sirolimus or everolimus, if possible
  - Mathurin P, et al. N Engl J Med 2011; 365: 1790-1800
  - Hasanin M, et al. Liver Transpl 2015; 21: 1449-1452

FATTY LIVER DISEASE: BACKGROUND

Non-Alcoholic Fatty Liver Disease (NAFLD): **Genetic Associations**

Eslam M and George J. Nat Rev Gastroenterol Hepatol 2020; 17: 40-52.

- Terminology
  - A genome wide association (GWAS) starts with a phenotype of interest followed by unbiased analyses of hundreds of thousands to millions of common genetic variants across the entire genome for association with the phenotype.
  - Phenome-wide association studies (PheWAS)
    - An unbiased systematic approach to test for associations between a specific genetic variant or series of variants, and a wide range of phenotypes in large cohorts.
    - Starts with one or more genetic variants of interest and systematically analyses multiple phenotypes for association with the variant.
  - Gene effects
    - The estimation of the genetic determination for a particular trait using mathematical models
      - Allows one to distinguish between environmental and genetic contributions.
  - HOMA-IR
    - Homeostatic Model Assessment of Insulin Resistance
      - A surrogate measure of insulin resistance.
  - Pleiotropy
    - A common phenomenon
    - Considered to be present when one genetic locus influences more than one phenotype
    - Two subtly distinct forms of pleiotropy have been suggested
      - Genic pleiotropy
      - Allelic pleiotropy
  - Genetic pleiotropy
    - Altered function of a gene than influences multiple traits
  - Allelic pleiotropy
    - One gene variant influences multiple traits
    - Pleiotropy in which the effect of a variant on one trait is second to the effects on another trait is termed mediated pleiotropy
    - Another distinction is horizontal versus vertical pleiotropy
      - Vertical pleiotropy refers to genetic variants that influence multiple biomarkers on the same pathway from exposure to disease
      - Horizontal pleiotropy refers to the situation in which a genetic variant influence distinct pathways that are causal in the traits

- Sophisticated methodologies demonstrate possible associations between NAFLD and genetics, using
  - Multi-train genome-wide association studies (GWAS)
  - Phenome-wide association studies (PheWAS)
  - Mendelian randomization and functional annotation studies simple steatosis to hepatocellular cancer (HCC).
- All known genetic variants explain only 10-20% of NAFLD etiology
- Genes associated with predisposition for progression and poor prognosis of NAFLD.
  - PNPLA3
    - Most “robust” variant involved in regulation of lipids with activity for triacylglycerol lipase and for acylglycerol acyltransferases activity.
  - TM6SF2 (transmembrane 6 super family 2)
    - Synthesis of cholesterol and secretion of lipoprotein
  - GCKD (glucokinase regulator)
    - Regulates
      - Influx of glucose into hepatocytes
      - Regulates glucokinase/lipogenesis
  - MBOAT7 (membrane band-o-acyltransferase domain containing 7)
    - Remodelling of arachidonic acid to phosphatidyl-inositol
  - HSD17B13 (hydroxy steroid 17B dehydrogenase)
    - Lipid droplet associated retinol dehydrogenase activity
- Gene modifiers shared with NAFLD and other liver disease
  - PNPLA3 and TM6SF2
    - Associated with steatosis in HBV/HCV infection
  - MB0AT7
    - Associated with inflammation/fibrosis in BV/HCV infection
  - MERTK
    - Activation of hepatic stellate cells (HSC)
    - Protective agonist fibrosis in NAFLD/HCV
- Favourable adiposity genes

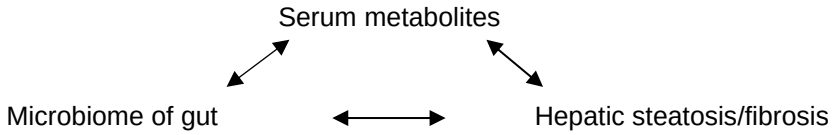
IRS1		PEPD
ARL15		PDGFC
ANKRD55	and/or	MAP3K1
GRB14		PPARG
FAM13A		LYPLAL1
RSP03		TET2

- Genetic pleiotropy

➢ Definition

- Epigenetic reprogramming in “response to environmental conditions” which is not explained by genome-wide association studies (GWAS), “…a phenomenon of a gene or genetic variant influencing multiple traits”

- Types
  - Vertical
    - "…genetic variants that influence multiple biomarkers in the same pathway from exposure to disease"
  - Horizontal
    - "…a genetic variant influences distinct pathway that are causal in the traits"
  - Genetic
    - "…altered function of a gene that influences multiple traits"
  - Allelic
    - "…one variant influences multiple traits"
  - Mediated
    - "…the effect of a variant on one trait is secondary to its effects on another variant"
- Metabolic traits
  - Shared genetic studies show an association between



  - Example
    - Some loci for NAFLD are associate with
    - ↑ risk of NAFLD and type 2 diabetes mellitus (T2DM)
- Pleotropic effects
  - Synergistic interaction between NAFLD and obesity e.g., PNPLA3148M, TM65SF2

❖ Obesity

- Classes of obesity
  - Metabolically unhealthy obesity (MUO), 25%
  - Metabolically healthy obesity (MHO), 45%
  - Metabolically obese normal weight (MONW), 30%
- MOU phenotype
  - Liver
    - NAFLD, ↑ meta-inflammation
  - Pancreas/endocrine
    - Insulin-resistance T2 diabetes
    - ↑ fasting blood glucose (FBS)
    - ↑ serum Triglycerides
  - Cardiovascular disease
    - Atherosclerosis
    - Hypertension

- Changes in metabolic obesity patients who are

Heathy (MHO)	All of these are	Unhealthy (MUO)
↓	− Liver fat − Blood pressure − Triglycerides − Insulin resistance − Fasting glucose level − Meta-inflammation ↓ ▪ NAFLD ▪ Hypertension ▪ Cardiovascular disease	↑

❖ Bile acids and enterohepatic circulation

- Fibroblast growth factor 21 (FGF21) is associated with ileocyte FXR (farnesoid) protein and with absorbed bile acids to influence the rate of conversion of hepatic cholesterol to primary bile acids (cholic and chenic acids)
  - "…genetic variants in genes regulating bile acid homeostasis have diverse metabolic effects, including effects on NAFLD"

Abbreviations: FBG, fasting blood glucose; FGF21, fibroblast growth factor 21; FXR, farsenoid; MHO, metabolically healthy obesity; MONW, metabolically obese, normal weight; MUO, metabolically unhealthy obesity; NAFLD, non-alcoholic liver disease; T2DM, type 2 diabetes mellitus

➢ Definition

- Non-alcoholic fatty liver disease (NAFLD)
  - Fat accumulation in at least 5% of hepatocytes, without excess alcohol intake (daily intake < 30 g in men and < 20 g in women)
  - The spectrum of disease extends from bland, simple steatosis to fatty liver, accompanied by inflammation and ballooning hepatocyte cell death, termed non-alcoholic steatohepatitis (NASH).
  - NASH can progress to fibrosis, cirrhosis, and to hepatocellular cancer (HCC)
  - NAFLD is the most common cause of liver disease in Western countries, and is likely to soon become the primary reason for liver transplantation.
  - NAFLD diagnosis
    - Liver biopsy (reference standard)
    - Imaging modalities
      - Ultrasonography
      - MRI proton density fat fraction (MRI-PDFF)
      - Transient elastography with controlled attenuation parameter
    - Blood test
      - ↑AST, ↑ALT, ALT < AST
      - NAFLD fibrosis score
      - Collagen marker-based score (such as ADAPT) that incorporates various clinical and laboratory parameters in predictive mathematical models

Non-alcoholic Fatty Liver Disease (NAFLD): **Importance of Intestinal Microbiota**

Aron-Wisnewsky J, et al. Nat Rev Gastroenterol Hepatol 2020; 17: 279-296.

- Definition
  - Gut microbiota
    - "…the microbial community within the gastrointestinal tract"
  - NAFLD
    - "…the pathological accumulation of lipid droplets in > 5% of hepatocytes"
  - NASH histological demonstration of steatosis, inflammation (lobular +/- portal), ballooning (apoptosis) of hepatocytes +/- fibrosis
  - Rapid advancement in areas with novel sophisticated technology, e.g.,
    - Shortening sequencing
    - Pyrosequencing

    } ▪ Metabolic signatures

- Demography
  - Affects > 40% of persons worldwide

- Hypothesis

- Possible mechanisms of adverse effect of gut microbiota on development of NAFLD
  - Direct
    - Passage of lipopolysaccharide (LPS) across "leaky" / ↑ permeable GI tract → ↑ inflammation locally/systematically
  - Indirect
    - Metabolites of bacteria, e.g.,
      - 2º/3º bile acids (BA)
        - ↓ size of BA pool → ↑ FXR → ↑ NAFLD
      - Choline → trimethyl amino (TMA) $\xrightarrow{\text{FMO}}$ TMAO
      - Ethanol
      - Lactate
      - Nitrites (triethylamine N-oxide [TMAO]
    - ↓ inflammation short-chain fatty acids (SCFA): acetate, butyrate, proprionate
      - Non-digestible carbohydrates + microbial fermentation → SCFA (FA: 2,4,6)
        - Absorption, energy source
        - ↑ activation of G protein coupled receptors (GPR41, GPR43) → ↑ hepatic triglycerides
        - ↓ Treg cells (CD4+, CD45RA+ CD20+)
        - ↑ Th17/T_{reg}

Abbreviations: 1º, primary; 2º, secondary; BA, bile acid; FA, fatty acid; FMO3, the hepatic enzyme which metabolizes TMA to TMAO; FXR, farsenoid x receptor; GPR, G-protein-coupled receptors; LPS, lipopolysaccharide; NAFLD, non-alcoholic liver disease; NAS, NAFLD activity score; NASH, non-alcoholic steatohepatitis; SAF, steatosis activity and fibrosis; SCFA, short chain fatty aids; TAMO, trimethyl-N-oxide; TGR, G-protein-coupled bile acid receptor; Th, helper T-cell; TMH, trimethylamine; Treg, regulatory T cell

- Pathophysiology
  - Strong association with persons with metabolic syndrome
    - Waist circumference
      - White men, ≥ 94 cm
      - Women, ≥ 80 cm

      Plus ≥ 2 of the following
    - Fasting blood glucose ≥ 5.55 mol/L (≥ 100 mg/dL), or type 2 diabetes mellitus (DMT2)
    - Systolic blood pressure (SBP) ≥ 130 mmHg, or
      - Diastolic BP ≥ 85 mmHg, or
      - Patient taking any hypertension lowering drugs
    - Serum triglyceride ≥ 1.69 mmol/L (≥ 150 mg/dL), or
      - Patient taking any kind of lipid lowering treatment
    - HDL cholesterol < 1.04 mmol/d
      - Man, < 1.04 mmol/d (< 40 mg/dL)
      - Women < 1.29 mmol/L (< 50 mg/dL), or
      - Patient taking any type of lipid-lowering treatment

- Hepatic steatosis
  - ↑ enterocyte chylomicron remnant free fatty acids (FFA) of adipocytes stored triglyceride (TG $\xrightarrow{\text{lipolysis}}$ FFA) → Liver
    - Mitochondrial oxidation
    - Esterification of FFA back to TG → phospholipids (PL) / cholesterol esters (CE)

      ↓

      VLDL in blood
  - ↑ hepatocyte FFA/fructose/TG
    - When lipolysis shifted to lipogenesis (↑ TG storage)
      - Shift occurs when amount of TG (↑ long chain saturated fatty acids [FA]) delivered to liver from enterocytes/adipocytes except mitochondrial oxidation, synthesis of PL/CE →
        - ↓ synthesis of lipoprotein
        - ↓ export of TG, PL, CE from liver
  - Insulin resistance
    - ↑ FFA
      - ↑ fat intake
      - ↑ lipogenesis

      } → ↑ FFA → ↓ insulin signalling in
        - Adipose tissue
        - Liver

- ↑ fructose intake → ▪ ↑ steroid regulatory element binding protein-1 (↑ REBP) ▪ ↑ carbohydrate response element binding protein (CREBP) } – ↑ lipogenesis
- ↑/dysfunctional adipose tissue →
  - ↑ insulin secretion om response to insulin resistance →
    - ↑ leptin / ↓ adiponectin → NASH
    - ↑ resistin
    - ↑ IL-6 / ↑ TNF
    - ↑ plasminogen activator inhibitor-1 (PAF1)

- Bile acids (BAs) and nuclear hormone receptors
- BAs trafficking through ileocytes modify enterocyte synthesis of farnesoid X receptor, FXR (a nuclear hormone receptor) FXR bound to BA enter portal blood, cross the sinusoidal membrane into hepatic cytosol, and modify 7α-hydroxylate conversion of cholesterol to BA.
- BA
  - Rate-limiting step ▪ 7α-hydroxylase
  - Master regulator ▪ FXR
- Functions of FXR
  - Signal 7α-hydroxylase to regulate hepatic synthesis of primary bile acids (cholic/chenic acids)
  - ↓ lipogenesis
  - ↑ β-oxidation of FFA
  - ↓ VLDL synthesis/assembly
  - Other nuclear receptors besides FXR
    - Pregnane X receptor (PXR)
    - Sphingosine 1 receptor 2 (S1R2)
    - G-protein coupled bile acid receptor (TGR-5)

- Steatohepatitis
  - ↑ FFA in liver TG (long chain fatty acid e.g., palmitic acid), cholesterol, lysophosphatidylcholine, ceramides) → lipotoxicity ER stress / oxidation stress → mitochondrial dysfunction → autophagy → ↑ activation of stellate cells / ↑ NK cells → fibrosis
    - Activation of hedge hog pathway → ↑ inflammatory response →
      - Hepatocytes ballooning
      - Portal inflammation
      - Fibrosis
      } NASH
  - GI tract
    - Microbiome dysbiosis → ↑ intestinal permeability of bacterial/fungal pathogens/antigens e.g., lipopolysaccharide [LPS]
    - Endotoxemia acts on toll-like receptor 4 (TLR-4) → activation of Kupffer cells → activation of Jun N-terminal kinase (JAK) and nuclear factor kappa β (NFκβ) → interleukin-1β (IL-1β) / tumour necrosis factor α (TNFα)

➢ Mechanisms of action of pharmacological agents for treatment of NAFL/NASH

Cell/Process	Pharmacological Action	Pharmacological Agent
○ Ileocytes	− ↓ bile acid transport − ↓ FXR / TGR5 − ↓ SREBP-1	▪ Volixibat ▪ FXR agonist ▪ Small heterodimer partner (SHR)
○ Adipocytes	− ↑ adiponectin − ↓ TNFα − ↓ FFA	▪ Aramchol
○ Metabolic function	− ↓ insulin resistance (↑ insulin/glucose)	▪ Insulin sensitizers
	− ↓ lipogenesis	▪ Acetyl CoA carboxylase
	− ↓ apoptosis arising from mitochondrial dysfunction	▪ Emricasan ▪ Selonsertib
○ Mitochondrial dysfunction	− ↓ lipogenesis	▪ ACC inhibitors
○ Anti-inflammatory	− Immune cell trafficking	▪ AOC3 inhibitor 2 (amine oxidase, copper contaning)
	− Kupffer cell ▪ ↓ TGF-β ▪ ↓ TNF-α ▪ ↓ IL-6	▪ CCR 2/5 inhibitors
	− Stellate cell ▪ ↓ activation / ↓ fibrosis	▪ SIM, anti-fibrotic GR-MD-O2

Abbreviations: ACC, acetyl CoA carboxylase; BA, bile acid; FFA, free fatty acids; FXR, farsenoid X receptor; IL, interleukin; NFκβ, nuclear factor κβ; NK, natural killer; PXR, pregnane X receptor; SREBP, sterol regulatory element binding protein; TGR-S, S-protein coupled bile acid receptor; TNF-α, tumour necrosis factor

Non-alcoholic Fatty Liver Disease (NAFLD): **Importance of Adaptive Immunity**

Sutti S and Albano E. Nat Rev Gastroenterol & Hepatol 2020: 17: 81-92.

- Innate and adaptive immune mechanisms play an important role in the development of NASH.
- Innate immunity in NASH: development of NAFLD

- Proinflammatory mechanisms
- Insulin resistance
- FFA/cholesterol
- Gut dysbiosis

→

- ↑ Kupffer cells in liver → ↑ stress-responsive kinases (JNK1, JNK2)
- ↑ neutrophils, monocytes → M1 activated macrophages
- ↑ natural killer (NK) / ↑ natural killer T cells (NKT)

→

- ↑ release of
  - Chemokines (CCs)
  - Cytokines
  - Eicosanoids
  - Nitric oxide (NO)
  - Reactive oxygen species (ROS)

➢ Roles of different immune cells in NASH

- Lymphocytes
  - ↑ lobular/portal infiltration, diffuse or focal
  - B-cells / CD4+/CD8+ T cells
    → CD25, CD44, CD69
    → Light cytokine
    → ↑ vascular adhesion protein 1 (VAP1)
  - Antigen stimulation
    → B1 cells → mature plasma cells → IgM antibodies
    → B2 cells + Th cells → proliferate → isotype class switching → plasma cells → IgD, IgG, IgE
  - B cells are profibrotic → stimulate
    - Hepatic stellate cells (HSCs) → retinoic acid → ↑ B cell
      - Maternal/survival
      - ↑ IgA (predicts advanced liver disease)
    - Hepatic macrophages
- B/T lymphocytes
  - ↑ insulin resistance → ↑ visceral adipose tissue (VAT)
- CD8+ cytotoxic T cells
  - IFNα mediated signals → ↑ activated cytotoxic CD8+ T cells in liver → insulin resistance

- Oxidative stress
  - Lipid peroxidation → Aldehydes, reactive
    → Phospholipids, oxidized
    → Act as DAMPs → hepatic inflammation
    → Oxidative stress epitopes (OSEs; antigen adducts with cellular macromolecules; e.g., malondialdehyde-acetaldehyde adducts [MAA])
    → Hormonal/cellular responses against OSEs
      - Hepatic inflammation

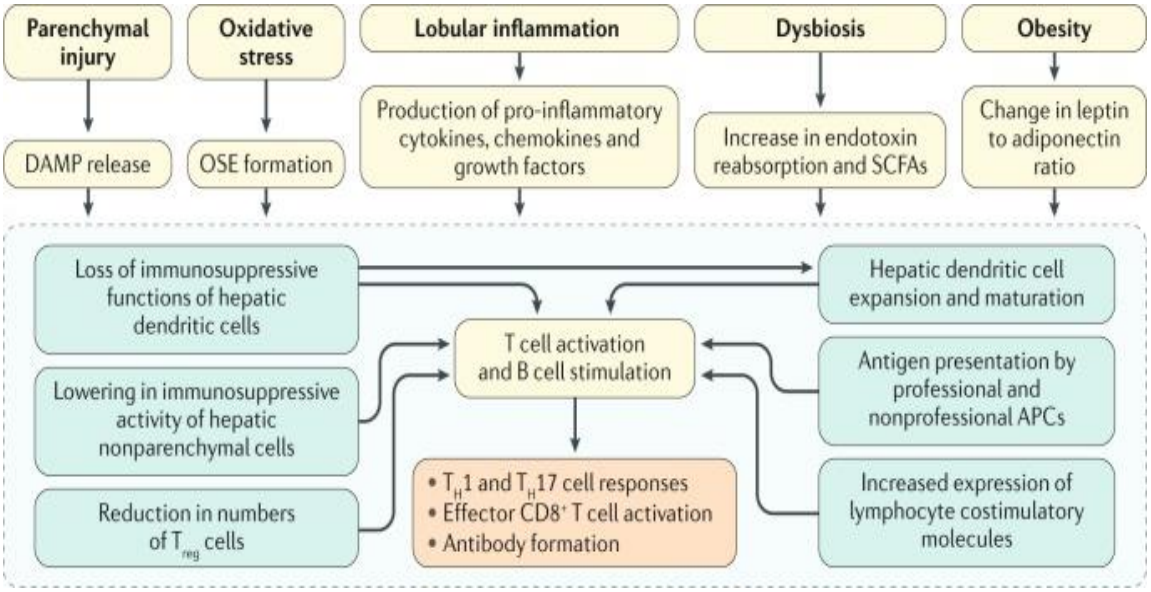
- Interplay between innate and cellular immunity
  - "The network of cytokines by Th1, Th17 and CD8+ lymphocytes activate hepatic M1" macrophages → release of lymphocyte mediators →
    - IL-12/3
    - CXCL 9, 10, 11
    - IL-15/-8 → ↑ NK cell activation

    (95% of liver NKT cells are type 1 / invariant NKT [I NKT] cells)
  - NKT cells surface receptor CD56/CD161 "…recognize lipid antigens presented by CD1-d-expressing antigen presenting cells (APCs) → secretion of IL-4/-10, IFN/TNF → ↑ activity of
    - Th1/2
    - Treg (CD4+, CD25+ regulatory T cells) → ↑ or ↓ inflammatory/immune responses

- Mechanisms to ↑ adaptive immunity
  - "Professional" APCs (Kupffer cells, dendritic cells [DCs])
    - Non-professional APCs (hepatocytes HSCs, sinusoidal endothelial cells)

    → Presentation of antigens to T cells → T cell
    - Apoptosis
    - Anergy differentiation (into CD4+, CD25+ Foxp3+ Tregs)

- Factors involved in stimulating the onset of adaptive immune responses during the evolution of non-alcoholic steatohepatitis



Printed with permission: Sutti S and Albano E. Nat Rev Gastroenterol & Hepatol 2020: 17: 81-92 (Figure 3).

- During the development of non-alcoholic steatohepatitis, the combined action of
  - Damage-associated molecular patterns (DAMPs) released by damaged hepatocytes,
  - Oxidative stress-derived epitopes (OSEs) and
  - Pro-inflammatory mediators → alters the tolerogenic action of
    - Liver dendritic cells
    - Kupffer cells
    - Sinusoidal endothelial cells
- These changes →
  - ↓ liver regulatory T (Treg) cells
  - ↑ expansion/activation of dendritic cells
- Alterations in the gut–liver axis due to dysbiosis and obesity-related changes in the adipokine network are additional factors that affect liver immune tolerance.
- As a result, ↑ antigen presentation to lymphocytes plus ↑ expression of costimulatory molecules → ↑ cellular and humoral immune responses

- Hepatic dendritic cells (DCs) classification
  - Plasmoid
    - Antigen presentation to CD4+ - Th/B cells
  - Myeloid (classical)

  → ▪ Telomeric environment of normal liver

  ↓

  ↑ myeloid HDCs in NAFLD

  ↓ ← TLR4 ← HMGB protein ← damaged hepatocytes

  ↑ stimulation of CD4+ T cells with high lipid content

  ↓

  - Fractalkine receptor CX3CR1 (CX3C-chemokine receptor 1)
    - Monocyte markers
    - TNF ← costimulatory effect of OX40 (CD134)

    ↓

    ↑ insulin resistance

    ↑ obesity-induced CD4+ T cells in VAT

- Hepatic regulatory T cells (Tregs)
  - CD4+ T cells (Treg) peripheral organs (thymus) → express FOXP3 (transcription factor Forkhead base protein 3)
    → IL-10 / kynurenine
    → CTLA-4 (cytotoxic T cells lymphocyte antigen 4), IL-10, TGF-β → PDL-1 (membrane-bound programmed cell death 1 ligand)

    ↓

    ↓ proliferation / ↓ effector function of CD4+ / CD8+ T cells

    ↓

    In NASH: oxidative stress
    - ↑ Treg → ↑ apoptosis

- Oxidative stress

Oxidative stress in hepatic inflammation and parenchymal injury

- Liver dendritic cells and other antigen-presenting cells (APCs) present oxidative stress-derived epitopes (OSE) to CD4+ T helper (TH) cells in the context of major histocompatibility complex class II (MHC II) molecules.
  - This signal, together with enhanced expression of costimulatory molecules such as OX40 → activation of CD4+ T cells / Th1 cell or Th17 cell polarization.

- CD4+ Th cells also support both
  - Cytotoxic CD8+ T cell responses and
  - B cell maturation of plasma cells secreting anti-OSE IgG. In turn, B cells can promote immune-inflammatory processes by antigen presentation to CD4+ T cells, and
  - Producing inflammatory cytokines.
- IFNγ and TH1 cell cytokines → ↑ liver macrophages to release
  - M1 pro-inflammatory cytokines and
  - Chemokines (IL-12)
  - CC-chemokine ligand 2 (CCL2) and
  - CXC-chemokine ligand 9 (CXCL9)) → ↑ recruiting of monocytes and lymphocytes.
- Macrophages and dendritic cells also release B cell stimulating cytokines such as B cell-activating factor (BAFF), which are critical for B cell maturation to plasma cells.
- IL-15 produced by both hepatocytes and liver macrophages → ↑ survival of CD8+ T cells and, together with CXCL16 → promotes liver natural killer T (NKT) cell differentiation and survival.
- NKT cells and CD8+ T cells → steatohepatitis through the secretion of LIGHT and IFNγ.

- Extrahepatic factors
  - Oxidative stress-derived epitome (OSEs) act as
    - DAMP2
    - Immunogenic antigens
    - ↓ hepatic immune tolerance
    - ↑ presentation by APCs to lymphocytes → ↑ activation of B/T cells
  - Dysbiosis
    - ↑ gut permeability → ↑ enterotoxin into intestine → ↑ IL-10
    - ↑ SCFA →
      - ↓ resting Treg cells
      - ↑ Th17: resting Treg cells
  - Adhesion protein VAP1 → ↑ hepatic lymphocytes
    - VAP1 neutralizing antibodies (BTT-1029) →
      - ↓ steatohepatitis
      - ↓ fibrosis

      } In exponential modes of NASH

Abbreviations: BAFF, B cell activating factor; CCL2, chemokine ligand; CXCL, chemokine ligands 9; DAMPs, damage-associated molecular patterns; DC, dendritic cells; FFA, free fatty acid; HDC, hepatic dendritic cell; HMGB, High mobility group box protein; HSCs, hepatic stellate cells; IFN, interferon; IL, interleukin; MAA, malondialdehyde-acetaldehyde adducts; MHC, major histocompatibility complex; NAFLD, non-alcoholic liver disease; NASH, non-alcoholic steatohepatitis; NK, natural killer; NKTs, natural killer T cells; NO, nitric oxide; OSE, oxidative stress-derived epitomes; PD-L1, programmed cell death 1 ligand 1; ROS, reactive oxygen species; SCFA, short chain fatty acids; Th, T helper cell; TLR, Toll-like receptor; Treg cell, regulatory T cell; VAP, vascular adhesion protein 1

Assessment and Management of Patients with Non-alcoholic Fatty Liver Disease (NAFLD): AASLD Practice Guidelines (2023)

Rinella ME, et al. Hepatology 2023 1;77(5):1797-1835

- Background
  - This practice guidance represents an extensive update of the AASLD publication of 2018
  - "Practice guidance" represents" …actionable statements decision-making) [to aid rather than formal recommendations (such as the Grading of Recommendations, Assessment Development and Evaluation [GRADE] system used for "Guidelines"
  - The major advances considered in the five-year period deal with biomarkers and non-invasive tests (NITs) and pharmacotherapy.

- Definitions
  - Non-alcoholic liver disease readily, with no identified other cause of macrosteatosis
    - Modest intake of ethanol is permitted in patients with diagnosis of NAFLD

	g/d
▪ Women	< 20`
▪ Men	<30

    - The spectrum of
      - NAFLD ≥ 5% hepatocytes with microvesicular fat
      - Non-alcoholic steatohepatitis – NASH macrovascular steatohepatitis plus:
        - Inflammation
        - Hepatocyte ballooning
        - Septal +/- fibrosis

        ↓

        Cirrhosis (F4)
  - Associated with obesity especially body fat distribution of subcutaneous and especially visceral fat → ↑ inflammation (↑ insulin resistance)
  - Clinically significant fibrosis
    - ≥ stage F2 ("at risk" NASH)
    - F3, bridging fibrosis
    - F4, compensated fibrosis

- Progression
  - Even with NAFLD without fibrosis, there is
    - ↑ morbidity liver-related complications such as HCC
    - ↑ mortality, such as liver associated and non-associated malignancy

- Rate of progression for each F score
  - NAFLD, 14 yr
  - NASH, 7 yr
  - Compensated fibrosis (F4)
    - Decompensated at rates of 3% to 20% per year
- The prognosis of the stage of fibrosis is associated with poorer prognosis
  - This progression of fibrosis is slowed/halted by
    - Diet and other lifestyle improvements
    - Pharmacotherapy
    - Bariatric surgery procedures (surgical, endoscopic)

Stage of Fibrosis	Mortality per 100 person-yr
0.1	0.32
2 (bridging fibrosis)	0.89
4 (cirrhosis)	1.76
Hepatic decompensation	HR, 6.8; 95% CI 2.2-21.3

➢ Pathophysiology

- Energy oversupply → ↑ de novo lipogenesis → limited expansion of adipose tissue → insulin resistance → metabolic disease
  - Saturated fats worse than unsaturated fats
  - White worse than brown adipose tissue (not usually energy consuming)
  - Liver
    - Lipotoxic injury
    - Activation of stellate cells
    - ↑ oxidative stress
  - Adipose tissue
    → ↑ release of FFA during fasting
    → lipotoxic injury
    → progression of NAFLD to NASH
    → adipokines

- Environmental (loss of function)
  - Uric acid production in hepatocyte
  - ↓ hepatocyte Mg concentration
  - Muscle
    - ↑ cytokine

- Genetic polymorphism
  - Non-protective
    - 148M of PNPLA3 → ↓ TG lipolysis in lipid droplets
    - TMG F2 (cholesterol metabolism)
    - MBOAT2 (phospholipid metabolism)
  - Protective
    - HSD17B13
    - CIDCB

- Guidance Statements: Screening/Surveillance
  - Treat patients with dyslipidemia and cardiovascular risk factor with statins
    - In patients with NAFLD plus decompensated cirrhosis plus dyslipidemia, statins can be used with careful monitoring
  - Treat patients with NAFLD plus lipidemia with lifestyle changes, omega-3 fatty acids, fibrates or icosapent ethyl
  - Patients with NAFLD should be screened for T2DM, and
    - Patients with T2DM should be screened for NAFLD
    - Periodically screen patients with NAFLD for chronic renal disease, and if they also have T2DM, screen for diabetes-associated microvascular renal disease
  - Perform age-appropriate
    - Screening in NAFLD patients for carcinoma
- Clinical
  - History/physical for
    - BMI, metabolic syndrome
    - ↑ alcohol intake
    - Complications of NAFLD CVS, lung, endocrine, cancer
    - Malnutrition / nutrient deficiency
    - Associated inherited disorders
      - Celiac disease
      - Wilson disease
    - Rare conditions
      - Hypobetalipoproteinemia ↓ LDL, ↓ TG, steatorrhea
      - Lysosomal acid lipase (LAL)
        - Xanthelasma
        - Hypersplenism
        - ↑↑ TG, advanced hepatic fibrosis at young age
        - Microvesicular steatosis on liver biopsy
- Comorbidities

- Cardiovascular
  - Atherosclerotic heart disease
    - Coronary artery disease (CAD)
    - Peripheral vascular disease
  - Arrythmias e.g., antral fibrillation
    - CVD risk factors
      - Accelerate disease across all NAFLD stage, F0 to F4

- Hypertension
  - Prevalence
    - Early, 6.5/100 persons-yr
    - Late, 14.5
      - ↑ hypertension with ↑ fibrosis

- Lung
  - Obstructive sleep apnea (OSA)
  - Associated with more advanced NASH
    - Intermittent hypoxia for OSA → mitochondrial dysfunction → abnormal metabolism of glucose / lipid
      → insulin resistance
      → ↑ de novo lipogenesis (DNL)
    - Screen all patients with NAFLD/NASH
      - Polysomnography

- Kidney
  - Chronic kidney disease (CKD)
    - Severity of CKD increase with ↑ fibrosis
    - Also associated with microvascular changes in kidney from associated diabetes

- Endocrine
  - Type 2 diabetes mellitus
    - ↑ prevalence with ↑ fibrosis (from 30% to 75%)
      - NASH → T2DM
      - T2DM → ↑ fibrosis
    - Timing
      - Early
        - ↓ insulin sensitivity
      - Later
        - ↓ insulin
        - ↑ insulin resistance
  - Type 1 DM also associated with NAFLD, but less common than T2DM
  - Dyslipidemia
    - ↑ atherogenicity
    - Statins safe in patients with compensated cirrhosis to ↓ risk of decompensated HCC
    - Options other than statins
      - ↑ cholesterol
        - Bempedoic acid “ezetimibe”
        - Fibrates (TG > 200 mg/dL, HCL-C < 40 mg/dL (adjunct to statins)
        - Inclisiran omega 3 fatty acid
        - PC5K-9 inhibitors
      - ↑ Triglycerides (TG > 500 mg/dL)

Treatment Alert

- Caution: ↑ risk of statin-induced myopathy when given with fibrates

➢ Associated Endocrine Disorders (other than T2DM)

- Hypothyroidism
  - ↑ risk of NAFLD by 24%
- Panhypopituitarism / Growth hormone (GH) Deficiency
  - ↑ risk of NASH/fibrosis
    - ↑ insulin deficiency
    - ↑ dyslipidemia
    - ↑ visceral adipose tissue mass

  } May be improved with GH replacement
- Hypogonadism
  - Serum free testosterone concentrations (Th) in persons with NAFLD
    - Women (premenopausal), ↑ Th
    - Men, ↓ Th
  - Th replacement in men → improvements of above metabolic changes
  - Thio ↑ Th in premenopausal women may ↑ risk of post-menopausal NAFLD as well as more severe disease

Treatment Tips

- When testosterone replacement therapy may benefit men with NASA and ↓ Th, it does not provide benefit in women.
  - An adverse of the supplementation in both women and men is worsening of obstructive sleep apnea (OSA)

- Polycystic Ovarian Syndrome (PCOS)
  - Associated with ↑ Th (androgens)
  - PCOS also associated with ↑ risk of
    - T2DM
    - ↑ severe NAFLD

Clinical Guidance

- Do **not** screen for hypothyroidism, hypogonadism, GA deficiency and panhypopituitarism, or patients with NALFD, but
  - Be aware of the associated and investigate if suggestive history/physical changes are present

❖ NAFLD in persons who are lean

- Prevalence of NAFLD in lean persons
  - US, 4%
  - Asia, 19%
- Risk factors
  - Genetics
    - More common in persons of Asian Hispanic origin
  - May be related to ↑ polymorphism of
    - PNPLA3
    - TM6SF2

Curiosity

- Lean persons with NAFLD may have ↓ risk of cardiovascular complications.
  - Exercise may also be of use for these individuals

➢ Laboratory

- ↑ ALT / ↑ AST 2x > ULN
  - Men, 29-33 U/L
  - Women, 19-25 U/L
- Reversal of usual ALT > AST (NAFLD, AST > ALT)
- ALT correlates
  - Reduction
    - Histopathology improvement
  - Normalization
    - Predicts resolution of NASH
- Drugs associated with hepatic steatosis (steatohepatitis)
  - 5-FU
  - Amiodarone
  - Corticosteroids
  - Irinotecan
  - Tamoxifen

➢ Alcohol intake and NAFLD

- Intake of alcohol (women 21-39 g/d; men, 31-59 g) increases probability
  - Advanced fibrosis
  - Cirrhosis
  - HCC
  - Extrahepatic malignancies
  - Death from liver disease

  Especially when associated with
  - Obesity
  - T2DM

Guidance Statements

- Assess the patient's intake of alcohol intake regularly when they have NAFLD
  - The patients with ≥ F2 fibrosis must completely abstain from any and all intake of alcohol
    - This abstinence of alcohol may reduce the resolution of NASH and reduce the risk of liver-related complications

➢ Screen

- Screen persons with NAFLD who are at ↑ risk of progressing to NASH
  - NAFLD plus
    - Metabolic syndrome (4-33%)
    - Intake of moderate amounts of alcohol (17%)
    - First degree relative with cirrhosis from NAFLD/NASH (18%)
    - T2DM (6-19%) / pre-diabetes
  - Non-related household members of a patient with NAFLD/NASH and also at risk, but about the benefit of screening are not available
- Persons with the risk factors have primary screening (in primary car with the FIB-4 test
  - Repeat FIB-4 surveillance q1-2 yr for persons with pre-DM/T2DM, or patients with ≥ 2 metabolic risk factors
  - These high-risk patients should also have a further test for NAFLD
    - Vibration-controlled elastography (VCTE)
    - Acoustic Radiation Force Impulse (ARFI)

    Preferred, rather than magnetic resonance elastography (MRE) or MRI corrected T1 (CT1)

- Enhanced Liver Fibrosis (ELF) test if above not available
  - Secondary screening
    - Portal hypertension
    - Sarcopenia
    - Intermittent or q6 to 12 mon repeated blood testing for ALT/AST
  - Exclude other conditions if steatosis established (e.g., autoimmune hepatitis [AIH], drug-induced liver injury [DILI], iron overload, alcoholic liver disease [ALD])
  - Consultant care
  - Percutaneous liver biopsy if diagnosis of NALFD/NASH remains unclear

MCQ Alert

- The FIB-4 test is used as the primary test for NAFLD, except
  - Persons ~35 yr (low) accuracy
  - Persons with an acute illness
  - If FIB-4 > 13, do VCTE +/- CAP or ELF test
  - MRI – protein density fat fraction (PDFF, MRI-PDFF) is useful for clinical research

Guidance Statement

- Perform FIB-4 test in persons with suspected NAFLD
  - Obesity
  - Metabolic syndrome
- ↑ FIB-4 plus high-risk factors (pre-DM / T2DM, complicated obesity, family history (first degree with NAFLD cirrhosis), mild alcohol intake) → advanced screening q1-2 yr
- If NASH cirrhosis diagnosed, provide surveillance for
  - Esophageal varices (EV)
  - Hepatic encephalopathy (HE)
  - Ascites
  - Hepatocellular cancer (HCC)
- If NASH / discordant non-invasive tests (NITs), consult expert

Management Alert – Normal ALT/AST do **not** exclude clinically advanced cirrhosis

- Advise first -degree family members and possibly also non-related household members of their ↑ risk of NAFLD
- The identification of persons at risk of NASH (NASH plus ≥ F2) is important because of their risk of progression to cirrhosis

- Why not use an abdominal ultrasound to screen for NAFLD?
  - Only a “subjective semiquantitative assessment of steatosis severity”
  - The absence of “detectable steatosis on ultrasound does not exclude the presence of NASH or the presence of fibrosis”

➢ Biomarkers (diagnosis, prognostication)

- FIB-4
  - Based on age of patients, ALT, AST, and platelet count
    - Sensitive to detect progression of risk
      - Low, < 1.3
      - Intermediate, 1.3-2.67
      - High, > 2.67
  - Performance characteristics
    - Sensitivity (Sn, rule in), 90%
    - Specificity (Sp, rule out), 90%

- ELF panel (proprietary)
  - Blood test of components of matrix tumour
  - ELF ≥ 98 indicates high risk patient (↑ progression to cirrhosis)

- Elastography
  - Vibration-controlled transient elastography; FibroScan®)
    - Use VCTE-derived liver stiffness (LSM) < 8 kDa (kilopascals) to rule out advanced fibrosis
      - VCTE-LSM of
        - 8-12 kDa, fibrosis
        - > 12 kDa, high likelihood of advanced fibrosis, but PPV (positive predictive value) is low (only 0.34-0.71)
    - ↑ LSM from VCTE or MRE predicts ↑ fibrosis progression / poorer prognosis (example, LSE by MRE of
      - ≥ 5 kDa suggests cirrhosis
      - < 5 kDa 1.6%
      - < 5 kDa 17%
      - > 8 kDa 17%

      } Risk of decompensation within 3 yr
    - ↑ kPa is also associated with ↑ risk of cardiovascular disease
  - Several blood tests +/- combined with imaging are in development

Guidance Statements

- Do **not** use standard abdominal ultrasound to diagnose NAFLD (low sensitivity)
  - MRI can be used with
    - Controlled attenuation parameter (CAP)
    - Proton density fat fraction (PDFF)

➢ Treatment'

- Lifestyle
  - Principles of lifestyle
    - Healthy diet / modified composition
      - ↓ calories
      - ↓ saturated fats
      - ↓ sugar in food, drink (especially ↓ fructose)
    - Exercise to ↑ cardiovascular health
    - Multidisciplinary team

- Diet
  - Moderate intake and feed groups
  - Weight loss to
    - ↓ steatosis, 3% - 5%
    - ↓ NASH / fibrosis, > 10%
  - Patient success to
    - Achieve target weight loss at 1 yr, < 10%
    - Maintain weight loss at 5 yr, ~5%

- Exercise
  - ↑ activity level > 60 min/wk, or
  - Moderate exercise > 150 min/wk

  → ↓ NAFLD / ↓ NASH; ↓ sarcopenia; ↓ frailty

➢ Guidance Statements

- Advise a diet low in saturated fats, refined carbohydrates (especially fructose), low fibre containing diets (such as the Mediterranean diet), protein, unsaturated fat, and ≥ 3 cups of coffee per day, with or without caffeine, but forget the cream and sugar
- Advise ↑ activity/exercise

❖ Bariatric procedures

- Surgery
  - Indication
    - BM ≥ 40 kg/m2
    - BMI ≥ 35 kg/m2 plus
      - Pre-diabetes mellitus (DM), T2DM
      - Hypertension, not controlled
      - Osteoarthritis knee, hip
      - Urinary incontinence

- Benefits
  - ↓ NASH, ↓ fibrosis
  - ↓ diabetes, cardiovascular disease
  - ↓ morbidity/mortality
  - Sustained weight loss in ~30%
  - Do **not** perform bariatric surgery in patients with patients with decompensated NASH cirrhosis / clinically significant portal hypertension (↑ risk of postoperative mortality)
    - Bariatric surgery may be performed in selected patients with compensated cirrhosis

Guidance Statements

- Consider bariatric surgery in obese persons in which weight loss surgery is indicated, and the patients must be carefully selected based on any decompensation or clinically significant portal hypertension
  - The type, safety, and efficacy of bariatric surgery in patients with well-compensated NASH cirrhosis is not established and requires a careful benefit-risk assessment…"

❖ Pharmacotherapy

- Mechanistic targets for pharmacotherapy
  - Targets for pharmacotherapy
  - Increases
    - Adipocyte sensitivity to insulin
      - PPARɣ (peroxisome proliferation-activated receptor ligands)
    - Oxidative metabolism
      - PPARɣ ligands
      - Thyroid hormone receptor B agonists
  - Inhibit
    - Lipogenesis, de novo
      - Inhibitors of
        - Acetyl-coenzyme A carboxylase
        - Fatty acid synthetase
    - Inflammation
    - Cell death
    - Fibrogenesis

- Vitamin E
  - A-tocopherol 800 IU po od for 96 wk vs. placebo
    - Clinical
      - ↓ hepatic decompensation (37% vs. 62%, P = 0.04)
      - ↑ transplant free survival (78% vs. 49%, P < 0.01)
      - Laboratory ↓ ALT to ≤ 40 U/L, and by ≥ 30% of baseline
      - Histopathology ≥ 2 point ↓ NAs without score
        - ↓ steatosis
        - ↓ inflammation
        - ↓ hepatocyte ballooning

- Possible adverse outcome
  - Conflicting evidence of ↑ prostate cancer
  - Use with caution in men with personal / family history of prostate cancer

MCQ Alert

- Vitamin E improves hepatic history in patients with NAFLD/NASH, but not fibrosis.
- The benefits are not adverse effects if the patient has diabetes
- Use with caution in men with personal/family history of prostate cancer

- Thiazolidinediones
  - Chemistry
    - Ligands of peroxisome proliferators-activated
  - Used to treat T2DM and used in patients with T2DM plus NAFLD
  - Benefits
    - Resolution of NASH (47% vs. 27% placebo, $P < 0.001$)
    - ↓ NAS, ↓ fibrosis (pooled network analysis)
  - Cautions
    - Patients with cardiac dysfunction
    - Post-menopausal women
    - ↑ body weight
    - Possible ↑ bladder cancer

- Glucagon-like peptide-1 receptor (GLP-1Ras)
  - Glucagon-like peptide-1 / glucose-dependent insulinotropic polypeptide receptor agonist
  - Approved for use in T2DM, off label for obesity, not approved for NAFLD/NAS
  - Examples
    - Liraglutide
    - Semaglutide (both 50%)
    - Tirzepatide
  - Benefits in NAFLD/NASH
    - ↓ steatosis
    - ↓ NASH (resolved) without ↑ fibrosis, 59% vs. 17% for placebo ($P < 0.001$)
    - ↓ progression of fibrosis (dose-dependent), but ↓ fibrosis, not statistically significant
    - ↓ liver fat content, 8.1%
  - ↓ BMI (non diabetic), 20-90 vs. 3.1% placebo

- SGLT-2
  - ↑ renal excretion of glucose →
    - ↓ body weight 2-3%
    - ↓ steatosis
    - ▪ Role in patients with NASH/NAFLD to be established
- Metformin
  - Used to treat pre-DM / T2DM, but does not ↓ NAFLD/NASH
- Drugs tested but not of benefit in patients with NAFLD/NASH
  - Ezetimibe, milk thistle
  - Polyunsaturated fatty acids
  - Ursodeoxycholic acid (UDCA)
  - Obeticholic acid (role to be established)

Guidance Statements

- Consider
  - Semaglutide
    - T2DM/obesity plus NASH to
      - ↓ NASH
      - ↓ CV risk
  - Pioglitazone
    - T2DM/NASH
      - ↓ NASH
  - Vitamin E
    - NASH +/- T2DM
      - ↓ NASH

VIRAL HEPATITIS

- **Hepatitis A Viral** (HAV) **Infection**

➢ Persons at ↑ risk of HAV infection

- Healthy persons who
  - Travel to endemic areas
  - Work in occupations with ↑ risk of exposure is high
  - Have infected family members
  - Adopt infants/children from an endemic area

➢ Risk factors for HAV infection

○ Poor hygiene/sanitization	− Contaminated food/water (e.g., raw shellfish)
○ Life-style	− Participation in ▪ Anal sex / men who have sex with men (MSM)
○ Children	− Exposure to children in daycare ▪ Day-care employees ▪ Families of children in daycare
○ Lifestyle	− Men who have sex with men (MSM)
○ Chronic disease	− Tested positive for HIV − Chronic liver disease − Clotting factor disorder − Inject drugs or users of non injection illicit drugs

➢ Virology

- Excreted in bile/stools in HAV-infected persons
- Incubation period for symptoms ~28 d
- Peak of viral excretion 2 wk after onset of symptoms

➢ Clinical symptoms

- Asymptomatic
  - Acute
  - Fulminant (incidence 0.01%); mortality rate 70% to 95%
- Symptomatic
  - Relapsing (symptoms/abnormal LEs 1-4 mon after resolution of initial symptoms; 3% to 20%) with anti-HAV antibody titre levels ≥ 10 mIU/mL
  - Cholestatic

- HAV does **not** cause chronic liver disease because of high rate of IgG seroconversion, leading to long-term immunity.

- Mortality rate
  - < 50 yr 0.3% to 0.6%
  - > 50 yr 1.8% to 5.4%

- Hepatitis A Viral (HAV) Immunization
  - Persons who have not previously been exposed to HAV (pre-exposure HAV vaccines, inactivated or live-attenuated)

- Treatment
  - Supportive/symptoms
    - Acetaminophen
    - Anti-emetics
    - Hydration
  - Total abstinence of alcohol

- Prevention
  - Pre-exposure vaccination with inactivated vaccines → induces cellular/luminal immune
  - Post-exposure prophylaxis (PEP)
    - Human immune globulin
      - 80% to 90% effective to prevent HAV infection; if given without 14 d of exposure
      - Prevents HAV symptoms and liver disease (hepatitis)
      - Usually does not prevent HAV infection

	Circumstance(s)	Dose	Simultaneous Administration of HAV Vaccine
Pre-exposure prophylaxis	– 1 mon of travel* to begin in < 2 wk	0.1 mL/kg	Yes**
	– 2 mon of travel* to begin in < 2 wk	0.2 mL/kg	Yes**
	– > 2 mon of travel* to begin in < 2 wk	0.2 mL/kg (repeat q2mon)	Yes**
Post-exposure prophylaxis	– < 12 mon and > 40 yr of age – Chronic liver disease – Contraindication of HAV vaccine ▪ Immunocompromised person	0.1 mL/kg	Yes**, but only if > 12 mon of age

*Travel to area of intermediate or high HAV endemicity
**Except when the vaccine is contraindicated (e.g., because of allergy)

Hepatitis B Viral (HBV) **Infection**

Reddy KR. Gastroenterol 2015: 148: 215-219.

- Prophylaxis
  - Patient at risk for HBV recurrence who are undergoing immunosuppressive drug therapy.
  - Moderate to high risk
    - Screen for HBV (HBsAg and anti-HBc and if these are positive, then measure HBV DNA
    - Use anti-viral prophylaxis
      - Immunosuppressive drug therapy → continue for ≥ 6 mon after stopping Rx
      - B-cell depleting agents → continue for ≥ 12 mon after stopping Rx
    - The risk of reactivation of HBV is small, so persons who are HBsAg negative "…may reasonably select no [HBV] prophylaxis over antiviral prophylaxis"
  - Low risk
    - Do **not** routinely screen or use antiviral prophylaxis
  - Do **not** use anti-HBs status to guide antiviral prophylaxis for all risk groups.
  - For prophylaxis against HBV recurrence in persons on immunosuppression
    - Use HBV drugs in the high barrier to resistance unless cost of drug therapy us an issue and if lamivudine is less costly.

- Risk stratification
  - Risk of flare of HBV with immunosuppression

	HBsAg+	HBsAg- / anti-HBe+
− Corticosteroids		
− Any dose for < 1 wk	+	+
− Prednisone		
▪ < 10 mg for > 4 wk	++	+
▪ > 20 mg for > 4 wk	+++	++
− Azathioprine, methotrexate	+	+
− Anti-TNF	++	++
− Anti-integrin / anti-cytokines / tyrosine kinase inhibitors	++	++
− Gliotoxin chemotherapy, liver transplant	++	+

- High-risk anticipated evidence for developing of HBV infection (HBV in > 10% if cases)

	Drug Exposure
○ HBsAg+ / anti-HBc+, or HBsAg-/Anti-HBc+ patients	− B cell depleting ▪ Ofatumumab ▪ Rituximab
○ HBsAg+ / anti-HBc+	− Anthracycline derivatives ▪ Doxorubicin ▪ Epirubicin − Prednisone ▪ 10 mg to 20 mg /d, or ▪ > 20 mg/d of adequate corticosteroids per d for ≥ 4 wk

- Moderate risk (HBV, 1% to 10%)

○ HBsAg+ / anti-HBc+, or HBsAg-/Anti-HBc+ patients	− Tumour necrosis factor alpha inhibitor ▪ Adalimumab, certolizumab, infliximab ▪ Other cytokine/integrin inhibitors − Abatacept, natalizumab, ustekinumab, vedolizumab ▪ Tyrosine kinase inhibitors − Imatinib, nilotinib
○ HBsAg+ / anti-HBc+	− Prednisone < 10 mg/d or equivalent corticosteroids for ≥ 4 wk − Immunosuppressive therapy: sensitive HBV DNA test (Strong recommendation; moderate-quality evidence − Prednisone ▪ 10 mg to 20 mg per day or equivalent corticosteroid ▪ > 20 mg per day or equivalent corticosteroid per day for ≥ 4 wk − Anthracycline derivatives epirubicin, doxorubicin

- Low risk: HBV, < 1%

○ HBsAg+ / anti-HBc+, or HBsAg-/Anti-HBc+ patients	−"Traditional immunosuppressive drugs ▪ Azathioprine ▪ 6-mercaptopurine ▪ Methotrexate ▪ Corticosteroids (intraarticular) −Any dose corticosteroids po per day for ≤ 1 wk
○ HBsAg+ / anti-HBc+	−Prednisone < 10 mg or equivalent per day for ≥ 4 wk

Risk of HBV_R	Anti-viral Prophylaxis	Duration of Antiviral Prophylaxis after Stopping Immunosuppression	Alternate to Drug Prophylaxis: No Prophylaxis
○ High > 10%	Yes	≥ 10 mon	-
○ Medium 1% to 10%	Yes	≥ 6 mon	+*
○ Low < 1%	No		+

*No recommendation made for HBV DNA monitoring as an alternate to anti-viral prophylaxis (knowledge gap)

- Do **not** use anti-HBs status to grade antiviral prophylaxis for all risk groups (weak recommendation: very low-quality evidence)
- Drug prophylaxis
  - Antiviral drugs with high barrier to resistance (weak recommendation; moderate quality evidence), especially in patients receiving immunosuppression (strong recommendation; moderate quality evidence).

Risk	Strength of Recommendation	Evidence Quality
High	Strong	Moderate
Medium	Weak	Moderate
Low	Weak	Moderate

- Risk of HBV reactivation (HBV_R) with Immunosuppressive drug
  - Azathioprine (AZA)
    - HBV_R
      - Monotherapy AZA or 6-MP (mercaptopurine) dose ≤ 2.5 mg/kg < 1%
      - Patient who is HBsAg negative, anti-HBc positive, 6-MP < 0.1%
  - Methotrexate, < 1%
  - Corticosteroids
    - Long term use in
      - HBsAg positive carrier > 10%
      - HBsAg negative, anti-HBc positive, much lower than 10%
  - Biologics, 1% to 10%
    - Rituximab HBsAg-positive/-negative, anti-HBc positive > 10%
      - Additive/effect of other chemotherapy drugs used for non-Hodgkin lymphoma synergistic → use anti-viral prophylaxis to ↓ risk of HBV_R

- Prophylaxis
  - Use drugs with high barrier to resistance for prophylaxis against HBV_R (e.g., entecavir)
    - The authors of this guideline conclude that "…the cost of testing [for HBV_R] is likely outweighed by the benefits [of anti HBV prophylaxis] when the baseline not for reactivation is moderate (≥ 1%, < 10%) or high (> 10%)
      HBsAg- / anti HBc+, recurring immunosuppressive therapy

Hepatitis B Viral Reactivation *(HBV_R)*

- Definition of terms
  - Acute exacerbation or flare of hepatitis B
    - Intermittent increase of aminotransferase activity to >10 × ULN and >2 × baseline value

- Azathioprine (AZA), 6-mercaptopurine (6-MP)
  - Risk
    - Little uncertainty when used as monotherapy < 1%
      - Moderate uncertainty risk of reactivation < 0.1%

Drug	Little Uncertainty	Moderate Uncertainty
Azathioprine, 6-mercaptopurine	1%	0.1%
Methotrexate	< 1%	
Corticosteroids high dose	10%	(lower in persons who are HBsAg-, anti-HBc+)
Biologicals	1% to 10%	(Lower in persons who are HBsAg-. Anti-HBc+, than in HBsAg+ persons)
Anti-TNF inhibitors	Lower risk in HBsAg-, anti-HBC+, than in HBsAg+ persons	
Rituximab in HBc+ persons	> 10%	

Prophylaxis Alert

- Persons taking high-risk immunosuppressants, and who are HBsAg+ and anti-HBc+
  - Reactivation rate of HBV (HBV_R) > 10% → recommended to use HBV prophylaxis (prophylaxis may also be of benefit when HBV_R rate is ≤ 2%.

Abbreviations: 6-MP, 6-mercaptopurine; AZA, azathioprine; HBVR, hepatitis B viral resistance; HBV, hepatitis B virus

- Screening for HBV_R
  - For patients taking high (>10%) or medium (1-10%) risk drugs
  - The need for screening should be determined according to the recommendations outlined by the US Preventive Services Task Force (USPSTF), which reflects the anticipated population prevalence.

- Prophylaxis
  - Entecavir, tenofovir
    - Remember “renal dosing” in persons with renal insufficiency

- Phases of CHB Infection

Phase	ALT	Liver histology
Immune tolerance phase	Normal or minimally elevated	Minimal activity; absent or scant fibrosis
Immune clearance phase (HBeAg-positive CHB)	Elevated, usually persistently or with intermittent elevations	Active; liver biopsy showing chronic hepatitis (necroinflammatory score ≥4)
Low viral replication	Persistently normal	Inactive; liver biopsy showing variable, usually minimal fibrosis (necroinflammatory score <4)
Reactivation phase (HBeAg-negative CHB)	Elevated, often fluctuating levels	Active; liver biopsy showing variable amounts of fibrosis (necroinflammatory score ≥4)
Resolution	Normal	Inactive; scant fibrosis

Serum HBV DNA, IU/mL	HBeAg	Anti-HBe
High levels: serum HBV DNA >20,000 IU/mL	+	-
High levels: serum HBV DNA >20,000 IU/mL	+	-
Low or undetectable levels: serum HBV DNA negative or <2000 IU/mL	-	+
Moderate, often fluctuating levels: serum HBV DNA >2000 IU/mL	-	+
No detectable serum HBV DNA (low levels may be detectable in the liver)	-	+

  - Note
    - For all the above, HBsAg is positive after 6 mon, except for when there is no elevated serum HBV DNA, when HBsAg is negative.

- Follow-up of untreated patients
  - HBeAg-positive or -negative CHB with HBV DNA ≥2000 IU/mL and normal ALT
    - Assess ALT levels every 3–6 mon
    - Consider liver biopsy or transient elastography to assess fibrosis
    - Consider initiating treatment when ALT levels increase or fibrosis is present
  - HBV DNA <2000 IU/mL and normal ALT
    - Assess ALT levels every 6–12 mon
    - If ALT levels become increased, check serum HBV DNA and exclude other causes of disease

- Anti-viral resistance

- Relating to Antiviral Resistance to Nucleoside and Nucleotide Analogue Treatment for CHB

○ Biochemical breakthrough	− ↑ in ALT level above ULN after achieving normalization during continued therapy
○ Cross-resistance	− ↓ susceptibility to more than 1 antiviral drug conferred by same amino acid substitution or combination of amino acid substitutions
○ Genotypic resistance	− Detection of viral populations bearing amino acid substitutions in reverse transcriptase region of HBV genome that have been shown to confer resistance to an antiviral in phenotypic assays during antiviral therapy. ▪ These mutations are usually detected in patients with virologic breakthrough but can also be present in patients with persistent viremia and no virologic breakthrough.
○ Viral rebound	− ↑ in serum HBV DNA to >20,000 IU/mL or above pretreatment level after achieving virologic response during continued therapy
○ Virologic breakthrough	− ↑ in serum HBV DNA level by >1 log10 IU/mL above nadir after achieving virologic response during continued therapy

Adapted from: Martin P, et al. Clin Gastroenterol Hepatol 2015; 13: 2071-87.

- Laboratory methods to detect antiviral resistance
  - Standard population-based sequencing
  - INNO-LIPA
  - Restriction fragment length polymorphism analysis
  - Allele-specific PCR
  - DNA chip
  - Ultradeep pyrosequencing

- Recommendations for treatment of HBV

	HBV DNA	ALT	Histopathology	Treatment*	Monitoring	Long-term treatment
HBeAg+	< 2000 IU/mL	N	N	-	q6-12 mon	
			ABN	+		
	≥ 2000 IU/mL	N	N	-	q12mon	
			ABN	+		
		↑	N	+		
			ABN	+		+
HBeAg-	< 2000 IU/mL	N	N	-	q6-12 mon	
			ABN	+		
	≥ 2000 IU/mL	N	N	-	+	
			ABN	+		
		↑	N	+		+
			ABN	+		

*treatment with entecavir (ENT), tenofovir (TEN), Peg IFNγ

- ULNs for serum ALT concentrations are 30 IU/L for men and 19 IU/L for women
- On initial diagnosis, monitor every 3 mon for 1 yr to ensure stability

Hepatitis B Virus (HBV) Infection*

* Some topics have not been revised recently for updated guidelines, and in this place a review article is provided

AS Wilson and A Thomson

- Transmission and Risk

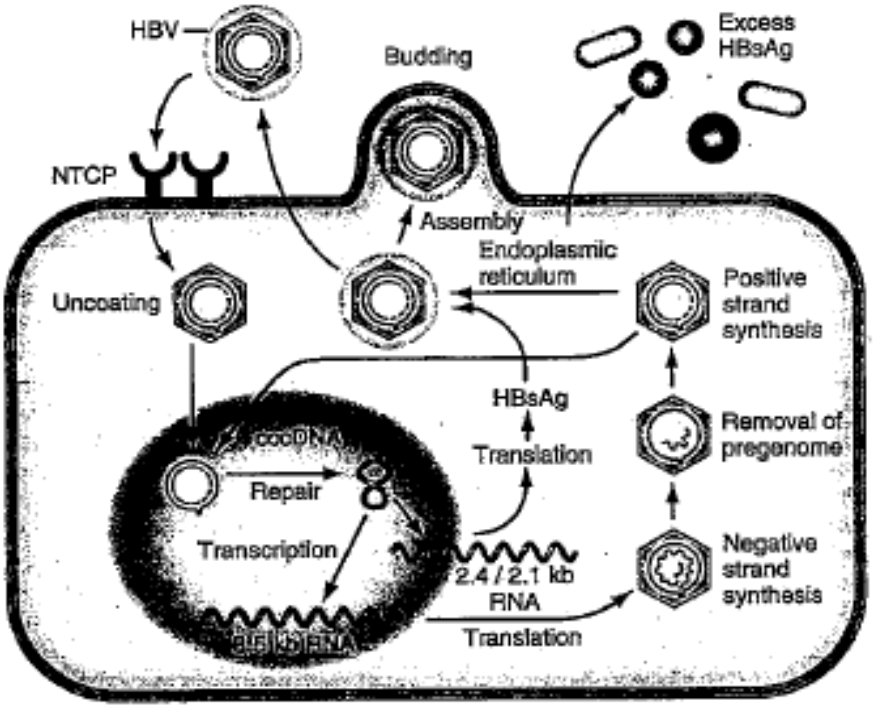
Geographical Area	Mode of Transmission	Life Risk of HBV Infection
○ NA, WE, SA, Au	− Horizontal person-to-person, young adults	< 20%
○ SEA, China, Africa	− Perianal − Horizontal, young children	60% to 80%

  - Once infected with HBV, males are more likely than females to remain persistently infected
  - Women are more likely
    - To be infected transiently and
    - To develop anti-HBs (antibody to hepatitis B surface antigen).

- Virology
  - HBV is a DNA virus which
    - Goes through an RNA intermediate
    - Requires an active viral reverse transcriptase / polymerase enzyme for encapsulation 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
    - Has a high point mutation rate, low replication fidelity
    - A gene encodes HBsAg, a viral surface, envelop protein
  - HBeAg, HBsAg, HbcAg
    - The core gene has
      - Precore region → HbeAg
      - Core region → core proteins
    - 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 endoplasmic reticulum (ER).
    - From the ER, the enveloped nucleocapsid bud off from the hepatocyte membrane, and enter the circulation.

➢ Pathophysiology

- Life cycle of HBV



  - The receptor for viral entry has not been identified, but studies have suggested that sodium taurocholate cotransporting polypeptide (NTCP) is likely to be the receptor for binding the HBsAg protein.
  - Once inside the hepatocyte
    - The virus undergoes uncoating, and
    - The HBV genome enters the nucleus, followed by repair of the single-stranded DNA strand, and
    - Formation of the currently closed circular (ccc) DNA template.
    - Viral transcripts are formed for the HBsAg, DNA polymerase, X protein, and RNA pregenome
    - The pregenome and polymerase are incorporated into the maturing nucleocapsid, and
    - Removed after translation
  - The surface protein enveloping process occurs in the endoplasmic reticulum (ER).
  - The surface protein enveloping process occurs in the ER.
  - Some of the non-enveloped nucleocapsid recirculates back to the nucleus, and the cycle begins again.
  - Excess tubular and spherical forms of HBsAg are secreted in great abundance and outnumber complete virions in serum by a factor of 10^3 or more.

Printed with permission: Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 11th Edition. Volume 2, 2020; Chapter 79, Figure 79.3, page 1219.

- The expression of HBV proteins and the release of virions precedes biochemical evidence of liver disease.
  - Large quantities of surface antigen can persist in liver cells of apparently healthy persons who are carriers.
  - HBV is therefore not directly cytopathic.
- Immune-modulated damage
  - An HLA class I restricted cytotoxic T-cell (CTL) response directed at HBcAg/HBeAg on HBV-infected hepatocytes.
  - ↑ expression / ↓ secretion of HBsAg.
  - A direct cytopathic effect of HBcAg expression in infected hepatocytes.
  - ↓ viral clearance by cytotoxic T lymphocytes (CTLs)
    - Liver damage from HBV is immune-mediated (not a direct hepatocyte cytopathic effect of HBV).
    - Cellular immune response
      - Innate and adaptive
  - CD4+ T cells produce antiviral cytokines which reduce the production of neutralizing

- Hepatocyte metabolism of HBV.
  - HBV uptaking into hepatocyte
    ↓
  - HBV uncoating
    ↓
  - Uptake into nucleus
    ↓
  - cccDNA transcription
    ↓
  - 2.4 kb RNA
    ↓ 3.5 kb RNA
  - Priming/encapsulation
    ↓
  - Translation
    ↓
  - Encapsulation
    ↓
    - Negative-strand synthesis
      - Assembly, budding, HBV exit from hepatocyte
        - Positive-strand synthesis
          - Removal of pregenome

- Adefovir
- Entecavir
- Lamivudine
- Tenofovir

} Inhibitor of HBV +/- strand synthesis

- HCC Development in HBV
  - HBV infection contracted early in life may lead to chronic hepatitis, then to cirrhosis, and finally to hepatocellular cancer (HCC), usually after a period of 30 to 50 yr.
  - HBV may not be carcinogenic by a direct viral mechanism.
    - HBV may cause chronic liver cell damage with associated host response of inflammation and liver regeneration that continues for many years.
    - This pathological process, especially when leading to cirrhosis, may be carcinogenic, without involving a direct oncogenic action of the virus.
  - No viral oncogene, insertional mutagenesis, or viral activation of oncogenic cellular genes has been demonstrated
  - Risk of developing hepatocellular cancer (HCC)
    - HBV, ~4/100 patient years
    - For comparison HCV, ~2/100 patient years
  - 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
      - Mitogen-activated protein kinase (MAP)
      - JAK/ STAT pathways (Janus kinase-signal transducer and activator of transcription)

➢ Laboratory

- Diagnostic Criteria for each HBV Infection Phase

	HBeAg-positive		HBeAg-negative		HBeAg-negative
	Chronic HBV Infection	Chronic Hepatitis B	Chronic HBV Infection	Chronic Hepatitis B	Resolved HBV Infection
Old terminology	Immune tolerant	Immune reactive HBeAg positive	Inactive carrier	HBsAg-negative chronic hepatitis	HBsAg-negative phase
HBsAg	High	High/ intermediate	Low	Intermediate	Negative
HBV DNA	≥10^7 IU/mL	10^4-10^7 IU/mL	<2000 IU/mL	≥2000 IU/mL	Undetectable
ALT	Normal	Elevated	Normal	Elevated	Normal
Liver disease	None/ minimal	Moderate/ severe	None	Moderate/ severe	None

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- Reactivation of hepatitis B
  - Reappearance of active necroinflammatory disease of the liver in a person known to be in the low viral replication state or to have resolved hepatitis B

- Give the differential diagnosis of hepatitis flares in persons with chronic hepatitis B.

Cause of Flare	Comment
• Therapy	
○ Spontaneous	− Factors that precipitate viral replication − Loss of immune control are unclear
○ Immunosuppressive	− During or shortly after withdrawal of the agent (pre-emptive antiviral therapy is required)
○ Antiviral therapy for HBV	
− Interferon	▪ Within the first 3 mon of initiating therapy with interferon in 30% of patients and may herald HBeAg seroconversion in some patients
− Nucleos(t)ide analog	
− During treatment	▪ Improve medication adherence
− Antiviral resistance	▪ Agents that have a low genetic barrier to resistance such as lamivudine and telbivudine ▪ Confirm genotypic resistance with resistance testing
− Off treatment	▪ Clinical relapse (re-elevation of serum ALT levels and re-appearance of HBV DNA in serum in those previously virally suppressed)
○ Coinfection with	
− HCV	▪ HBV may be suppressed in HCV-coinfected patients ▪ HBV reactivation in co-infected patients undergoing DAA therapy for HCV infection
− HDV	▪ HBV is usually suppressed in HDV coinfected patients ▪ ↑ risk of liver disease progression
− HIV	▪ The direct toxicity of ART, or ▪ With immune reconstitution (HBV increases the risk of anti-retroviral drug hepatotoxicity)
○ Other liver disease	− Alcohol overuse − Autoimmune liver disease − Drug and toxin-induced liver injury − NAFLD

Abbreviations: ART, antiretroviral therapy; HBeAg, hepatitis B e antigen

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- Give the clinical conditions and examples of drugs associated with ↑ risk of reactivation of HBV in persons who are HBsAg+.
  - Rituximab, ofatumumab (↑↑↑ anti-CD20 B cell-depleting agents)
  - Hematopoietic stem cell transplantation
  - Doxorubicin, epirubicin (anthracycline)
  - High-dose prednisone (> 20 mg daily) for > 4 wk
  - Alemtuzumab (anti-CD 52)
  - Infliximab, Adalimumab (↑↑ anti-TNF)
  - Abatacept, natalizumab, ustekinumab, vedolizumab (cytokine integrin inhibitors)
  - Imatinib, nilotinib, sorafenib (tyrosine kinase inhibitor)
  - Cytotoxic chemotherapy
  - Low dose prednisone (< 10 mg daily) for > 4wk
  - Antirejection regimens for solid organ transplant
  - Azathioprine, methotrexate, 6-mercaptopurine (immunosuppressive therapy)
  - Any dose of glucocorticoids for 1 wk
  - Antra-articular glucocorticoids

Adapted from: Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 11th Edition. Volume 2, 2020; Chapter 79, Table 79.4, page 1226.

➢ Treatment

❖ **General management strategy**

- Give the pre-treatment baseline evaluation of the patient with HBV infection.
  - Revised normal ALT levels (30 IU/L for men, and 19 IU/L for women) should be used as criteria for treatment
  - Baseline evaluation should include HBV genotype, particularly if peginterferon therapy is considered
  - Preferred first line treatment options: adefovir, entecavir, peginterferon alfa-2a, and possibly telbivudine
    - Lamivudine is not first-line choice because of the high rate of resistance to Interferon alfa-2b

- Give the potential management strategies for HBV by on-treatment virologic response categories.
  - Virological response - HBV DNA < 2000 IU/mL at 0, 6 and 12 mon after the end of therapy
  - Sustained virological response - HBV DNA < 2000 IU/mL at 12 mon 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)

Category	Strategy
Primary treatment failure at wk 12	– If noncompliant, counsel patient on importance of adherence toprescribed drug regimen – If compliant, change therapy to more potent drug / possibly a drug combination
Complete virologic response at wk 24	– Continue therapy with same drug; monitoring may be extended to 6-mon intervals
Partial virologic response at wk 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-mon intervals and continue beyond 48 wk – If drug has a delayed antiviral effect e.g., adefovir, repeat monitoring at 3-mon intervals, and – If response becomes complete at 48 wk, continue therapy; but – If response remains partial or becomes inadequate at 48 wk, add a more potent drug
Inadequate virologic response at wk 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-mon intervals – Monitoring after 48 wk may be extended from 3 to 6 mon if response becomes complete

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

➢ Definition
- HBeAg clearance
  - Loss of HBeAg in a person who was previously HBeAg-positive
- HBeAg seroconversion
  - Loss of HBeAg and detection of anti-HBe in a person who was previously HBe-positive and anti-HBe-negative, associated with decrease in serum HBV DNA to <20,000 IU/mL
- HBeAg reversion
  - Reappearance of HBeAg in a person who was previously HBeAg-negative, anti-HBe-positive

- Resolution
  - Loss of HBsAg and no further virologic, biochemical, or histologic evidence of active virus infection or disease
- Seroreversion
  - Reappearance of HBsAg in a person with previously resolved HBV and loss of HBsAg
- Occult hepatitis B
  - Having detectable HBV DNA while being negative for HBsAg

- Give factors that are predictive of a viral response (VR) to treatment of HBV infection.
  - Patient
    - Immunocompetent
  - HBV
    - Adult-acquired infection
    - Low HBV-DNA level
      - ↑ response to interferon
      - HBV recurrence with liver transplantation
    - Absence of HDV or HIV co-infection
    - HBeAg +ve
  - Biopsy
    - Active liver disease—ALT > 5x upper limit of normal (ULN), active hepatitis on biopsy
    - Should be considered for HBV-infected patients with normal ALT levels, especially if age >35 yr
  - Specific treatment algorithms
    - HBeAg+
    - HBeAg-
  - PEG-IFN or NA monotherapy used for finite duration
    - PEG-IFN (in the absence of contraindications) for HBeAg- positive and -negative patients for 48 wk
  - Treatment strategies
    - NA monotherapy for long-term duration (suppresses but does not eradicate HBV)
  - Do **not** combine PEG-IFN with lamivudine or telbivudine (↑ risk development of severeneuropathy)
  - Entecavir or tenofovir for 12 mon after seroconversion in about 2/3 of those initially HBeAg-positive HBV patients
  - Entecavir or tenofovir monotherapy for
    - HBeAg-positive patients who failed to seroconvert
    - HBeAg-negative patients
    - All HBV cirrhosis
  - NA for long term maintenance (continuously duration)
  - Monitoring and applying stopping rules

- HBV Serology patterns

HBV Diagnosis	Serological Pattern
○ Acute hepatitis B	− HgsAg+, HBeAg+, Anti-HBC IgM+ − Anti-HBc-IgM+, HBeAg+/-
○ Chronic hepatitis (CHB)	− Active viral replication: HBsAg+, HBeAg+. Anti-HBe IgG+ − Heterotypic anti-HBs: HBsAg+. Anti-HBs+, HBeAg+/-, anti-HBe+/- − Inactive HBV carrier (low HBV DNA): HBsAg+, anti-HBe+, anti-HBe+ − HBeAg- CHB, active viral replication (high HBV DNA) − Recovery (immunity) from/to HBV − Vaccination immunity ▪ Anti-HBs+, anti-HBc IgG+, anti-HBe+/- − False-positive (past infection) ▪ Anti-HBC+ ▪ Immunity, vaccination

- HBV Serological Patterns and HBV Disease Diagnosis

HbsAg+	Anti-HBC	Anti-HBC IgM	Anti-HBC IgG	HbeAg	Anti-HBe
○ AHB		+		+	
○ CHB					
− Viral replication					
− Low HBV DNA					
− Heterotrophic anti-HBS	+		+	+/-	+/-
− Recovery	+				+/-
− Vaccination	+		+		

Papdakis MA and McPhee SL. Current Medical Diagnosis and Treatment. Chapter 16, Freedman LS. 2020. Adapted from Table 16-5, page 698

- First-line therapies for treatment-naïve patients with chronic hepatitis B after 1-yr of treatment

Outcome (%)	PegIFN-α	ETN	TDF	TAF
○ HbeAg-positive chronic hepatitis B (immune active phase)				
− Viral suppression	32 (< 4 log IU/mL)	67 (< 60 IU/mL	66 (< 60 IU/mL	64 (< 29 IU/mL
− HBeAg loss	34	22	21	14
− HBsAg loss	3	2	3	1
− ALT normalization	41	68	68	72
− Histologic response	49	72	74	N/A
○ HBeAg-negative chronic hepatitis B (reactivation phase)				
− Viral suppression	43 (< 3 log IU/mL)	90 (< 60 log IU/mL)	71 (< 60 log IU/mL)	94 (< 29 log IU/mL)
− HBsAg loss	4	< 1	0	0
− ALT normalization	59	78	76	83
− Histologic response	55	70	72	N/A

Printed with permission: Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 11th Edition. Volume 2, 2020; Chapter 79, Table 79.5, page 1230.

- The first and second therapies for 8 different clinical situations of HBV infection requiring treatment with DAAs.

	Therapy	
	First-line	Second-line
○ Treatment		
− Naïve		
▪ GFR > 60 mL/min	ENT, TAF, or TDF	TEL
▪ GFR < 60 mL/min	ENT, or TAF	TEL
− TAF, TDF, or ENT, but continued low-level viremia while on treatment	TAF, TDF or ENT continued, or switch to one of the other of those DAAs with high magnetic barrier	-
○ Prior exposure		
− LAM, or TEL	TAF, TDF	ENT
− LAM and ADS	TAF, TDF, or ENT	TEL
○ Proven resistance		
− ADE	ENT	TAF, or TDF
− ENT	TAF, or TDF	Ade/ADE
− LAM	TAF, or TDF	Ade/ADE
− TEL	TAF, or TDF	Ade/ADE

Abbreviations: ADE, adefovir; ENT, entecavir; LAM, lamivudine; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; TEL, telbivudine

Adapted from Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 11th Edition. Volume 2, 2020; Chapter 79, Table 79.6, page 1231.

❖ **DRUG CHOICES**

- IFN (interferon)
  - PEG-IFN (pegylated IFN)
- Nucleosides
  - Emtricitabine (EMT)
  - Entecavir (ENT)
  - Lamivudine (LAM)
  - Telbivudine (TEL)
- Nucleotides
  - Adefovir (ADE)
  - Tenofovir (TEN)

- **Nucleoside** (NS) **/ Nucleotide** (NT) **Analogs** (NA)
  - "Competitive inhibitors of reverse transcriptase and DNA polymerase".
  - "Replace natural nucleoside during the synthesis of the first or second strand (or both) of HBV DNA".

- The advantages and disadvantages of nucleosides and nucleotide analogs for the treatment of chronic HBV infection.

Agent	Advantages	Disadvantages
○ Lamivudine (LAM)	− Oral administration − Excellent tolerance − Use in ESLD and adefovir failures	▪ Drug resistance: common (~20%/yr, and up to 70% with 4-5 yr of therapy)
○ Adefovir (ADE)	− Oral administration − Excellent tolerance − Use in ESLD − Use in lamivudinefailures	▪ 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 (ENT)	− 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 LAM resistance (6% at year 1, 14% at year 2, and 32% at year 3)
○ Telbivudine (TEL)	− Oral administration − Excellent tolerance − High potency in lowering HBV DNA levels	▪ Drug resistance: intermediate rates (5% at year 1, and 21.6% at year 2 in HBeAg-positive patients, and 8.6% in HBeAg-negative patients)
○ Tenofovir (Ten)	− Resistance not seen	

Abbreviation: ESLD, end-stage liver disease

- **Lamivudine** (LAM)
  - High rate of viral mutation and viral resistance
  - ~40% at 2 yr, 65% at 5 yr
  - Higher rate of resistance with treatment of co-infection with treatment of co-infection with HIV.
  - HBV viral suppression
    - Lam < adefovir (Ade) < entecavir < telbivudine (Tel) < tenofovir (Ten)
  - HBV resistance
    - Ten > Tel > Ent >Ade

- Pros and cons of Lamivudine versus interferon (IFN) for the treatment of HBV.

Favouring Lamivudine	Favouring IFN
○ Needle phobia	– Young Asian person
○ HIV co-infection	– Genotype A
○ Other immunosuppression (e.g., transplantation)	– Recent infection
○ Patients with depression	– AST > 100
○ Low WBC count	– Low serum HBV-DNA
○ Low platelet count	– Active liver biopsy
○ Autoimmune disease	– HBeAg+
○ Decompensated cirrhosis	– Possibility of seroconversion (eAg+→eAb+)
○ Vertical transmission	– Marginal benefit to baby
○ Cost concerns	– Contraindicated with depression, renal failure
○ Pregnancy, may be used	– Do **not** use in pregnancy
○ Has 70% resistance rate at 5 yr. – It acts as an immunomodulatory agent resulting in ▪ Loss of circulating HBeAg and HBV DNA in 30-40% of cases, and to a lesser extent ▪ An antiviral agent resulting in loss of HBsAg in less than 5% of cases.	
○ Cross resistance with tenofovir	

- **Interferon** (IFN)
- Give the advantages and disadvantages of interferon for the treatment of chronic HBV infection.

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

- The early and late adverse effects of interferon.
  - Early
    - Flu-like illness; headaches, nausea
    - Tenderness at site of infection
  - Late
    - General
      - Fatigue
      - Irritability Anxiety and depression
    - Eyes
      - ↑ retinopathy DM
      - Optic tract neuropathy
    - CNS
      - Neuropsychiatric issues
    - MSK
      - Muscle aches
    - Skin
      - Alopecia
      - Lichen planus worsens
    - GI
      - Weight loss
      - Diarrhea
      - Anorexia
      - IBD worsens
    - Endocrine
      - Autoimmune autoantibodies
      - Worsening thyroid disease
      - Autoimmune diseases worsen
    - Pregnancy class C
    - Bone marrow suppression
      - Bacterial Infections

Abbreviations: CNS, central nervous system; DM, diabetes mellitus; GI, gastroenterology; IBD, inflammatory bowel disease; MSK, musculoskeletal

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

- **Adefovir dipivoxil**
  - Acyclic phosphate nucleotide analog of adenosine monophosphate
  - ↓ HBV polymerase and reverse transcriptase
  - HBV resistance
    - Ten > Tel > Ent >Ade

- **Entecavir**
  - Deoxyguanosine nucleotide analog which selectively inhibits replication of HBV
  - ↓ priming of HBV DNA polymerase
  - ↓ synthesis of positive strand of HBV DNA
  - Low rates of resistance (1.2% after 5 yr), and
  - 20% rate of eAg seroconversion after 48 wk
  - Development of resistance is associated with flares.

- **Telbivudine**
  - Nucleoside analog of thymidine
  - Because telbivudine develops resistance mutations at the same site as for lamivudine, telbivudine is not effective in persons who have lamivudine resistance

- **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
  - The diagnosis of chronic HBV infection in an HIV patient is an indication to start tenofovir-based therapy

❖ Recommendations regarding monitoring and stopping HBV treatment.

- PEG-IFN
  - HBeAg-positive
    - On treatment
      - Every 6 and 12 mon: anti-HBe antibodies, serum HBV DNA, ALT, HBsAg
    - Off treatment
      - Every 12 mon: HBeAg, anti-HBe antibodies, serum HBV DNA, ALT, HBsAg
    - HBeAg seroconversion (HBeAg-positive → negative)
      - Test HBsAg every 12 mon (seroreversion)
    - No HBeAg seroconversion (serum HBsAg > 20,000 IU/mL, or no ↓ HBsAg at 3 mon)
      - Stop PEG-IFN
  - HBeAg-negative
    - On treatment, at mon 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 mon HBeAg, anti-HBe, HBV DNA, serum creatinine
    - Measure HBsAg every 12 mon after HBe seroconversion
    - Stop NA 12 mon after anti-HBe seroconversion, or
    - Do **not** Stop NA unless loss of HBsAg (with or without antibodies to HBsAg), especially if there is severe fibrosis or cirrhosis.

- Give when HBV therapy should be reassessed or stopped.
  - HBeAg+: HBeAg seroconversion and – HBV DNA
  - HBeAg-: Long term therapy
  - Inadequate viral response (VR) (<2,000 IU/mL) at week 24
  - Development of antiviral drug resistance
  - If HBV DNA reappears during treatment of HBV, then resistance to the drug has likely occurred.
  - In fulminant HBV, the HBsAg may have disappeared, but the diagnosis can be made by finding HBV DNA in serum.

❖ Treatment strategy

- **HBeAg-positive compensated patients** (based on their HBV DNA and ALT)

HBV DNA	ALT	Treatment Strategy
○ <20,000 IU/mL (inactive)	Normal	− No treatment − Monitor every 6-12 mon − Consider therapy in patients with known significant histological disease even if low-level replication
○ ≥20,000 IU/mL (active)	Normal	− Low rate of HBeAg seroconversion for all treatments − Monitor every 3-12 mon − Younger patients often immune tolerant − Consider liver biopsy; particularly if age > 35-40 yr − In the absence of a liver biopsy, observe for rise in ALT levels.
○ ≥20,000 IU/mL	Elevated	− If “high” HBV DNA: adefovir, entecavir or telbivudine preferred over peginterferon alfa-2a.

- **HBeAg-negative compensated patients** (based on their HBV DNA and ALT)

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

- Comparisons
  - Treatment of chronic hepatitis B at 6 mon following 48-52 wk of pegylated interferon alpha (PEG-IFNα), and at 48-52 wk of nucleos(t)ide analog (NA) therapy.

	PEG-IFN		Nucleotide Analog			Nucleoside Analogs	
	PEG IFN-2a	PEG IFN-2b	LAM	TEL	ENT	ADE	TEN
• HBeAg Positive							
○ Dose	180 µg	180 µg	100 µg	600 mg	0.5 mg	10 mg	245 mg
○ Anti-HBe seroconversion (%)	32	29	16-18	22	21	12-18	21
○ HBV DNA < 60-80 IU/mL (%)	14	7	36-44	60	67	13-21	76
○ ALT normalization (%)	41	32	41-72	77	68	48-54	68
○ HBsAg loss (%)	3	7	0-1	0.5	2	0	3
• HBeAg Negative							
○ 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 normalization (%)	59		71-79	74	78	72-77	76
○ HBsAg loss (%)	4		0	0	0	0	0
○ Drug resistance1/5 yr	0/0		24/70	41	0.2/1.2	0/29	0/0

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

Adapted from: European Association for the Study of the Liver. J Hepatol. 2012;57(1):167-85 (Table 2 and 3)

Comparisons between current nucleos(t)ide analogues in treatment-naïve patients withchronic hepatitis B, in terms of (by reduction and undetectable) HBV-DNA (PCR) and HBeAg seroconversion and drug resistance

	LAM		ADE		ENT		TEL		TEN	
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%	-	71%	74%	-	5.6%	82%	78%	99%
Year 3	20%	40%	-	77%	-	-	-	-	-	-
Year 4	-	34%	-	73%	-	-	-	-	-	-
HBeAg Seroconversion										
Year 1	20%	NP	13%	NP	21%	NP	23%	NP	23%	NP
Year 2	26%	NP	29%	NP	31%	NP	30%	NP	26%	NP
Year 3	40%	NP	37%	NP	-	NP	-	NP	-	NP
Year 4	47%	NP	35%	NP	47%	NP	-	NP	-	NP
Drug resistance										
Year 1	11%	6-27%	0%	0%	0%	0%	5%	2%	0%	0%
Year 2	14%	26%	-	3%	0%	NP	25%	11%	0%	0%
Year 3	40%	54%	-	11%	1.2%	NP	-	-	-	-
Year 4	56%		20%	29%	1.2%	NP	-	-	-	-

Abbreviations: ADE, adefovir; EN, tenofovir; ENT, entecavir; HBeAg, hepatitis B e antigen;HBV, hepatitis B virus; LAM, lamivudine; NP, not applicable; PCR, polymerase chain reaction; TEL, telbivudine

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

- Note:
  - Reduce the dose of NAs (NTs and NSs) if creatinine clearance < 50 mL/min.
  - Screen all HBV positive patients for HIV before starting HBV treatment with lamivudine, entecavir or tenofovir (since these drugs have activity against HIV and should not be used as more therapy for HBV for fear of causing HIV resistance).
    - PEG-IFN, adefovir and telbivudine are not active against HIV.

- PEG-IFN has advantages over nucleos(t)ide (NA) because of
  - The absence of resistance
  - The possibility of seroconversion (HBsAg-positive → negative) in about 25% of patients
  - The ~4% change of loss of HBsAg in persons who achieve and maintain undetectable HBV DNA (by sensitive testing).
  - IFN therapy responders enjoy a ~ 50% reduction in cirrhotic complications and 80% reduction in liver- related mortality.

- Overview of response rates in HBeAg+ and HBeAg- 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 (LAM)	19%	12%	65%	10%
- Adefovir (AFE)	12%	NA	51%	NA
- ADE in LAM resistance	20%	NA	19%	NA
- Entecavir (ENT)	21%	NA	90%	NA
- ENT in LAM resistance	8%	NA	26%	NA
- TEL	22%	NA	88%	NA
- TEN	21%	NA	92%	NA

Abbreviation: NA, not applicable

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

Mutants and Mutations

- HBsAg mutants
  - Vaccine escape
    - In persons for whom HBIG does not prevent HBV, ~50% 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…."(Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier, Philadelphia, 2010, page 1291).
- Viral resistance may occur weeks to months before a virologic breakthrough
  - Virologic breakthrough
    - "> 1 $\log_{10}$ (10-fold) increase in serum HBV DNA levels above the previous nadir" (Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier, Philadelphia, 2010, Table 78.3, page 1304).
  - Virologic rebound may follow virologic breakthrough; define "virologic rebound".
    - Virologic rebound HBV DNA > 10^5 (20,000 IU/mL)
- **Before starting immunosuppressive therapy or chemotherapy**
  - HBe-Ag-positive
    - NA before, during and for 12 mon after immunosuppressive therapy or (preferably entecavir or tenofovir) chemotherapy, regardless of serum HBV DNA level
  - HBeAg-negative patients with detectable HBV DNA –treat as above
  - HBeAg-negative, anti-HBe antibody positive, detectable serum HBV DNA – treat as per above,
  - HBeAg-negative, anti-HBe antibody positive, undetectable serum, HBV DNA – monthly monitoring of ALT and HBV DNA.
  - Anti-HBe positive patients receiving bone marrow or stem cell transplantation – NA prophylaxis
  - HbsAg negative recipient of liver graft from anti-HBe-positive donor – indefinite lamivudine prophylaxis
  - Polyarteritis nodosa (PAN) – consider possible of HBV/HCV infection

- **Corticosteroid withdrawal / Immune Rebound**

- Give the reason why acute liver failure (ALF) may occur during steroid withdrawal for treatment of polyarteritis nodosa (PAN) in HBV, but not in HCV.
  - Hepatic damage in HBV (but not in HCV) is immune-mediated, and would cause aggressive necrosis upon immune reconstitution resulting from withdrawal of steroids fortreatment of PAN.
  - 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.

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

- 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

❖ Treatment Flare

- Idiopathic
- Iatrogenic
  - Interferon
    - 30% of interferon-treated patients experienced a flare usually within the first 3 mon may occur before HBeAg seroconversion
  - Nucleoside/nucleotide analogs
    - Development of antiviral drug-resistance
    - Non-adherence
    - Previously treated effective, drug stopped → flare clinically, ↑ ALT, ↑ HBV DNA
- Infection/co-infection
  - HCV
    - Treated HCV in HBV plus HCV infection → HBV flare (HCV may ↓ HBV)
  - HDV
    - Usually suppressed HDV
  - HIV
    - Antiviral / anti-HIV drugs
      → Direct toxicity to liver (HBV → ↑ toxicity of ART)
      → Immune reconstitution

- HBV
  - HBeAg-
    - Development of core/precure promoter mutants may ↑ALT
  - Immunosuppressants
    - Most immunosuppressants may cause of flare during/after use of immunosuppressants

- HBV Reactivation During Immunosuppressive Therapy

Estimated Risk	
> 10%	Treat
1-10%	Treat - If prophylaxis declined, monitor q1-3mon
< 1%	Monitor q1-3 mon

- Post-exposure prophylactic treatment for HBV
  - No previous vaccination
    - HBIG, 0.06 mL/kg, plus HBV vaccination
  - Previous vaccination
    - Known responder
      - HBIG, as above, given in two doses a mon apart, or
      - HBIG, 1 dose plus HBV revaccination
    - Unknown antibody response
      - Anti-HBs < 10 mIU/L, HBIG 1 dose plus HBV booster revaccination

HBV Infection Related Extrahepatic Manifestations

- Polyarteritis Nodosa (PAN)

➢ Clinical

- As compared to primary PAN, patients with HBV-related have ↑ risk of
  - CNS
    - Neuropathy (82% vs. 64%)
    - Microaneurysms (71% vs. 49%)
  - CVS
    - Hypertension
      - Recent (49% vs. 27%)
      - Severe (11% vs. 5%)
    - Cardiac involvement (13% vs. 4%)
  - GI
    - Gut involvement (50% vs. 30%)
    - Weight loss (8% vs. 5%)
  - GU
    - Orchitis (24% vs. 13%)
  - Activity/severity
    - Birmingham Vasculitis Activity Score (BVAS)
    - Five-factor score (FFS)

➢ Treatment

- Corticosteroids
- Anti-HBV drugs
- Plasma exchange
- The only clinical feature of HBV-related PAN vs. primary involvement of the skin (35% vs. 58%)

- Mixed Cryoglobulinemia Vasculitis

➢ Definition

- Systemic vasculitis of small and medium-sized immune complement-mediated inflammation of blood vessels associated with
  - IgG, polyclonal
  - IgM, polyclonal or monoclonal

➢ Clinical

- Skin, purpura, 100%
- Joints, arthralgia, ~70%
- Nerves, peripheral, ~30%
- Kidney, glomerulonephritis, ~20%

➢ Treatment

- Glomerular Nephritis (GN)
  - Membranes (MGN)
    - HBV DNA in epithelial cells nucleus/cytoplasm mesangial cells
    - Does not correlate with severity of HBV infection
    - Associated with
      - Acquired missense nucleotide mutations of the HBX-X gene
  - Membranoproliferative (MPEN)
    - Association with nephrotic syndrome
  - Mesangial proliferative
  - IgA nephropathy

- Hematological Malignancies
  - Infection associated with
    - Non-Hodgkin B cell lymphoma (B-NHL)
      - ↑ RR 2-5X
      - HBsAg- / anti-HBc+ / HBs+ (naturally acquired immunity)
      - aOR for B-NHL, 2.3
      - HBsAg+ / HBeAg+ (current HBV infection), aOR for B-NHL, 6.2
      - NHL treated with rituximab (B cell depleting) → ↑ HBV reactivation in HBeAg+ patients
    - ↓ risk of HBV
      - Reactivation when using rituximab for HNL by using ETV prophylaxis (7% vs. 30%)
      - HBV hepatitis (0% to 13%)
    - Diffuse large B-cell lymphoma (DLBCL)
      - ↑ HR 2.2 vs. non-HBV infected cohort
      - ↓ 2- / ↓ 5 yr overall survival
      - ↓ 2- / ↓ 5 yr progression free survival

Hepatitis C Viral (HCV) **Infection**

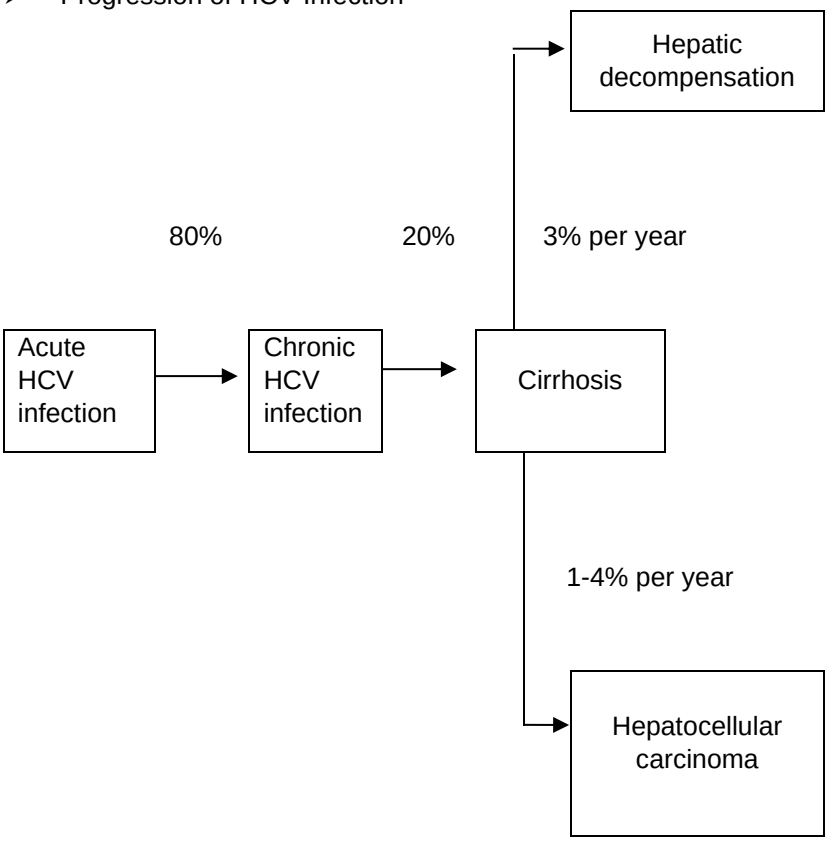
- Demography
  - Perinatal exposure
    - Transmission rate
      - HCV, ~ 5%
      - HCV + HIV, ~ 15%
    - Breast feeding dangerous for baby when HCV > 10^8 copies/mL
  - Percutaneous
    - Blood products ($1/2x10^6$)
    - IV drug use (60% to 90% HCV-infected)
    - Needlestick accidents
    - Hemodialysis
  - Non-percutaneous
    - Sexual contact
    - Intercourse
      - Per rectum
      - During menstruation

- Pathogenesis

- Life Cycle of HCV
  - Receptor binding of HCV
    ↓
  - Endocytosis into hepatocyte
    ↓
  - Cytosolic fusion/uncoating
    ↓
  - Translation into polyprotein precursor
    ↓
  - Structural proteins C (core), as well as envelop proteins E1/E2 cleaved by endoplasmic reticulum (ER)
    - A host signal dipeptidase
    - A viroporin protein
      ↓
  - Ion channel assembles / releases infections virions
  - NS cysteine protease itself (autocatalytically) from the polyprotein
  - Formation replication complex
    ↓
  - NS3 unwinds double-stranded RNA
    ↓
  - Generation of (-) strand RNA templat
    ↓
  - Disproportionate synthesis of (+) strar genomic RNA from (-) template
    ↓
  - Assembly/packaging
    ↓
  - Virion transport and glycoprotein matu
    ↓
  - Fusion of vesicles and release of mat virion (infections)

- NS3 protease cleaves the non-structural proteins
  - NS3
    - Serine protease
    - RNA helicase
  - NS4A
    - NS3 protease factor
  - NS4B
    - Unknown
  - NS5A
    - RNA binding site
  - NS5B
    - RNA dependent RNA polymerase (RdRp)
- About 75% of persons with acute HCV develop chronic HCV because the HBV escapes the immune response to clear the infection.
- 75% of persons with acute HCV progress to chronic HCV infection because of ineffective immune against the HCV
- HCV-enters hepatocytes by attachment and transport, using proteins
  - E1 and E2
    - Envelop proteins
  - CD81
    - Tetraspanin superfamily
  - SR-B1
    - Scavenger receptor class B type 1
  - LDL-R
    - LDL receptor

➢ Progression of HCV Infection



➢ Risk factors

- Groups of persons at risk for HCV infection, and the estimated prevalence of these persons, in these groups in industrialized countries.

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

Abbreviation: ALT, alanine aminotransferase

➢ Screening

- Groups/types of persons who should be screened for HCV.
  - ○ Concurrent disease
    - – Hemodialysis
    - – Transfer
    - – Immunosuppressed patients
    - – Hemophilia
    - – Blood transfusion before approximately 1990 (depends on country)
  - ○ At risk occupations
    - – Needle stick injury
      - ▪ The person pricked with an HCV-contaminated needle should be tested for HCV RNA within 4 wk, then tested for anti-HCV and ALT at 12 and 24 wk.
    - – Inmates
  - ○ At risk behavior
    - – IV drug users
    - – HIV-positive patients
    - – Men who have sex with men (MSM)
    - – Sex trade workers (STWs)
    - – Those with > 50 lifetime sexual partners
    - – Sexually transmitted disease (STD)
    - – Those with a history of STD
  - ○ Regular folks
    - – Those with unexplained elevated ALT
    - – New Canadians (recent immigrants)

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

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

➢ Clinical

- Skin
  - Vitiligo
  - Lichen planus
  - Porphyria cutanea tarda (PCT)
    - Sporadic or autosomal dominant heredity
    - Sun exposed areas, especially dorsal aspect of hands
  - Mixed cryoglobulinemia
  - Palpable purpura in legs (leukocytoclastic vasculitis)
  - 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
- Lung
  - Idiopathic pulmonary fibrosis
- Endocrine
  - Diabetes mellitus
  - Autoimmune thyroiditis
  - Thyroid cancer
- Bacterial infections
  - Please see next chapter

- The likely diagnosis of a patient who presents with abdominal pain, leukocytoclastic vasculitis, palpable purpura, and ↓ complement.
  - Hematology
    - B cell non-Hodgkin lymphoma
    - Mixed cryoglobulinemia
    - Monoclonal gammopathies
    - Henoch–Schönlein purpura; usually in young adults
    - Mixed cryoglobulinemia (e.g., associated with HCV)
  - Musculoskeletal disorders (MSK)
    - Chronic polyarthritis
    - Sicca syndrome

- Kidney
  - Cryoglobulinemic nephropathy
  - Non-cryoglobulinemic nephropathies
  - Renal cell carcinoma
  - Membranous/membranoproliferative nephropathy
  - Glomerulonephritis

Adapted from: *Sleisenger and Fordtran's Gastrointestinal and Liver Disease: Pathophysiology/ Diagnosis/ Management.* 11th edition, 2020. Chapter 90

- The clinical and laboratory findings in the patient with HCV which suggests associated cryoglobulinemia.
  - Skin – Purpuric leukocytoclastic vasculitis
  - CNS/PNS – Peripheral neuropathy
  - GI – Vasculitis → abdominal pain
  - Kidney – Acute/chronic renal failure
    – Nephrotic syndrome
    – Glomerulonephritis (membranoproliferative)
  - Laboratory – RF (rheumatoid factor) positive
    – ↓ complement

➢ Treatment

- Genotype of HCV and Recommended Direct-acting Antiviral Agents (DAAs)

	Protease Inhibitor 1,4 NS3/4A	NS5A	Non-nucleos(t)ide Polymerase Inhibitor 1-6 NS5B
Daclatasvir	+		
Dasabuvir		+	+
Elbasvir	+		
Glecaprevir	+		
Grazoprevir	+		
Ledipasvir		+	
Ombitasvir		+	+
Paritaprevir	+		
Pibrentasvir	+		
Simeprevir	+		
Sofosbuvir	+		
Velpatasvir	+		
Voxilaprevir	+		

Adapted from: Papdakis MA and McPhee SL. Current Medical Diagnosis and Treatment. Chapter 16, Freedman LS. 2020, Table 16-6, page 707

- Classification of mechanism of action of DAAs for HCV infection and dosage*

NS3 4A Protease Inhibitors		NS 5A Inhibitors (Favirs)	
− Glecaprevir	300 mg	− Daclatasvir	60 mg
− Grazoprevir	100 mg	− Elbasvir	50 mg
− Paritaprevir	150 mg	− Ledipasvir	90 mg
− Simeprevir	150 mg	− Ombitasvir	25 mg
− Voxilaprevir	100 mg	− Pibrentasvir	120 mg
		− Velpatasvir	100 mg

NS5B Nucles(t)ide Polymerase Inhibitor**		NS5B Non-nucleos(t)ide Protease Inhibitors**	
− Sofosbuvir	400 mg	− Dasabuvir	250 mg

* All medications given po od, except Dasabuvir 250 mg po b.i.d.

** “the favirs”

DAA Treatment Combinations Genotype

1,4	1-6	1,4
− Sofosbuvir (NS5B) plus ▪ Ledipasvir (NS5A) − Grazoprevir (NS3/4A) plus ▪ Elbasvir (NS5A)	Sofosbuvir (NS5B), plus Velpatasvir (NS5A) Glecaprevir (N33/4A) plus Pibrentasvir (NS5A) DAA-experienced Sofosbuvir (NS5B), plus Velpatasvir (NS5A) plus Voxilaprevir (NS3/4A) also for DAA-experienced genotype 1	Sofosbuvir (NS5B) plus Daclatasvir (NS5A)

Adapted from: Papdakis MA and McPhee SL. Current Medical Diagnosis and Treatment. Chapter 16, Freedman LS. 2020, Table 16-7, page 708

BACTERIAL INFECTION

Latent Tuberculosis Infection (LTBI) **in the Patient with GI/Liver Disorder**

Chitnis AS, et al. Am J Gastroenterol 2021; 116; 2155-58.

- Definition
  - Mycobacterium tuberculosis infection with no clinical symptoms or signs
- Demography
  - Rate of conversion of LTBI to symptomatic tuberculosis ~85/10^5 person yr
- Guidelines for LTBI (California Department of Public Health [2016, 2017])
  - Identify persons with high risk and perform
    - Blood-based interferon-gamma release assay (IGRA)
    - Tuberculin skin test (TST) ≥ 5 mm cut-off if patient is immunosuppressed
    - If indeterminant results
      - Repeat IGRA or do TST
    - If patient immunosuppressed with indeterminant IGRA and TST negative
      - Initiate empiric LTBI treatment
    - Chest X-ray showing
      - Fibrosis/scarring → perform
        - 3 sputum collections for acid-fast bacilli smear/culture
        - 1 additional sputum sample to be used for polymerase chain reaction (PCR) to detect TB
      - Nodules, non-calcified
        - Suggests microbiologically inactive TB disease
- Treatment
  - LTBI
    - Isoniazid 300 mg od for 6 to 9 mon
    - Isoniazid 900 mg plus
      - Rifapentine 900 mg q1wk for 12 wk
      - Rifampin od for 3 mon

      } − ↑ likelihood of completion of treatment; − ↓ rates of hepatotoxicity
    - Rifampin 600 mg od for 4 mon

- LTBI plus anti-TNF therapy
  - Start anti-TNF 3 to 6 mon after LTBT treatment completed
  - If waiting 3 mon not possible, use rifamycin-based treatment for ≥ 4 wk before starting anti-TNF
  - If waiting 4 wk not possible
    - Start treatment of LTBI
    - Start anti-TNF
    - Follow-up for development of TB symptoms and medication adherence.
- LTBI plus HBV
  - Use rifampin-based LTBI therapy, plus tenofovir disoproxil fumarate (do **not** use tenofovir alafenamide): ↑ hepatotoxicity from the LTBI medications
- LTBI plus liver transplant (LT)
  - Pre-LT
    - Rifampin-based LTBI therapy
    - If this fails, use levofloxacin
  - Post-LT
    - Isoniazid-based LTBI therapy (rifampicin have ↑ risk of drug-drug interactions)
    - If this fails, use levofloxacin

IMMUNE-MEDIATED LIVER DISEASE

IgG4-related Secondary Cholangitis (IgG-RSC), **Primary Sclerosing Cholangitis** (PSC) **and Overlap Syndrome: BSG** (2019)

Chapman MH, et al. Gut 2019; 68(8):1356-1378.

❖ Primary Sclerosing Cholangitis (PSC)

➢ Definition

- A progressive, immune-modulated biliary disorder in which the biliary epithelial cell is targeted, and is associated with disease-specific antigens and with ulcerative colitis (UC)

➢ Demography

- Mean age of diagnosis, 32-41 yrs
- Incidence, PSC
  - Large duct, $1/10^5$
  - Small duct, $2/10^6$

  } person yrs
- Racial background
  - Most commonly in persons of Northern European descent
- Mean time from diagnosis to death 10-22 yr
- Causes of death
  - CCA, 30%
  - Liver failure, 30%
  - Variceal bleed, 9%
- Small duct PSC
  - Better prognosis
  - Less CCA
  - 20% develop large duct changes over time

➢ Clinical

- In > 50% of PSC patients
  - Fatigue
  - RUQ pain
  - Fever / ↓ body weight
  - Portal hypertension
  - Pruritis
  - Jaundice
  - Cholangiocarcinoma (CCA)

- Histopathology
  - Indications for liver biopsy to diagnose PSC
    - Patients with typical biochemical / diagnostic imaging
    - Small duct PSC
    - PSC overlap / variant syndromes
      - ↑ ALT/AST (ALT > 5x ULN)
      - ↑ IgG (2x ULN)
      - ↑ AIH autoantibodies (ANA, SMA, LVIM)
    - IgG4-SCIgG4
    - Idiopathic cholestasis
  - Typical features
    - Ducts “onion skin” periductal fibrosis
    - Duct proliferation
    - Periportal chronic inflammation
    - Cholangiectasis
    - Fibrosis/cirrhosis
  - Stages
    - Periportal inflammation
    - Periportal fibrosis
    - Ductopenia and bridging fibrosis
    - Cirrhosis

Recommendations

- Monitor fibrosis
  - FibroScan® (elastography)
  - Serological enhanced fibrosis test
  - Magnetic resonance
- Use liver biopsy to diagnose
  - Small duct PSC
  - Overlap syndromes
  - Unclear diagnosis

  (Strength of recommendation: strong; quality of evidence, moderate)

❖ IgG-related secondary cholangitis (IgG-RSC)

- Definition
  - “…multisystem characterized by the presence of IgG4-positive lymphoplasmacytic infiltrate in affected organs (multisystem), most commonly pancreas and biliary tract
  - Pancreas
    - Type 1 autoimmune pancreatitis / IgG4-related pancreatitis (IgG4-RRP)

- Biliary tree (IgG4-RSC), types
  - 1 Stenosis of lower CBD, often associated with IgG4
  - 2a Intrahepatic stenosis, prestenotic dilation
  - 2b Intrahepatic stenosis, pruning of peripheral bile duct
  - 3 Hilar and lower CBD stenosis
  - 4 Hilar stenosis
- Association
  - IgG4-SC has associated IgG4-RD in 77%
  - IgG4-RD has associated in ~30% to 60%

➢ Clinical

- Common presentation
  - Obstructive jaundice
  - IgG4-RSC is misdiagnosed as CAA in 8%
  - Progression to hepatic cirrhosis in ~8%

➢ Laboratory

- ↑ IgG4 in 50% to 80%, but
  - Not distinguished
    - ↑ IgG4 in PSC (~10%) and in PBC (1%)
  - Distinction in
    - IgG4-SC vs PSC on basis ↑ IgG4
    - IgG4 / IgG1 rates > 0.24
    - IgG > 4x ULN
    - IgG4/IgG RNA ratio > 5% (quantitative PCR)
      - Sensitivity, 94%
      - Specificity, 99%

} More suggestive of IgG4-SC

Abbreviations: CBD, common bile duct; EUS, endoscopic ultrasound; FNA, fine needle aspiration; IgG4-RD, IgG4-related disease; IgG4-SC, IgG4-sclerosing cholangitis; MRCP. Magnetic resonance cholangiopancreatography; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis; ULN, upper limit of normal

➢ Diagnostic imaging

- MRCP
  - Characterization of subtype
  - In Type 1, IgG4-SC +/- IgG-RD
    - Long stricture of > 1/3 length of MPD, with prostatic dilation
  - No biliary pseudodiverticula

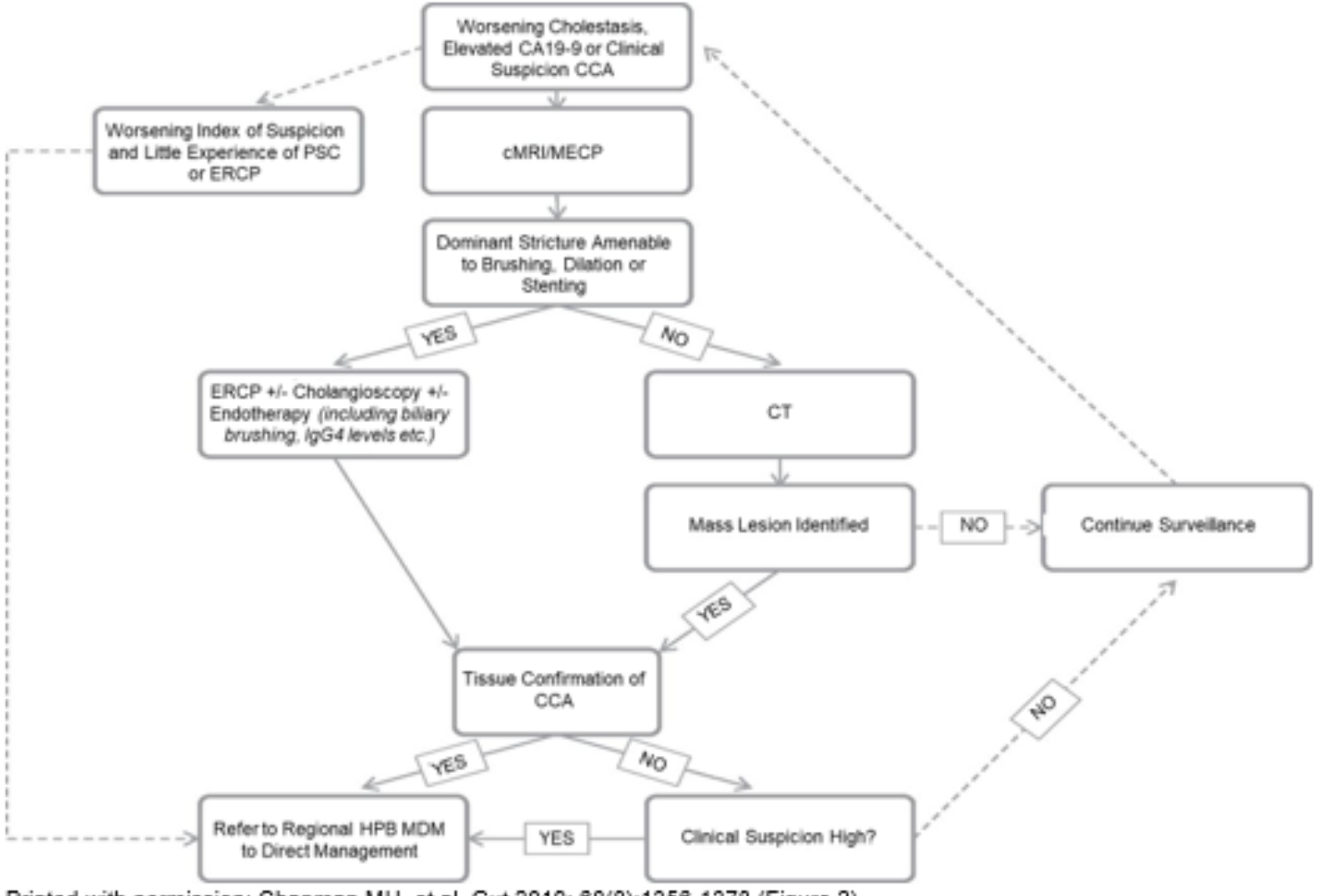
➢ Histopathology

- Lymphoplasmacytic infiltrate
  - IgG4-positive plasma cells/hpf on endoscopy biopsies > 10 /hpf
  - IgG4+/IgG+ plasma cells > 40%

} ▪ Suggestive of IgG4-SC

- Biopsy
  - Cholangioscopy
  - Endobiliary
  - Major papilla biopsy positive (~65%)
  - Fine needle aspiration (FNA)

- Diagnosis
  - Not clear if IgG4-SC is an overlap syndrome of PSC or is a separate condition



Printed with permission: Chapman MH, et al. Gut 2019; 68(8):1356-1378 (Figure 2).

Recommendation

- Use international → National consensus guidelines (Strength of recommendation; Strong quality of evidence: Moderate)

➢ Differential (iGG4-SC vs. PSC)

- Presence of multisystem involvement suggests IgG4-SC / IgG4-RD, rather than PSC
- Presence of IBD 6% vs. 70% in PSC
- MRCP differences (please see above)
- Pancreatic
  - Duct involvement
  - Insufficiency
  - Mass

❖ Overlap Syndromes

- PSC/AIH (AIH with PSC overlap 1% to 17%) use EASL guidelines for management of AIH
  - Use EASL guidelines for management of AIH
  - Respond to corticosteroids
  - Good prognosis
    - AIH-PSC > PSC

- PSC/PBC
  - Very rare, especially when
    - MRCP shows only small duct PSC, or
    - Biopsy is not diagnostic

- PSC plus UC
  - PSC may be associated with other autoimmune conditions

➢ Natural history

- Asymptomatic patients have a better prognosis
- Examples of scoring (best to predict time to LT)
  - Revised Mayo score; (age, albumin, bilirubin, AST, ALD); MELD (Model for End Stage Liver Disease); UKCLD (UK Models for End Stage Liver Disease)
  - Child-Pugh score closely compares with above complex models for survival
    A, 90%
    B, 65%
    C, 25%

"No single method can be recommended"

Recommendation

- Use risk stratification based on non-invasive measures
  - Patients should have life-long follow-up (Strength of recommendation: strong; quality of evidence: very low)

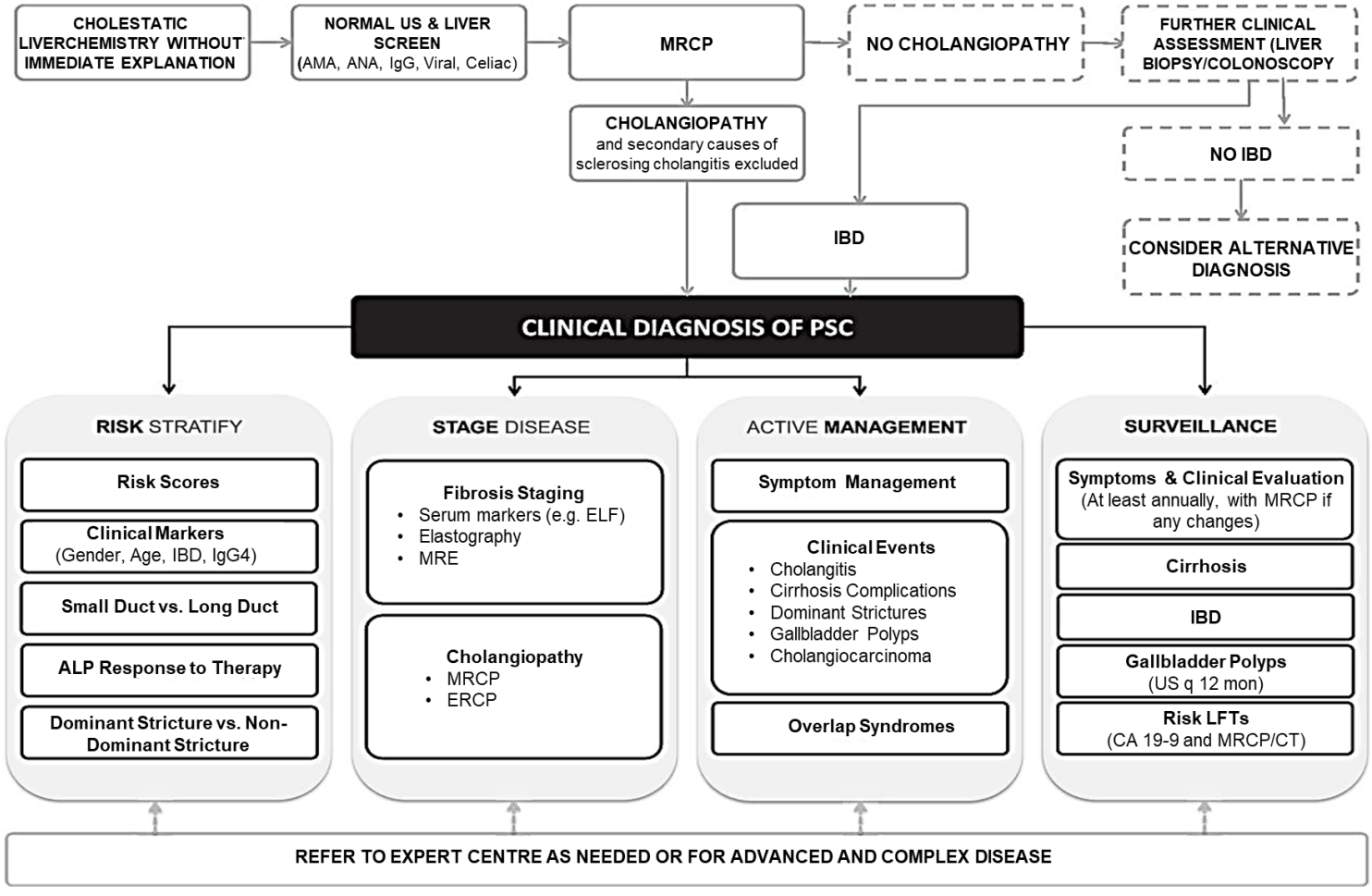
➢ Demography

- IBD is present in UC, 7% and in CD, 9%
- PSC in IBD
  - Northern European descent, 62-83%
  - Others ~20%
- Features of UC in PSC
  - ↑ pancolitis
  - ↑ rectal sparing
  - ↓ backwash ileitis
  - Fewer symptoms but more aggressive IBD
  - ↑ symptoms of IBD after liver transplantation for PSC, despite patient's immunosuppression of IBD and PSC are not correlated
- UC in IgG4-RSC
  - Rare

	PSC	IgG4-SC
○ Males	+	++
○ Younger age	++	+
○ Pancreatic exocrine insufficiency	-	++
○ Other associated systemic fibrosclerotic disease	-	++
○ Presence of inflammatory bowel disease	++	+/-
○ Improvement with steroid treatment	+/-	+++
○ Raised serum IgG4	+/-	++
○ Pancreatic mass or enlargement on CT	-	++
○ Pancreatic ductal abnormalities	+/-	+++
○ Cholangiographic changes	++	++
○ Ampullary biopsy with > 10 IgG4 plasma cells per high power field	-	+++
○ Liver/tissue biopsy with > 10 IgG4 plasma cells per high power field	+/-	+++

➢ Treatment

Algorithm for the management of suspected primary sclerosing cholangitis.



Printed with permission: Chapman MH, et al. Gut 2019; 68(8):1356-1378 (Figure 1).

- Rapid response to corticosteroids
  - Clinical, biochemical, radiological (within 8-12 wk)
- Frequent (60%) relapse, especially if multisystem involvement
  - Maintenance
    - Low dose prednisone
    - Azathioprine
      ↓
    - Rituximab (anti-CD20 monoclonal antibody)
- Active disease
- Multiorgan involvement

Recommendation

- Refer to experienced multidisciplinary growth IgG4-SC patients who are
  - Complex
  - May have malignancy

  (Strength of recommendation: STRONG; Quality of evidence: LOW)

Ductopenia and Primary Biliary Cholangitis (PBC)

Hercun J, et al. Am J Gastroenterol 2022; 117: 2075-2078

- Definitions
  - A slowly progressive chronic cholestatic liver disease, which can ultimately progress to cirrhosis and chronic end-stage liver disease
    - There is progression over time of
      - Fibrosis (such as evaluated by the Ishak scoring system)
      - ↓ bile ducts (bile duct paucity, "ductopenia")
    - Fibrosis and ductopenia do **not** progress at the same rate
    - Progression of ductopenia is associated with
      - ↑ alkaline phosphatase (AP) 2x ULN
      - ↑ AST / platelet count index

- Comorbidities (Asrani SK, et al. Am J Gastroenterol 2022; 117: 2009-2016)
  - Comorbidities are common in persons with cirrhosis

Number of Commodities		Adjusted Risk of Mortality (HR)
1	29%	2.5 (95%, CI, 2.23-2.8)
2	18%	3.27 (95% CI, 2.9-3.69)
3	13%	(95% CI, 3.99-5.12)

    - Survival rate of
      - Compensated cirrhosis plus 3 chronic disease comorbidities 68%
      - Decompensated cirrhosis plus 1 to 3 comorbidities, 63%
  - Non-invasive tests to predict hepatic fibrosis
    - LS FibroScan®: liver stiffness 0.688
    - FIB-4 fibrosis score (from "AARP 0.572": age (ALT, platelet count) AUROC (area under the receiver operating characteristic) 0.845
    - FIB-5 score: FIB-4 plus LS 0.868
    - The best non-invasive predictor for complications from chronic liver disease and compensated cirrhosis (hepatic encephalopathy, ascites, and bleeding esophageal varices) is the combination of the patients' age, ALT, AST and platelets

DISORDERS OF HEPATIC VASCULATURE

Vascular Liver Disorders, Portal Vein Thrombosis, and Procedural Bleeding in Patients with Liver Disease: AASLD Guidelines (2020)

Northup PG, et al. Hepatology 2021; 73: 366-413

- **Coagulation and Hemostasis in Patients with Cirrhosis**

➢ Pathophysiology changes in the hemostatic system in patients with cirrhosis.

- ↓ hepatic synthetic capacity
  - ↓ factors for
    - Coagulation
    - Fibrinolysis
- ↓ platelets
  - ↓ thrombopoietin (TPO) synthesis
  - ↓ megakaryocyte production
  - ↑ turnover
  - ↑ sequestration (splenomegaly)
- Altered platelet function
  - Posttranslational modification of hemostatic proteins (e.g., fibrinogen)
- ↑ endothelial cell synthesis of hemostatic proteins
- ↑ activation (hepatic/systemic) / consumption of hemostatic proteins
- These changes interact and counteract each other

Observation	Counteraction
↓ platelets	↑ VWF (↑ von Willebrand factor [platelet adhesive protein])
↓ procoagulants	↓ anticoagulant protein
↓ antifibrinolytic proteins	↓ profibrinolysis

- ↑ INR or ↓ platelet numbers in a patient with cirrhosis do **not** necessarily reflect the hemostatic system
  - These patients may be prothrombotic, as suggested clinically by their ↑ risk of thrombosis, because of the counterbalancing factors.
  - It is unclear whether ↓ fibrinogen → ↑ bleeding in cirrhosis, and if so, at what threshold
  - Platelet aggregation (function) is underestimated when there is thrombocytopenia
    - The major ↑ risk factor for bleeding esophageal varices is ↑ portal vein pressure / ↑ hepatic venous wedged pressure (HVWP)

Rebalance of Hemostasis System Components in Patients with Cirrhosis

	Platelets	Coagulation	Fibrinogen	Fibrinolysis
○ Changes ↑ bleeding	▪ Thrombocytopenia ▪ Platelet dysfunction ▪ Anemia (less platelet margination when hematocrit is low)	▪ ↓ levels of factors II, V, VII, IX, X, and XI ▪ ↓ platelet procoagulant surface	▪ ↓ plasma levels ▪ Hypersialylation leading to ↓ rates of fibrin polymerization ▪ ↓ FXIII	▪ ↑ tPA not balanced by ↑ plasminogen activator inhibitor-1 ▪ ↓ levels of α2-antiplasmin and TAFI
○ Changes ↑ clotting	▪ ↑ VWF ▪ ↓ ADAMTS13 ▪ ↑ *in vivo* platelet activation ▪ Activated endothelium	▪ ↓ levels of protein C and S and antithrombin; ↑ factor VIII	▪ ↓ permeability of the fibrin clot	▪ ↓ plasminogen
– Net effect	▪ Poorly studied; ↑ VWF compensates at least partly for thrombocytopenia	▪ Normal / ↑ thrombin-generating capacity	▪ Poorly studied	▪ Controversial; decompensation → hyperfibrinolysis, but ACLF/sepsis can severely inhibit fibrinolysis

Abbreviations: ACLF, acute-on-chronic liver failure; ADAMTS13, a disintegrin and metalloproteinase thrombospondin type 1 motif 13; TAFI, thrombin activatable fibrinolysis inhibitor

Printed with permission: Northup PG, et al. Hepatology 2021; 73: 366-413 (Table 1).

- Give the global tests of hemostasis which are used in patients with cirrhosis to predict the patients risk of bleeding/thrombosis.
  - Fibrinolysis
  - Thrombin generation
  - Viscoelastic

  } − Plasma-based viscoelastic tests
    - Rotational thromboelastography (ROTEM)
    - Thromboelastographic (TEG)

Treatment Alert
- Despite these global tests of hemostasis (above), the coagulation capacity of the patient with cirrhosis may still be underestimated.
  - TEG/ROTEM are sensitive only for severe hyperfibrinolysis

➢ Guidance Statements
- Patients with cirrhosis have an altered balance in hypo-/hypercoagulable features and
  - INR (PT), aPTT, and platelet count do **not** reflect well the hemostatic state of patient with cirrhosis and thus
    - Do **not** predict procedure bleeding
- Global tests of hemostasis "… better capture the status of a patient with cirrhosis..", but await validation

- **Procedure-Related Bleeding**

❖ Bleeding Risk
- The risk of bleeding from endoscopic procedures in a patient with cirrhosis is based upon
  - The underlying liver and other diseases
    - Acute-on-chronic liver failure (ACLF)
    - Systemic inflammatory response syndrome (SIRS)
    - Infection
    - Renal disease (acute/chronic)
- Post-esophageal variceal ligation (EVL) bleeding in patients with Child-Turcotte-Pugh (CTP) C (severe cirrhosis)

Child Turcotte Pugh Score

	1 Point	2 Point	3 Points
Ascites	None	Mild/moderate	Severe
Encephalopathy	None	Grade I-II	Grade III-IV
Bilirubin	< 2 mg/dL (34.2 µmol/L)	2-3 mg/dL (34.2-51.3 µmol/L)	> 3 mg/dL (51.3 µmol/L)
Bilirubin	> 3.5 g/dL (35 g/L)	2.8-3.5 g/dL (28-35 g/L)	< 2.8 g/dL (28 g/L)
Prothrombin time / INR	< 4 s / < 1.7	< 4-6 s / < 1.7-2.3	> 6 s / > 2.3

- Give high-risk endoscopic, dental, percutaneous and vascular procedures in patients with cirrhosis considered to have high bleeding risk (a procedure is considered high risk if major bleeding is expected in > 1.5% of procedures or if even minor bleeding is likely to result in permanent organ damage or death)
    - Endoscopic
        - GI
            - Endoscopic stricture dilation or mucosal resection
            - Percutaneous endoscopic gastrostomy placement
            - Cystogastrostomy
            - Balloon-assisted enteroscopy
            - Endoscopic polypectomy
            - Endoscopic retrograde cholangiopancreatography with sphincterotomy
            - Endoscopic ultrasound with fine-needle aspiration
        - Lung
            - Therapeutic bronchoscopy or diagnostic bronchoscopy with biopsy
    - Dental
        - Teeth extraction
    - Percutaneous
        - CNS/eye
        - Lung
        - Joint
        - GI
        - GU

        - Procedures
        - Injections
        - Biopsies
        - Biopsy, ablation, drain
        - Nephrostomy tube
        - Solid organ biopsy
    - Vascular
        - Heart
        - Liver

        - Therapeutic coronary angiography/venography
        - Transjugular intrahepatic portosystemic shunt (TIPS)i Transhepatic arterial chemoembolization/radioembolization (TACR)

➢ Guidance Statements

- Specialist collaboration needed to assess risk/benefit for
    - Procedures
    - Management of hemostasis
- "…there is no data-driven specific INR or platelet cut-off in which procedural bleeding is reliable increased"
- Before high risk elective procedures, identify and manage treatable risk factors for bleeding

- Preprocedural Homeostasis Testing or Prophylaxis

- Platelets
  - In the patient with thrombocytopenia
    - Platelet transfusions do **not**
      - ↑ thrombin generation capacity
      - Improve viscoelastic markers of bleeding risk
      - Provide protective valve bleeding complication of procedures
      - There is no accepted platelet threshold before procedures
      - Platelet transfusion may cause transfusion-related lung injury syndromes
    - Thrombopoietin receptor agonists (avatrombopag and lusustrombopag) correct thrombocytopenia, but do **not** benefit bleeding or thrombolytic complications
    - DDAVP (1-deamino-8-D-arginine vasopressin)
      → AVWF from endothelium
      → ↑ platelets, but no effect on primary hemostasis/platelet function

- Recommendations of Selected Professional Societies for Minimum Threshold Values of Common Coagulation and Bleeding Parameters in Patients With Cirrhosis Before Invasive Procedures With a High Risk of Bleeding

Organization	Platelet Count (× 1,000/μL)	INR	Fibrinogen Level (mg/dL)
AASLD (this document), 2021	No routine preprocedure correction		
American College of Gastroenterology (ACG), 2020	>50	No correction	>120-150
American Gastroenterological Association (AGA), 2019	>50	No correction	>120
Society of Interventional Radiology (SIR), 2019	>30	<2.5*	>100

  - Generally, there are no minimum threshold levels for any of the laboratory values recommended for procedures with a low risk of bleeding.
    - Each specific guidance document specifies threshold values to achieve before the procedure to reduce bleeding risk.
    - Specific recommendations on the preprocedural intervention recommended to reach threshold values vary by society.

*Correction of INR using vitamin K, not FFP, is recommended by this society.

➢ Guidance Statements

- Perform low and high risk procedures without prophylactically correcting platelet counts in persons with thrombocytopenia
  - In persons with cirrhosis, use "…and individualize approach to patients with severe thrombocytopenia before procedures"

- Give the adverse effects of using FFP in non-vitamin K deficiency and cirrhosis.
  - No benefit
  - ↑ risk of
    - ↑ volume of blood
    - ↑ portal pressure
    - ↑ risk of transfusion-related lung injury (TRLI)

- Recombinant factor VIIa
  - Do **not** use for prophylaxis from bleeding from procedures
    - No benefit
    - ↑ thrombosis (venous/arterial)

➢ Guidance Statements

- In cirrhotic patient not taking vitamin K analogs (VKA)
  - Do **not** use INR to assess procedure-associated risk of bleeding
  - Do **not** give FFP transfusion before procedures
    - No benefits
    - ↑ risks

- Fibrinogen
  - Venous bleeding from percutaneous bleeding or submucosal bleeding may be associated with plasma fibrinogen < 100 mg/dL
    - There is **no** accepted lower threshold for plasma fibrinogen when
      - Bleeding may occur, or when
      - Fibrinogen should be replaced
  - Furthermore, the diagnosis of post-procedural bleeding being due to hyperfibrinolysis is made clinically
  - Epsilon-amino caproic acid (EACA)
    - Stops plasminogen / tissue plasminogen activator from binding to fibrin → antifibrinolytic / ↓ fibrinolytic bleeding, but no supporting data in cirrhosis
    - Tranexamic acid also is antifibrinolytic, but
      - No benefit to ↓ post-procedural bleeding
      - ↑ risk of venothromboembolism (VTE)
  - There is also **no** data to support using cryoprecipitate/fibrinogen concentrate to ↓ post-procedural bleeding in patients with cirrhosis

➢ Guidance Statements

- Critically ill patients with cirrhosis have ↑ risk of bleeding, and have ↓ fibrinogen concentrations
  - Cryoprecipitate and fibrinogen concentrate → ↑ plasma fibrinogen levels in cirrhosis, but the data is awaited that this will decrease post-procedural bleeding.

"Declaration of Lack of Consensus"

- This guidance document from the AASLD recommends the routine preprocedural correction of platelet count, INR or fibrinogen concentration **not** be routinely corrected before a procedure in patients with cirrhosis.

➢ Common/anticoagulants

- Mechanisms of action
  - Vitamin K antagonists (VKAs)
  - Low molecular weight heparin (LMWH)
    - ↑ antithrombin → ↓ IIa/Xa
  - Dabigatran
    - ↓ IIa
  - "BANS"
    - ↓ Xa
  - Anticoagulants and renal effects
    - All anticoagulants contraindicated in patients with creatinine clearance (CrCl), < 15 mL/min
    - Adjustment of dose for CrCl of 15-30 mL/min
      - Low molecular weight heparin
      - BETRIXA
      - EDOXA
      - RIVAROXA

      } "BANs" → ↓ factor Xa
  - INR monitoring for VKDs
  - Contraindicated in patients with chronic liver disease
    - BETRIXA
    - EDOXA
    - RIVAROXA

      } Also caution with Child-Turcotte Pugh (CTP) B/C

Abbreviations: AASLD, American Association for the Study of Liver Diseases; ACLF, acute-on-chronic liver failure; CTP, Child-Turcotte-Pugh; DDAVP, 1-deamino-8-D-arginine vasopressin; EACA, Epsilon-amino caproic acid; EVL, esophageal variceal ligation; FFP, fresh frozen plasma; HVT, hepatic vein thrombosis; HVWP, hepatic venous wedged pressure; INR, international normalized ratio; PVT, portal vein thrombosis; ROTEM, rotational thromboelastography; SIRS, systemic inflammatory response syndrome; TACR, transhepatic arterial chemoembolization/ radioembolization; TEG, thromboelastographic; TPO, thrombopoietin; TRLI, transfusion-related lung injury; VKA, vitamin K analogs; VTE, venothromboembolism; VWF, von Willebrand factor

The Common Anticoagulants Available in the United States, Dosing Adjustments, and Treatment Considerations

	VKAs	**LMWH**	**Dabigatran**	**Apixaban**
○ Mechanism of action	↓ factors II, VII, IX, X, PC, and PS, among others	↑ antithrombin (indirect inhibitor of IIa/Xa)	↓ factor IIa	↓ factor Xa
○ Dosing	Variable daily; based on INR	Weight based; daily or b.i.d.	b.i.d.	b.i.d.
○ Elimination	Renal: 92%	Renal: 40%	Renal: 80%	Renal: 27%
	Hepatobiliary /intestinal: 8%	Hepatobiliary/ intestinal: 60%	Hepatobiliary/ intestinal: 20%	Hepatobiliary/ intestinal: 73%
○ Initiation	Overlap with LMWH until INR > 2	See above	≥5 d LMWH, then switch	10 mg b.i.d. for 7 d
○ Standard dose	Overlap with LMWH until INR > 2	See above	150 mg b.i.d.	5 mg b.i.d. from day 8
○ Dose reduction	NA	CrCl 15-30 mL/min and then reduce dose	110 mg b.i.d. for ≥80 yr, or concomitant verapamil, and consider for other high-risk groups	2.5 mg b.i.d. from 6 mons
○ INR monitoring	Yes	No	No	No
○ Liver disease labeling	Yes	Yes	Limited experience (n = 12): no change in exposure in CTP B	≤ CTP B without significant coagulopathy
○ CKD adjustment	No	↓ dose for CrCl 15-30 mL/min	No	No
	No, with CrCl <15 mL/min			

	Betrixaban	Edoxaban	Rivaroxaban
○ Mechanism of action	↓ factor Xa	↓ factor Xa	Inhibits factor Xa
○ Dosing	OD	OD	Once-daily
○ Elimination	Renal: 11% Hepatobiliary/ intestinal: 85%	Renal: 50% Hepatobiliary /intestinal: 50%	Renal: 66% Hepatobiliary/ intestinal: 34%
○ Initiation	160-mg loading dose	5 d LMWH and then switch	15 mg b.i.d. for 3 wk
○ Standard dose	80 mg OD	60 mg OD	20 mg OD from day 21
○ Dose reduction	CrCl 15-30 mL/min, and then ↓ dose	30 mg daily for CrCl <50 mL/min or weight <60 kg	Consider dose reduction to 10 mg from 6 mon.
○ INR monitoring	No	No	No
○ Liver disease labeling	Contraindicated in chronic liver disease	– Contraindicated in chronic liver disease with coagulopathy; – Caution with mild/moderate liver disease, ALT/AST >2 × ULN or total bilirubin ≥1.5 × ULN	– Contraindicated in liver disease with coagulopathy or – Bleeding risk, including CTP B/C
○ CKD adjustment	↓ dose for CrCl 15-30 mL/min	30 mg for CrCl 15-50 mL/min No, with CrCl <15 mL/min	No

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; b.i.d., twice-daily; CKD, chronic kidney disease; CrCl, creatinine clearance; PC, protein C; PS, protein S; ULN, upper limit of normal.

Printed with permission: Northup PG, et al. Hepatology 2021; 73; 366-413 (Table 9).

❖ **Portal Vein Thrombosis** (PVT)

➢ Classification

- Not generally used in clinical practice

Descriptor	Definition
Time course	
− Recent	▪ PVT presumed to be present for <6 mons
− Chronic	
Percent occlusion of main PV	
− Occlusion	
▪ Completely occlusive	▪ No persistent lumen
▪ Partially occlusive	▪ Clot obstructing >50% of original vessel lumen
▪ Minimally occlusive	▪ Clot obstructing <50% of original vessel lumen
▪ Cavernous transformation (recanalization within 6 mon)	▪ Large portoportal collaterals, no PV seen
Response to treatment or interval change in thrombus	
− Progressive	▪ ↑ size / progresses to more complete occlusion
− Stable	▪ No change in size / occlusion
− Regressive	▪ Thrombus ↓ size / degree of occlusion

➢ Guidance statement

- In a clinical setting it is helpful to describe the clot's
  - Initial site, extent, degree of obstruction of the usual, and chronicity
    - Assessments may be made of clot regression (spontaneous), or
    - Responsive to treatment

➢ Demography

- Incidence within 1 yr of diagnosis of cirrhosis ~4%, depending upon risk factors:
  - Severity of liver disease / portal hypertension
  - Portal flow rate < 10 to 15 cm/sec
  - Obesity/metabolic syndrome / non-alcoholic steatohepatitis (NASH)
  - Thrombophilia (work up may not be necessary for all patients with cirrhosis)
    - Including prothrombin gene mutation

- Comorbidities (~30% have a systemic)
  - Appendicitis/diverticulitis, inflammatory bowel disease (IBD)
  - Bariatric surgery
  - Pancreatitis
  - Splenectomy
- Malignancy (invading PV/HV thrombosis)

➢ Guidance Statements

- In patients with cirrhosis
  - Not necessary to routinely perform extensive evaluation for thrombotic condition, but
  - Necessary to rule out
    - Malignant transformation of PV/HV
    - Myeloproliferative disorder / other thrombophilic conditions
- PVT does not independently cause disease progression of liver disease
  - Follows decompensation, rather than causing it
  - PVT predicts poor post-LT survival

➢ Goals of treatment

- PVT in patients
  - **With cirrhosis**
    - Formation of portosystemic collaterals →
      - Lower risk of intestinal ischemia from PVT than in persons with cirrhosis
      - Aim of treatment to ↓ worsening / ↓ progression of thrombosis to mesenteric veins
      - Safe to perform esophageal variceal band ligation (EVBL) in patient with PVT without stopping anticoagulation
    - In patient who requires EVBL or prophylactic non-specific beta blockers (NSBBs), proceed with anticoagulation for PVT
  - **Without cirrhosis**, targets include
    - ↓ worsening / ↓ progression of thrombosis to mesenteric vein, and to thereby ↓ intestinal ischemia
    - ↓ risk of development of portal hypertension
    - Because of ↑ risk of PVT being associated with ↑ hematological malignancy / ↑ thrombophilic disorder→ thoroughly exclude these conditions (especially in patient with PVT but no cirrhosis)
    - Treat septic pylephlebitis with antibiotics plus anticoagulants

➢ Guidance Statements

- Anticoagulation
  - All patents with recent PVT
    - Initiate anticoagulation to
      - ↓ intestinal ischemia
      - ↓ chronic PVT / portal hypertension
    - Consider possibility of intestinal ischemia
      - Investigate
      - Consult (multidisciplinary)
    - If intestinal infarction/gangrene suspected → consult for possible early surgery
  - In patient with cirrhosis
    - Anticoagulation if
      - Recent occlusion
        - 50% obstruction of main PV / mesenteric vein (↓ extension / ↓ PHT development)
    - If anticoagulation indicated
      - Start immediately, even before EVBL/NSBB initiation
    - No anticoagulation
      - Complete occlusion of main PV / cavernous transformation of PV
      - < 50% occlusion
        - No anticoagulation
        - CT q3mon (↓ progression)

- Fibrinolysis
  - Indication
    - Intestinal ischemia persisting despite anticoagulation
    - Not manageable medically/endoscopically, and associated with
      - Recurrent bleeding +/-
      - Refractory ascites
    - Attempt to achieve PV recanalization (PVR) using transplenic/hepatic approach to PVT +/- TIPS (chronic PVT plus recent bleeding, +/- recurrent bleeding +/- refractory ascites)

❖ **Budd Chiari Syndrome** (BCS): Hepatic Vein Thrombosis

➢ Definition

- Primary HVT/BCS is an obstruction of hepatic versus outflow from any location of small hepatic veins (HNs) to the junction of the inferior vena cava (IVC) and the right atrium.

➢ Demography

- Rare
  - Incidence < $1/10^6$ — Associated with
    - 1 prothrombotic condition, ~75%
    - ≥ 2 prothrombotic conditions, ~35%
  - Prevalence ~$5/10^6$

➢ Clinical

- Variable
  - Asymptomatic (20%), to acute liver failure (ALF)
  - Depends upon
    - HV obstruction
    - Development of decompressive collaterals

    } - Extent - Rapidity
- Common symptoms
  - Ascites ~85%
  - Hepatomegaly ~65%
  - Abdominal pain, ~60%
  - Esophageal varices, > 50%
- IVC compression (thrombosis, hypertrophic caudate lobe)
  - Leg edema
  - Abdominal wall varices

➢ Diagnostic imaging

- Hypertrophy of caudate lobe
- Nodular regenerative hyperplasia (NRH)
- Hepatocellular adenoma (HA)
- Hepatocellular cancer (HCC), cumulative incidence 1% per yr

➢ Laboratory

- Perform an investigation for associated thrombophilia

Laboratory Tip

- In patients with HVT/BCS plus α-fetoprotein (AFP) > 15 ng/mL → ↑ risk of HCC.
- Diagnostic imaging tip
  - When liver is nodular, HCC may be suspected, and CT/MRI may be performed to assess for possible HCC
  - However, in HVT/BCS, there may be altered vascular pattern, but the LI-RADS (liver Reporting and Data System) criteria for HCC are not reliable
    - Do **not** diagnose HCC in HVT/BCS by applying the usual criteria for vascular changes on enhanced CT/MRI.

➢ Pharmacological Choices

❖ Traditional anticoagulants

- Heparin (unfractionated, UFH) / low molecular weight heparin (LMWH)
- Vitamin K antagonists (VKA, e.g., warfarin)

- Patient with cirrhosis
  - Compensated cirrhosis plus PVT
    - Spontaneous recanalization in ~40% within 3 mon
  - Cirrhosis plus anticipated LT
    - "…unclear which specific patients may benefit the most from therapy". but
    - "…therapy with traditional anticoagulation likely promotes recanalization, which may benefit selected patients, particularly these associated with portal hypertension syndromes"

❖ Direct Oral Anticoagulants (DOAC)

- The efficacy and safety of DOAC to treat PVT in patients with cirrhosis is not established

- Patients with cirrhosis
  - Low molecular weight heparin (LMWH), vitamin K antagonist (VKA2) successful (38%) to achieve canalization in patients with DVT, but **no** cirrhosis
  - PVT may be complicated by esophageal varices in these patients without cirrhosis
    - Perform EGD to assess whether EV present
  - DOAC vs. VKAs for PVT in non-cirrhotic patients
    - ↑ thrombosis resolution
    - ↓ bleeding

- Guidance Statements
  - Individualize the choice of anticoagulant using multidisciplinary team consultation
  - Patients with cirrhosis and portal hypertension
    - No ↑ risk of non-portal hypertensive bleeding using anticoagulants
  - In patients with/without cirrhosis
    - Limited data on efficacy/safety
    - In patients with cirrhosis
      - Limited data on efficacy/safety
      - In patients with cirrhosis
        - Cautious use, multidisciplinary team

- Treatment
  - Goals
    - Manage associated
      - Portal hypertension
      - Malignancy
      - Thrombophilia condition
      - Restore outflow from hepatic vein
  - Anticoagulation
    - LMWH VKAs
      - ↓ progression of thrombus
      - ↑ recanalization

      } – Use AC, even if a thrombotic disorder is not present
    - Progression is poor, 5 yr survival rate only 25%
  - Thrombolysis
    - Recent/incomplete thrombosis
      - Local infusion of streptokinase/urokinase / recombinant + percutaneous angiography (PA) plus
      - Angioplasty/stenting
  - Percutaneous transluminal angioplasty
    - Indication: short segmental stenosis at
      - HV, cranial part
      - IVC, suprahepatic part
  - Vascular decompression
    - Stenting for failed angioplasty
    - Mesocaval shunt superior to portocaval side-to-side shunt
    - Do mesoatrial/mesocavoatrial shunt when
      - Intrahepatic IVC pressure > 20 mm Hg, or
      - IVC to right atrial pressure gradient > 15 mm Hg

      } ▪ Inadequate shunt function
    - TIPS with polytetrafluoroethylene (PTFE) -covered stents
    - Direct intrahepatic portosystemic shunt (DIPS) directly from IVC to the right portal vein (RPV)

- Liver transplantation (LT)
  - Mild/moderate
    - When donor therapies fail
  - Severe (acute liver failure [ALF])
    - LT may be first step
    - May need to insert TIPS to “bridge” patient to LT
- 5-yr survival rate
  - LMWH, VKAs alone 25%
  - TIPS (transplant-free) ~70%
  - LT > 70% (liver donors)
- Monitor HVT/BCS treatment response with hepatic elastography

➢ Guidance Statements

- Suspected HVT/BCS in any patient with
  - Acute or chronic liver disease, or
  - Prothrombotic disorder
- Investigation
  - Abdominal ultrasound for diagnosis
  - CT/MRI
    - Confirm diagnosis
    - Management planning
- When diagnosis made of HVT/BCS
  - Start anticoagulation
  - Investigate for possible thrombophilic disorder
  - Multidisciplinary consultation
- Perform ultrasound HCC surveillance +/- alpha-fetoprotein q6mon
  - Alpha-fetoprotein q6mon
  - CT/MRI inadequate to diagnose HCC → perform liver biopsy
- Refer patient early to centre of excellence with ability to enact “step-up” therapeutic strategy of above choices of anticoagulation to liver transplantation
- Medical therapy (anticoagulation) → TIPS/ direct intrahepatic portosystemic shunt (DIPS) with polytetrafluoroethylene (PTFE) covered stents → LT

❖ **Sinusoidal Obstruction Syndrome** (SOS) (old terminology, hepatic veno-occlusive disease)

➢ Definition

- A post-sinusoidal cause of portal hypertension in which inflammatory damage to the sinusoidal endothelial cells leads to necrosis and partial/total obstruction of the small hepatic venules

- Causes/associations
  - Myeloablative chemotherapeutic drugs (used for hematopoietic stem cell transplantation (HSCT)
  - Especially following allogeneic HSCT
    - HSCT-related
      - Busulfan
      - Cyclophosphamide
      - Melphalan
    - Platinum complexes
      - Carboplatin
      - Cisplatin
      - Oxaliplatin
    - Thiopurine
      - Azathioprine
      - Mercaptopurine
      - Thioguanine
    - Biologicals
      - Gemtuzumab
      - Inotuzumab

- Clinical
  - Onset
    - Acute
      - 1-3 wk post-exposure
      - RUQ pain / hepatomegaly
      - Ascites/edema
      - ↑↑ ALT/ ↑↑ AST
      - AP N/↑ ↑ bilirubin
    - Subacute
    - Chronic / post sinusoidal vascular disorder (PSVD)
      - Occurs months to years post exposure
    - Complications
      - Hepatic encephalopathy (HE)
      - Esophageal varices (EV)

Abbreviations: AP, alkaline phosphatase; N, normal; PSVD, post sinusoidal vascular disorder

- Laboratory
  - Hepatic venous pressure gradient (HVPG) may be done at time of transjugular liver biopsy
    - HVPG ≥ 10 mm Hg indicates portal hypertension
      - In the HSCT setting, and with no other obvious cause of portal hypertension, the diagnosis of SOS is supported

- Histopathology
  - Early changes
    - Sinusoids dilated
    - Red blood cells (RBCs) in space of Disse
    - Perivenular necrosis
  - Later changes
    - Central veins destroyed by fibrosis
  - The main reasons to obtain liver biopsy
    - Diagnosis of SOS
    - Exclude other liver diseases/cirrhosis (↑ risk of severe disease 3x)
  - Because of cytopenia, liver biopsy may need to be done by transjugular route

- Hepatic elastography
  - Limited use to assess SOS / hepatic fibrosis (perivenular) because
    - HSCT might be done for
      - Hematological malignancy or iron overload → ↓ hepatic elasticity, and falsely suggest HSCT

- Severity and High-risk

% of Cases	Mortality Rate	Features of ↑ Risk
○ Mild (8%)	1%	− Allogenic HSCT
○ Recover with treatment (64%)	18%	− Second HSCT
○ Severe (28%)	67%	− Previous liver disease (OR, 3.35; 95%CI, 1.71-6.58; P < 0.001)

- Prophylaxis
  - Ursodeoxycholic acid (UDCA)
    - 12 mg/kg po, divided doses po b.i.d., start day before conditioning and continue for 3 mon post-HSCT, or
  - Defibrotide 25 mg/kg per day for 21 d, or until resolution of SOS
    - Expensive!
      - Used for treatment of severe SOS
      - Prophylactic benefit not known

- Treatment
  - Manage hepatic complications, e.g., ascites/edema

- Guidance Statement
  - Suspect SOS in post-HSCT setting, especially
    - 1 to 3 wk post-HSCT
    - RUQ pain, hepatomegaly
    - Edema, ascites

- Give UDCA 12 mg/d in 2 divided doses, starting 1 d before conditioning and for 3 mon after HSCT
- Role of TIPS unknown
  - Not recommended

❖ **Hepatic Vascular Manifestations**

- Hereditary Hemorrhagic Telangiectasis (HHT) (aka Osler-Weber-Rendu Syndrome)

➢ Definition

- Rare, autosomal-dominant genetic disease causing
  - Macro-/microscopic arteriovenous
  - Arteriovenous malformations (AVM)

➢ Demography

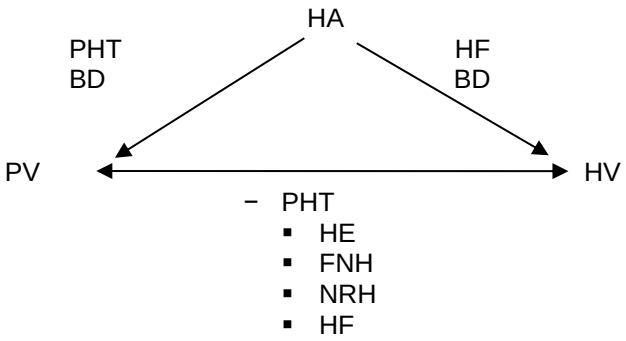
- Prevalence, $20/10^5$
- Liver vascular malformations (LVM) in ~50%

➢ Pathology

- Sites involvement with AVM
  - Brain
  - ENT
    - Eyes (conjunctive), nose, mouth (throat)
  - Lungs
  - Liver (liver vascular malformations, LVM)
    - Hepatic bruit
    - Portal hypertension
    - Focal nodular hyperplasia (FNH)
    - Nodular regenerative hyperplasia (NRH)
- Other organs affected indirectly
  - Biliary
    - Secondary sclerosing cholangitis (ischemic cholangiopathy)
    - Biloma/biliary necrosis
  - Intestine
    - Ischemia (“steal” of blood away from mesenteric to hepatic artery (HA)
    - Bleeding/anemia
  - Heart
    - High output failure
    - Arrhythmias

➢ Complications

- Shunting of Blood



Abbreviations: BD, biliary disease; FNH, focal nodular hyperplasia; HA, hepatic artery; HE, hepatic encephalopathy; HF, heart failure; HV, hepatic veins; NRH, nodular regenerative hyperplasia; PHT, portal hypertension; PV, portal vein

➢ Diagnostic imaging

- FNH, NRH → nodular liver (might be confused as HCC)
- CT/MRE with contrast have different flow pattern for HTT-associated nodules than does HCC
  - Liver
    - Heterogenous enhancement/hypervascularization
    - Hepatic artery, enlargement
- MRCP
  - Secondary biliary cholangitis (SBC)
  - Biloma / biliary necrosis → antibiotics, percutaneous drainage
- ERCP
  - Useful
  - Perform ERCP to investigate/treat dominant stricture

➢ Treatment

- Symptoms of AVM and complications
  - Successful in > 60% of HHT patients
- Bevacizumab (monoclonal antibody which ↓ activity of vascular endothelial growth factor (VEGF) in endothelial cells
  - 5 mg/kg IV q2wk
  - Maintenance therapy for persist/recurrent symptoms
  - Benefit
    - ↓ epistaxis
    - ↓ heart failure (HF) / ↑ cardiac index (CI)
    - ↓ ischemic cholangiopathy

- Liver transplantation (LT)
  - 4 yr survival, 86%
  - Adverse events
    - Perioperative complications
    - Post-operative recurrence of LVMs

Treatment Faux Pas

- For HHT, do **not** perform
  - Hepatic arterial embolization, or
  - Surgical ligation

➢ Guidance Statements

- Suspect HHT-associated LVM from family history (autosomal dominant)
  - Bleeding
    - Nose
    - Brain
  - Heart
    - Failure, high output
- Asymptomatic LVM
  - No imaging surveillance
  - No treatment
- Symptomatic LVM
  - Standard treatment of complications
  - Non-responders
    - Give bevacizumab, or
    - Liver transplantation

} – Multidisciplinary team

❖ Idiopathic Non-cirrhotic Portal Hypertension (INCPH) (aka Idiopathic Portal Hypertension [IPH])

➢ Definition

- "Portal hypertension in the absence of cirrhosis, portal vein (PV) obstruction, or hepatic vein obstruction / Budd Chiari Syndrome}, … as well as absence of
  - Other causes of non-cirrhotic portal hypertension
    - Congenital hepatic fibrosis
    - Sarcoidosis
    - Schistosomiasis
  - Pre-cirrhotic stage of conditions that progress to cirrhosis
    - HBV/HCV infection
    - NASH
    - Metabolic liver disease

- Post-sinusoidal vascular disease (PSVD)
  - Hypervascular portal tracts
  - Abnormal periportal vessels
  - Herniated portal vein
  - Sinusoidal dilation
  - Regenerative hepatocytes
- Vascular lesions without cirrhosis
  - Obliterative portal venography (OPV, aka intrahepatic PV stenosis [IPVS])
  - Nodular regenerative hyperplasia (NRH)
  - Incomplete septal cirrhosis (ISC)

➢ Causes/associations

Please see “Definition” for numerous conditions to be excluded (idiopathic non-cirrhotic portal hypertension [INCPH] and post-sinusoidal vascular disease [PSVD])

- Blood diseases
- Infection
- Inflammation
- Injury/drugs

SO YOU WANT TO BE A GASTROENTEROLOGIST!

- Give the two hepatic conditions which may cause portal hypertension by way of their association with INCPH/PSVD, as well as through the associated liver disease itself.
  - Autoimmune hepatitis (AIH)
  - Hereditary hemorrhagic telangiectasia (HHT)

➢ Histopathology

- If patient needs to have a percutaneous liver biopsy but has a severe thrombocytopenia
  - Obtain liver biopsy through the transvenous route
- Establish the absence of advanced fibrosis/cirrhosis, and delineate subtle changes in vascular architecture (for diagnosis of PSVD; use reticulin stains)

- Clinical
  - Bleeding is more frequent than are ascites and hepatic encephalopathy (HE)
    - Bleeding may trigger the onset of the ascites/HE
  - ↑ risk of
    - Portal vein thrombosis (PVT), 32%
    - Focal nodular hyperplasia, 14%
    - Renal dysfunction
  - Treat underlying/associated comorbidities/complications
    - No specific treatment
    - No data on prophylaxis for bleeding esophageal varices from associated non-cirrhotic portal hypertension

- Prognosis
  - The main determinants of outcome are related to concurrent severe comorbidities, particularly renal dysfunction.

- Guidance statements
  - Suspected INCPH in patient with
    - No cirrhosis
    - No known cause of non-cirrhotic portal hypertension
  - Exclude conditions associated with INCPH/PSVD
  - Liver biopsy is required to make the diagnosis
    - May be necessary for expert review of histopathology and use of special stains such as reticulin
  - Do **not** do routinely screening for portal vein thrombosis (PVT)

❖ Arterial Aneurysm

- Definition
  - Aneurysm (“true aneurysm”)
    - Involves 3 layers of arterial wall
  - Pseudoaneurysm
    - Involves 1 or 2 layers of arterial wall
    - Usually
      - Intrahepatic
      - Caused by trauma, e.g., liver biopsy, transhepatic drainage of biliary tree, surgery including liver transplantation (LT)

❖ **Hepatic Artery Aneurysms** (HAAs)

➢ Causes/associations

- Vascular disease
  - Other sclerosis
  - Vasculitis
    - Kawasaki disease
    - Polyarteritis nodosa (PAN)
    - Systemic lupus erythematous (SLE)
    - Takayasu arteritis (TA)
  - Connective tissue disease
    - Hereditary hemorrhagic thrombocytopenia (HHT)
    - Ehlers-Danlos syndrome (EDS), Marfan syndrome
  - Degeneration of medio intima
- Trauma
- Infection

➢ Clinical

- Pain, epigastric/abdominal
- Jaundice
- Bleeding (HA → PV)
  - Haemobilia
  - Intraperitoneal
- Mortality rate > 30%

➢ Diagnostic imaging

- Doppler ultrasound / CT scan
  - Mean diameter of HAA, 2.3 cm

➢ Treatment

- Endovascular or surgical approaches

❖ **Splenic Artery Aneurysms** (SAAs)

➢ Demography

- F > M, 7:1
- Usually diagnosed age 60-70 yr

- Causes/Associations
  - True aneurysm
    - Pregnancy/multiparity
    - Portal hypertension (~15%, with/without cirrhosis)
    - Pancreatitis
    - Vascular disease
      - Atherosclerosis
      - Fibromuscular dysplasia
      - Hereditary hemorrhagic thrombocytopenia (HHT)
    - Alpha-1 antitrypsin deficiency
    - Severe, advanced liver disease which requires liver transplantation (LT)
  - Pseudoaneurysms
    - Injury/pancreatitis
    - Infection
    - Injury/Trauma

- Clinical
  - Rupture/bleeding
    - Size, > 2 cm
    - Incidence, ~3%
    - Mortality, ~30%

    } Penetrates into
    - Stomach
    - Peritoneal space
  - Risk of rupture greater for pseudoaneurysms than for true aneurysms

- Treatment
  - Indications
    - Symptoms
    - > 3 cm, or
    - ↑ size on repeat angiography
  - Endovascular or surgical repair

SAA Repair	30-day Mortality	Repeat Investigation
- Endoscopic	- (0.6%)	↑ (3.2%)
- Surgical	↑(5.1%)	-(0.5%)

- Guideline Statement
  - Diagnostic imaging of hepatic/splenic artery aneurysms (HAAs/SAAs)
    - Diagnosis, doppler ultrasound, CT scan / CT angiography (CTA)
    - Characterization for treatment planning

- Follow-up
  - If HAA/SAA < 2 cm
    - Repeat diagnostic imaging to determine if there has been growth (> 3 cm), and if so, then endovascular or surgical repair

- Treatment
  - Asymptomatic uncomplicated → multidisciplinary approach
    - First choice, endovascular repair
      ↓
    - Surgical repair
  - Symptomatic/complicated → urgent treatment
  - Planned pregnancy / planned liver transplant (LT)
    - Elective repair

Abbreviations: AASLD, American Association for the Liver Disease; ACLF, acute-on-chronic liver failure; AIH, autoimmune hepatitis; ALT/AST, transaminases; AP, alkaline phosphatase; ArLD, alcohol-related liver disease; AVM, arteriovenous malformation; BCS, Bud-Chiari Syndrome; BMD, bone mass density; BN/B, biliary necrosis/biloma; CI, cardiac index; CI, confidence ratio; CMV, cytomegalovirus; CTA, CT angiography; CTP, Child-Turcotte Pugh; DIPS, direct intrahepatic portosystemic shunt; DOAC, direct oral anticoagulant; EACA, epsilon-amino caproic acid; EDS, Ehlers-Danlos Syndrome; ENT, ear nose and throat; ERCP, endoscopic retrograde cholangiopancreatography; EV, esophageal varices; EVL, esophageal variceal ligation; FNA, focal nodular hyperplasia; HA, hepatic artery; HAA, hepatic artery aneurysm; HCC, hepatocellular cancer; HE, hepatic encephalopathy; HF, heart failure; HHT, hereditary hemorrhagic telangiectasia; HOHF, high output heart failure; HSCT, hematopoietic stem cell transplantation; HV, hepatic vein; HVPG, hepatic venous pressure gradient; HVT, hepatic vein thrombosis; INCPH, incomplete non-cirrhotic portal hypertension; INR, International Normalized Ratio; IPH, idiopathic portal hypertension; ISC, incomplete septal cirrhosis; IVC, inferior vena cava; LMWH, low molecular weight heparin; LT, liver transplant; LVM, liver vascular malfunction; MCQ, Multiple choice questions; mon, month; MRCP, magnetic resonance cholangiopancreatography; MRI, magnetic resonance imaging; N, normal; NASH, Non-alcoholic steatohepatitis; NRH, nodular regenerative hyperplasia; NSBB, non-specific beta blocker; OR, odds ratio; PHT, portal hypertension; QoL, quality of life; PSVD, post sinusoidal vascular disease; PT, prothrombin time; PTFE, polytetrafluoroethylene; PV, portal vein; PVR, portal vein recanalization; PVT, portal vein thrombosis; RBC, red blood cell; ROTEM, rotational thromboelastography; RUQ, right upper quadrant; SAA, splenic artery aneurysm; SIRS, systemic inflammatory response syndrome; SOS, sinusoidal obstruction syndrome; SSC, secondary sclerosing cholangitis; TACE, transhepatic arterial chemoembolization/radioembolism; TACR, transhepatic arterial chemoembolization; TEG, thromboelastography; TIPS, transjugular intrahepatic portosystemic shunt; TPO, thrombopoietin; TRLI, transfusion-related lung injury; UDCA, ursodeoxycholic acid; uFH, unfractional heparin; VKA, vitamin K agonist; VKR, vitamin K replacement; VNF, von Willbrand factors; VTE, venothrombo-embolism; wk, week; yr, year

HEPATIC DECOMPOSITION

Hyponatremia and Cirrhosis

Alukal JJ, et al. Am J Gastroenterol 2020; 115: 1775-1785.

- Definition of hyponatremia (↓ Na^+_s)
  - Overall < 135
  - Cirrhosis < 130
  - Prevalence of Na^+_s < 130 mEq/L in cirrhosis < 130 ~20%; < 125 ~5%; < 120 ~1%
    - Na^+_s < 130 mEq associated with
      - Decompensated liver disease
      - ↓ prognosis after liver transplantation (LT)

- Hyponatremia
  - ↓ serum osmolality (< 280 mOsmol/kg)
    - Hypovolemic hyponatremia
      - Diarrhea
      - Use of kinetics
    - Hypervolemic hyponatremia
      - ↓ renal excretion of solute-free water
  - Normal osmolality (280-295 mOsmol/kg)
    - Pseudohyponatremia
      - TG > 1500 mg/dL
      - Serum proteins > 10 g/dL
  - ↑ serum osmolality (> 295 mOsmol/kg)
    - Translocational
      - Infusion of glucose / inactivated (translocational)
  - Hypotonic (< 280 mOsmol/kg), hyponatremia (true hyponatremia)

	Volume Status	
	TBW	Total body Na
– Hypovolemic	↓	↓
– Euvolemic	↑ (slightly)	N
– Hypervolemic (common in chronic liver disease)	↑↑	↑↑

Abbreviation: TBW, total body weight

- Hypovolemia hyponatremia
  - ↑ use of diuretics / vomiting / diarrhea
  - No ascites or edema

- Causes of hypervolemia hyponatremia
  - Liver – Cirrhosis
  - Heart – Heart failure
  - Kidney – Failure
  - Combinations of the above

- Pathophysiology of hypervolemic hyponatremia (< 130 mEq/L), < 280 mOsmol/kg
  - Features
    - ↓ Na^+_s (< 130 mEq/L), ↑ ECV (free water), ↑ total body weight, ↑ total body Na^+

Abbreviations: ECV, extracellular volume; Na^+_s, serum sodium concentration

- Splanchnic arteriolar vasodilation
  - Vasodilative
    - ↑ adrenomedullin
    - ↑ carbon monoxide (CO)
    - ↑ endocannabinoids
    - ↑ endothelium-derived hyperpolarizing factor (EDHF)
    - ↑ hydrogen sulfide (H2S)
    - ↑ nitric oxide (NO) release from endothelial cells
    - ↑ platelet activating factor (PAF)
    - ↑ prostacyclin
    - ↑ vasoactive intestinal peptide (VIP)
  - Bacteria/bacterial antigens/products
    - Pathogen-associated molecular patterns (PAMPs)
  - Hepatocytes
    - Danger associated molecular patterns (DAMPs)
      - Apoptosis/necrosis
      - Inflammation
  - Extrahepatic ↓ reactivity to vasoconstrictors
    - Functional defect in F protein coupled transmembrane receptors
      - Angiotensin II receptor
      - Vasopressin receptor
      - ↓
      - ↓ protein kinase C (PKC)
      - ↓
      - Myosin light chain kinase phosphorylation
      - ↓
      - Vascular smooth muscle (↑ vasodilation)

- ↓ effective arterial volume (EAV) ← splanchnic arterial vasodilation
  ↓
  Renal vasoconstriction
  ↓
  Retention of Na^+/H_2O (hypervolemic hyponatremia Na^+_s)
  - ↑ baroreceptor activity on atria, aortic arch, carotid sinus
    ↓
    ↑ ADH binds to V2 receptors in basolateral membrane of renal collecting ducts
    ↓
    ↑ cAMP / ↑ PKA
    ↓
    ↑ translocation of water channel protein (AQP2) to apical membrane of collecting ducts
    ↓
    ↓ excretion of free water
    ↓
    ↑ permeability of collecting duct to H_2O
    ↓
    ↑ total body water / hypervolemia / hyponatremia

    ↓
    − ↑ activity of renin-angiotensin aldosterone system (RAAS), ↑ activity of sympathetic nervous system (SNS)
    ↓
    − ↑ angiotensin I/II
    ↓
    − Aldosterone
    ↓
    − ↑ renal Na^+ absorption

➢ Clinical

- Any rapid/acute ↓ Na^+_s → HE, rather than necessarily the chronic Na^+_s
- Symptoms
  - ↑ cognitive impairment
  - ↑ ataxia/falling
  - ↑ nausea/vomiting
  - ↑ hepatic complications
    - Refractory ascites
    - ↑ need for large volume paracentesis (LVP) / ↓ time between need for LVPs
    - ↑ spontaneous bacterial peritonitis (SBP)
    - ↑ hepatorenal syndrome (HRS; aka acute kidney injury)
  - ↓ quality of life
  - ↑ mortality

➢ Neurological changes of hyponatremia (hypotonic, hypervolemic)

- Brain
  - Water moves from extracellular compartment to cytoplasm of astrocytes → tendency to swell (cerebral edema)
    ↓
  - As a result of limitation of swelling of astrocytes because of restraining effect of bony skull, the ↑ intracellular osmolality in the astrocytes must be corrected by movement of solute out of astrocytes (K^+, glutamine, choline, taurine, organic osmolytes)

- Liver
  - ↑ glutamic acid / ↑ NH_3
  - ↑ oxidative stress
  - ↑ inflammatory cytokines

  → − ↓ activation of N-methyl-D-aspartate receptors

  → ↑ astrocyte swelling

  ↓ function of glial-neuronal communication

  → ▪ HE

➢ Assessment/Complications of hyponatremia

- **Refractory ascites** (RA)

➢ Pathophysiology

  - Similar pathophysiology as ascites
    - ↑ splanchnic vasodilation
    - ↓ effective arterial volume (EAV)
    - ↑ ADH, ↑ RAAS, ↑ SNS, ↑ angiotensin, ↑ aldosterone
    - ↑ translocation of AQP2
    - ↑ retention of Na+ / ↓ excretion of free water
  - Plus
    - Hypoalbuminemia / oncotic pressure
    - ↑ intestinal permeability
    - ↓ renal perfusion
      - Factors which ↓ efficacy of diuretics

➢ Demography

  - ↑ refractory ascites (RA) with natremia (Na^+_s) < 130 mEq/L

➢ Prognosis

  - ↑ 5-yr probability of RA with ↓ Na^+_s
  - ↓ prognosis

- **Hepatorenal syndrome** (HRS)

- In the patient with the triad of “ascites, hyponatremia and renal dysfunction”, give the clinical factors which contribute to the worsening of the renal dysfunction (↑ Cr_s)
  - Bleeding
  - Infection, e.g., spontaneous bacterial peritonitis (SBP)
  - Treatments
    - Large volume paracentesis (LVP)
    - Diuretics

➢ Treatment (hypernatremia)

- Na^+_s < 130 mEq/L
  - Ice chips with strict ↓ intake of salt/water (500 cc/d)
  - Temporarily stop diuretics
  - Correct hypokalemia (↓ K^+_s)
    - Shifts of Na^+/K^+
    - ↑ renal glutaminase (from ↓ K^+_s) → ↑ NH_3 / ↑HE
  - Albumin solution, 25%, ≥ 40 g/L
    - Useful to treat hyponatremia in cirrhosis, not just hypervolemia, hyponatremia, including
      - Acute kidney injury (AKI)
      - Large volume paracentesis (LVD)
      - Spontaneous bacterial peritonitis (SBP)

- Na^+_s < 110 mEq/L, or severe symptoms (e.g., seizures, coma)
  - Hypertonic saline (3%)
  - Desmopressin (DDAVP)
    - Anti-diuretic synthetic analogue of V2 receptors on basolateral membrane of renal collecting ducts
  - Vasopressin receptor antagonists (vaptans)
  - Continuous venovenous hemofiltration (CVVH)

- Hypertonic saline (3% Na) for dilutional hypovolemia
  - Use for cirrhosis-associated hyponatremia
    - Na^+_s < 110 mEq/L, or
    - Symptoms of hyponatremia
      - Cardiopulmonary stress
      - Neurological changes
        - Seizures
        - Coma
  - Acute (< 24 h) symptomatic hyponatremia
    - 100 cc 3% saline over 15-30 min, repeated maximum of 3x to ↑ Na^+_s by ~5 mEq/L in 6 h
  - Chronic hyponatremia
    - Symptomatic or severe (< 110 mEq/L)
    - 3% saline at 15-30 cc/h, to Na^+_s by ≤ 8 mEq/L per day (especially in first 24 h)
    - Complication of 3% Na infusion is ↑↑ free water diuretic clearance with correction of hyponatremia)

- Desmopressin (DDAVP)
  - For treatment of ↑↑ free water clearance after correction of hyponatremia with 3% saline.
  - DDAVP
    - Acute diuretic, analog to vasopressin
    - Binds to V2 receptors → ↑ renal water reabsorption / ↓ clearance of free water
    - The ↑ water reabsorption → ↓ Na^+_s slows the ↓ Na^+_s from 3% Na and ↓the enhanced clearance of free water (↓ Na^+_s caused by overcorrection of hyponatremia with 3% Na^+)
    - Consider giving DDAVP for prophylaxis of possible excessive correction of hyponatremia using 3% Na^+
    - More effective this proactive way with
      - Slower rate of Na^+_s correction
      - ↑ urine osmolality
      - ↓ urine output

      } More effective when given prophylactically

- Vasopressin receptor antagonists (vaptans)
  - Non-peptide drugs which block the action of ADH on their V1/V2 receptors
    - Location of receptors
      - V1 vascular smooth muscle
  - Tolvaptan
    - Do **not** use in patients with cirrhosis due to complications
      - Acute kidney injury (AKI)
      - Osmotic demyelination syndrome (ODS)
      - GI bleeding
    - Exception: correction of hyponatremia pre-liver transplantation (LT) (please see next section)

- **Post-paracentesis circulatory dysfunction** (PPCD)

- Give the meaning of the term “post-paracentesis circulatory dysfunction” (PPCD).
  - PPCD is the triad of “ascites, hyponatremia and renal dysfunction which results from large volume paracentesis (LVP) producing ↓ effective criterial volume (ECV), and thereby possible ↑ mortality.

❖ **Acute or chronic liver failure (ACLF)**

➢ Definition
  - “…rapidly progressive liver failure with established chronic liver disease resulting in multiorgan failure and a very high short-term mortality”

➢ Prognosis

- Na_s^+ < 130 mEq/L is
  - Predictor of poor prognosis in ACLF
  - ↓ 90 d survival vs. persons with ACLF and no hyponatremia ~60% vs. 35%
  - ↑ risk of
    - Progression into severe ACLF
    - Infection (SBP, urinary tract infection [UTI], respiratory tract infection [RTI], cellulitis)
    - Hospitalization
- In patients with cirrhosis who are hospitalized for acute decompensation yet who do **not** develop ACLF, their prognosis is better determined with the Chronic Liver Failure (CLF) Consortium Acute Decompensation (CAD) Score, than with MELD-Na Score.
  - The CLF-CAD score is comprised of age, INR, serum creatinine (Cr_s), WBC, and Na^+_s
- ACLF and large volume paracentesis (LVP)
  - Without ACLF, AASLD suggests albumin replacement only when LVP > 5L
  - In persons with ACLF, give albumin replacement even for LVP < 5 L to ↓ risk of
    - Hyponatremia (23% vs. 63%)
    - Acute kidney injury (AKI) (30% vs. 63%)
    - Mortality in hospital (28% vs. 63%)

❖ Liver transplantation (LT)

- In persons listed for LT with a MELD score > 11, the addition of serum sodium concentration (Na^+_s) better predicts waitlist mortality
  - Each mmol ↓ Na^+_s between 125 and 140 mEq/L is associated with a hazard ratio of 1.05 (United Network for Organ Sharing 2015)
  - The rational is related to hyponatremia being associated with
    - ↑ ICU length of stay (LOS)
    - ↑ hospital LOS
    - Renal failure
    - ↑ mechanical ventilation
    - Sepsis
    - Neurological complications
    - Effect of ↓ Na^+_s on post-LT survival is debated
      - Negative effect of hyponatremia observed in European but not in US studies

- **Osmotic demyelination syndrome** (ODS)

➢ Definition

- "…destruction of the myelin sheath in the pontine and extrapontine areas of the brain (cerebral cortex, subcortex, cerebellum, thalamus) … as a consequence of rapid over correction of hyponatremia…"

- Pathophysiology
  - ↑ extracellular Na+ causes osmotic movement of intracellular water, shrinking glial cells → exonal shear damage → opening of tight junctions (↑ permeability) → ↑ apoptosis → destruction of myelin sheath

- Causes/associations
  - Hyponatremia
    - Causes ODS in about 1% of LT patients
  - Other biochemical changes
    - Hypokalemia (↓ K^+_s)
    - Hypophosphatemia
    - Hypoglycemia
  - Patient
    - Males
    - Previous HE

  - "Rather than the absolute value of [serum] sodium, it is the overcorrection [of hyponatremia] over a short period of time that pass the greatest risk of development of ODS" (rate of ↓ Na^+_s)

- Clinical
  - Encephalopathy (differentiate from HE from other neurological symptoms plus typical ODS MRI) (please see below)
  - CNS
    - Agitation
    - Delirium
    - Dysarthria
    - Parkinson
    - Seizures
  - MSK
    - Ataxia
    - Dystonia
    - Quadriplegia
  - GI
    - Dysphagia

- Diagnostic imaging
  - MRI of head
    - Weighted sequences T1
      - ↓ intensity lesions
    - Weighted sequence T2
      - ↑ intensity lesion
      - Fluid-attenuated inversion recovery imaging in the central positive and extrapontine structures
  - Repeat MRI may be necessary
    - Changes in MRI may occur after the start of clinical symptoms

- Pre-liver transplantation hyponatremia
  - Preoperative
    - ↓ neurological complications (e.g., ODS) but correcting hyponatremia pre-LT (≥ 120 mEq/L) correct Na^{+}_{s} to > 125 mEq/L
  - Operative
    - Administer transfusions of PRBC/FFP as indicated
    - Use 0.45% saline replacement IV, as indicated
    - Treat metabolic acidosis with tris(hydroxymethyl) aminomethane (THAM) (a weak amino acid alcohol which binds CO_2 and metabolic acids)
      - Do **not** use THAM in patient with acute kidney injury (AKI)
  - Continuous venovenous hemofiltration (CVVH)
    - During LT surgery patients receive Na+ by way of IV, FFP, PRBCs
      - Replacement fluid may be by 0.45% saline
      - Correct metabolic acidosis with THAM rather than NaHCO3
      - Give continuous venovenous, hemodilution, using sterile water added to the dialysate solution

Abbreviations: ADH, anti-diuretic hormone; AKI, acute kidney injury; AQP2, aquaporin water channel protein; CO, carbon monoxide; CO_2, carbon dioxide; CVVH, continuous venovenous hemofiltration; DAMPs, danger-associated molecular patterns; DDAVP, desmopressin; EAV, effective atrial volume; EDHF, endothelium-derived hyperpolarizing factor; FFP, fresh frozen plasma; h, hour; H_2O, water; H_2S, hydrogen sulfide; HE, hepatic encephalopathy; HRS, hepatorenal syndrome; ICU, intensive care unit; IV, intravenous; K^+, potassium; K^{+}_{s}, serum potassium; L, litre; LOS, length of stay; LT, liver transplant; MELD, Model for End Stage Liver Disease; Na^+, sodium; Na^{+}_{s}, serum sodium; NH_3, ammonia; NO, nitric oxide; ODS, osmotic demyelination syndrome; PAF, platelet activating factor; PAMPs, pathogen-associated molecular patterns; PKA, protein kinase C; PRBC, packed red blood cells; RA, refractory ascites; RAAS, renin-angiotensin aldosterone system; SBP, spontaneous bacterial peritonitis; SNS, sympathetic nervous system; SP, substance P; THAM, tris(hydroxymethyl) aminomethane; VIP, vasoactive intestinal peptide; yr, year

Diagnosis, Evaluation, and Management of Ascites and Hepatorenal Syndrome (HRS)

Biggins SW, et al. Hepatology 2021;74(2):1014-1048.

- Ascites

➢ Demography

- ~20% of persons with cirrhosis develop ascites (ascites is often first feature of decompensation)
- 42 randomized clinical trials of 2870 persons with treated ascites were analysed to compare the outcomes with different therapeutic modalities.
- The difference of paracentesis plus fluid replacement (PFR) in persons with decompensated cirrhosis (but without other features of decompensation) was enhanced with addition of
  - Transjugular intrahepatic portosystemic shunt (TIPS): RR 9.44; 95%CI: 1.93 to 62.68
  - Aldosterone RR 30.63; 95%CI: 5.06 to 692.98
  - These additions to PFR are likely not of benefit on mortality rate (MR), need for liver transplantation (LT) or frequency of adverse event s (AEs), 1/3 of patients given PFR for their ascites died with 11 mon
- Adding aldosterone plus loop diuretics to PFR resulted in ↑ complications (RR 2.07; 95%CI: 1.37 to 3.10; very low certainty evidence)
  - Hepatic encephalopathy (HE)
  - Hepatorenal syndrome (HRS)
  - Variceal bleeding (VB)
- Based on very low certainty, there is considerable uncertainty about whether interventions for ascites in people with decompensated liver cirrhosis decrease
  - Mortality
  - Adverse events
  - Liver transplantation compared to paracentesis plus fluid replacement in people with decompensated liver cirrhosis and ascites.
- Based on very low certainty evidence
  - Transjugular intrahepatic portosystemic shunt and adding aldosterone antagonists to paracentesis plus fluid replacement may ↑ resolution of ascites compared to paracentesis plus fluid replacement.
  - Aldosterone antagonists plus loop diuretics may ↑ decompensation rate compared to paracentesis plus fluid replacement.

➢ Causes/association

- Usually first decompensation event in patients with cirrhosis
- Development of ascites associated with reduction in 5-yr survival from 80% to 50%.

- The ↑ mortality is due to

	Treatment
− Renal sodium retention	▪ Diuretics
− Arterial underfilling	▪ Albumin infusion
− Portal hypertension	▪ Portal decompressive procedures

- Diagnostic paracentesis (DP) should be performed in all patients with new-onset ascites that is accessible for sampling
  - Some authorities also suggest DP on every hospitalization, or clinical visit where new decompensation is suspected.
- The initial laboratory investigation of ascitic fluid should include ascitic fluid neutrophil count, ascitic fluid total protein, ascitic fluid albumin, and serum albumin to calculate the serum albumin ascites gradient (SAAG).
  - Exclude malignancy, heart failure, TB, and pancreatic disease (please see table below)

Medical History	Physical Exam	Investigations
○ Risk factors for chronic liver disease − Alcohol − Metabolic − Viral hepatitis, − Family history of liver − Heart disease − Hematologic disorder (thrombosis, excessive bleeding) − Thyroid disease − Autoimmune disorder − Malignancy − Pancreatitis − Travel history − TB risk factors	− Shifting dullness − Abdominal masses/tenderness/ guarding − Hernias − Hepatic hydrothorax − Stigmata − Heart failure signs (JVD) − Malnutrition − Thyroid disease signs − Malignancy or infection signs	▪ U/S with doppler ▪ CBC, LFTs, Cr_s, Lytes ▪ Ascitic fluid analysis ▪ SAAG >11 g/L = portal HTN ▪ Total protein >25 g/L, cardiac source of ascites

- Grading severity (see table below)

According to amount	According to Tx response
− Grade 1 mild = only detected by US No treatment recommended	▪ Responsive: becomes grade 1 ascites with diuretics +/- sodium restriction
− Grade 2 moderate = moderate symmetric distension of abdomen	▪ Recurrent: recurs 3 times in 12 mon despite diuretics + sodium restriction
− Grade 3 large = marked distension	▪ Refractory: cannot be prevented by medical therapy or treatment limited by side effects

➢ Treatment

Treatment for ascites in adults with decompensated liver cirrhosis: a network meta-analysis (Benmassaoud A, et al. Cochrane Database of Systematic Reviews 2020, Issue 1. Art. No.: CD013123. DOI: 10.1002/14651858.CD013123.pub2)

- Diet
  - Moderate sodium restriction (2 g or 90 mmol/day) and diuretics (spironolactone with or without furosemide) are the first-line treatment in patients with cirrhosis and grade 2 ascites.
    - Education on food sodium content, avoiding adding salt and guarding against nutritional deficiency (dietician consultation)
  - Fluid restriction is not necessary for ascites management unless there is concomitant moderate or severe hyponatremia (serum sodium 125 mmol/L).

- Diuretics
  - Spironolactone with an initial dose of 100 mg/day up to 400 mg/day
    - Long half-life, and effects may not be seen up to 3 days
    - Eplerenone 50 mg, or Amiloride 10 mg are equivalent
  - Furosemide with an initial dose of 40 mg/day titrated up to max 160 mg/day
    - Initially use spironolactone alone, then combined with furosemide
    - Patients with CKD need more loop diuretic

- Monitoring
  - Daily weight monitoring at the same time of day
  - Safe limits of weight loss= 0.5 kg/day without edema, 1 kg/day with edema
    - More diuresis may cause renal injury due to the peritoneal membrane's inability to re-absorb more than 500 mL ascites per day
  - Urine sodium excretion < 80 mmol/day indicates insufficient diuretic dose
  - Spot urine sodium/potassium ratio > 1 indicates that the patient should lose weight
    - If no weight loss, then suspect dietary non-compliance
  - After ascites is adequately mobilized, attempts should be made to taper the diuretics to the lowest dose necessary to maintain minimal or no ascites to prevent the development of adverse effects.
  - In patients receiving diuretics, body weight and serum creatinine and sodium should be regularly monitored to assess response and to detect the development of adverse effects (see table below).
    - Daily weight monitoring with the same scale and at the same time of day

- Muscle cramps
    - Human albumin solution (20-40 g/wk) or baclofen administration (10 mg/day, with a weekly increase of 10 mg/day, up to 30 mg/day) can be considered in cases of severe muscle cramps.

Loop diuretic adverse effects	Aldosterone antagonist adverse effects
− Acute kidney injury (AKI) − Hyponatremia − Hypokalemia − Hepatic encephalopathy − Muscle cramps	− Hyperkalemia − Gynecomastia: may respond to drug switching − Muscle cramps

- Large volume paracentesis (LVP)
    - Large volume paracentesis (LVP) is the first-line treatment of grade 3 ascites.
        - After paracentesis, sodium restriction and diuretics should be started.
            - INR > 1.5 and platelet count <50 are **not** contraindications
            - Disseminated intravascular coagulopathy (DIC) and thrombocytopenia with uremia are relative contraindications
    - Referral for LT evaluation should be considered in patients with grade 2 or 3 ascites.
    - Nonsteroidal anti-inflammatory drugs (NSAIDs), angiotensin-converting enzyme (ACE) inhibitors, and angiotensin receptor blockers (ARBs) should be avoided in patients with cirrhosis and ascites
        - Will further ↓ effective arterial volume (EAV) / ↓ renal perfusion
    - Do **not** use aminoglycosides should be avoided whenever possible in the treatment of bacterial infections.
        - Nephrotoxic
    - For patients with cirrhosis and diuretic-responsive ascites, controversial data suggest potential benefits of long-term infusion of human albumin solution.
        - Two trials showing conflicting effects on survival with chronic albumin
            - At present, **no** recommendation can be made for its use in routine clinical practice

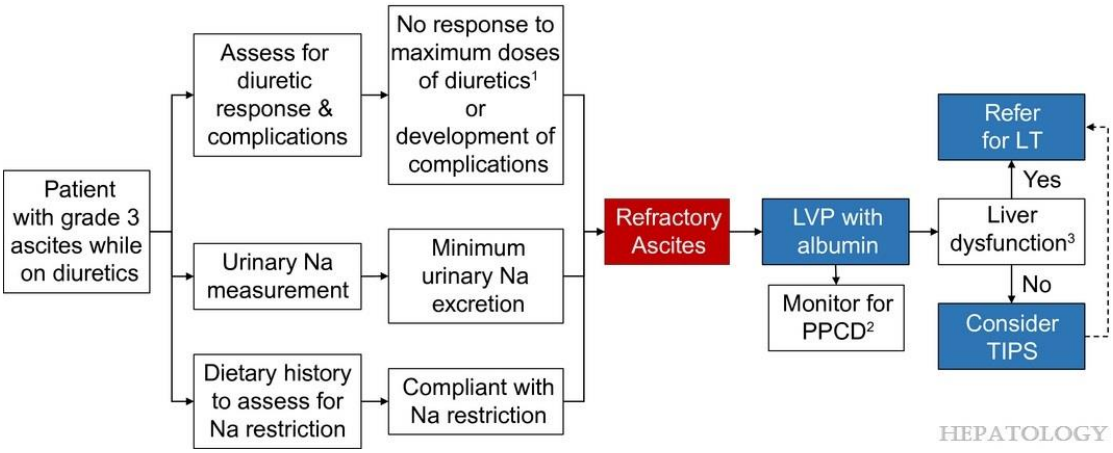
- **Refractory Ascites** (RA)
    - Continued dietary sodium restriction (<2 g/day) is required in patients with RA to reduce the rate of ascites accumulation.
        - Review patient's food diary
        - Discontinue diuretics for refractory ascites to minimize adverse events
    - Fluid restriction is ineffective for the management of RA, but restricting fluid intake to less than 1000 mL/day is recommended for treatment of hyponatremia (e.g., <125 mEq/L).

- In the management of RA, there are insufficient data to recommend the long-term use of albumin infusions outside the setting of large-volume paracenteses
- LVP is the first-line treatment for RA.
  - Lower incidence of electrolyte abnormalities, renal dysfunction, and hemodynamic disturbances than diuretics when done repeatedly
- Albumin infusion at the time of LVP of >5 L is recommended to mitigate the risk of post-paracentesis circulatory dysfunction (PPCD).
  - The risk of PPCD may increase with >8 L of fluid evacuated in one single session.
    - PPCD may results in renal impairment (HRS), dilutional hyponatremia, hepatic encephalopathy, and death
    - Consider giving albumin for smaller volume paracentesis in patients with SBP < 90 mmHg, sodium <130 mmol/L, and/or presence of AKI
- The recommended dose of albumin replacement, based on expert opinion, is 6-8 g for every liter of ascites removed.
  - There are no dose-response studies

- Ascites - Transjugular Intrahepatic Portosystemic Shunt (TIPS)
  - Careful patient selection is the key to the success of TIPS in the management of RA
    - High MELD score (>18) suggests that the patient is a poor candidate for TIPS
    - Best: younger patients with low MELD scores, receiving smaller diameter covered stent, complete response to TIPS with total elimination of ascites
    - Worst: advanced age, cardiopulmonary insufficiency pulmonary hypertension (PHT) and sarcopenia
  - With correction of PHT: there is gradual suppression of activated neurohormonal vasoconstrictive systems over 4-6 mon
    - Discontinue diuretics after TIPS as they ↓ intravascular volume, and may delay ascites clearance
    - Continue sodium-restricted diet after TIPS
  - A small diameter coated stent of less than 10 mm is preferred to ↓ likelihood of post-TIPS complications, including hepatic encephalopathy
  - If ascites recurs after initial clearance
    - TIPS venogram should be considered, and
    - TIPS revision should be performed if stenosis is identified
      - In these patients, periodic Doppler ultrasound surveillance should be considered.
    - Complications may arise from the insertion procedure, TIPS prosthesis, or presence of a shunt
  - Do **not** use indwelling catheters
    - The average bacterial infection rate was 13%

- An automatic low flow ascites pump is not available in Canada
  - This implantable battery powered pump transports ascites from peritoneal cavity to bladder
  - ↓ need for paracentesis, ↑ QoL / nutritional status
- LT should be considered in patients with RA (please see diagram below)
  - Ascites after LT may take weeks to months to correct
- Based on currently available data, NSBBs are **not** necessarily contraindicated in patients with RA.
  - However, caution is recommended in patients with hypotension, hyponatremia, or AKI.
  - There is conflicting data between studies on development of AKI and mortality

- Treatment algorithm for management of RA



All three criteria should be met for diagnosis of RA.

1. Typically 160 mg furosemide and 400 mg spironolactone used without success
2. Post-paracentesis circulatory dysfunction (PPCD)
3. For example, MELD >18. Abbreviation: LT, liver transplant.

Printed with permission: Biggins SW, et al. Hepatology 2021;74(2):1014-1048 (Figure 3).

➢ Ascites Complications

- **Hyponatremia** (↓ Na_s^+)
  - Mild hyponatremia (Na_s^+ 126-135 mEq/L) in cirrhosis without symptoms does not require specific management apart from monitoring and water restriction.
    - Acute natremia much less common than chronic ↓ Na_s^+
    - Hypovolemic hyponatremia
      - Discontinue diuretics/laxatives, and provide fluid resuscitation with 5% albumin or Ringer's lactate
    - Euvolemic = treat underlying cause
    - Hypervolemic = fluid restriction, reduction/discontinuation of diuretics/laxatives
    - Give 25% albumin and/or vasopressin receptor antagonists ("vaptans")
  - Water restricted to 1,000 mL/day and cessation of diuretics is recommended in the management moderate hyponatremia (120-125 mEq/L), and
    - A more severe restriction of water intake with albumin infusion is recommended for severe hyponatremia (<120 mEq/L).
    - Greater water restriction is poorly tolerated
  - The use of vasopressin receptor antagonists in cirrhosis can ↑ Na_s^+ during treatment.
    - However, they should be used with caution only for < 30 days
      - Tolvaptan **not** approved for treatment of hyponatremia in Canada
  - The use of hypertonic saline is reserved for short-term treatment of
    - Symptomatic or
    - Severe hyponatremia, or
    - Those with imminent LT
    - Patients who undergo LT and have ↓ Na_s^+ are at risk of infections, renal failure and ODS (rare)
  - When correction of chronic hyponatremia is indicated in patients with cirrhosis, the goal rate of increase of serum (Na_s^+) is 4-6 mEq/L per 24-h period, and not to exceed 8 mEq/L per 24-h period to ameliorate the risk of ODS.
    - ODS more common with advanced liver disease, alcoholism, severe ↓ Na_s^+, malnutrition and prior encephalopathy
  - Severe hyponatremia (<120 mEq/L) at time of LT → ↑ risk of osmotic demyelination syndrome (ODS) with LT. A multidisciplinary coordinated care may ↓ risk of osmotic dysfunction syndrome (ODS).

- **Hepatic Hydrothorax** (HH)
  - Transudative pleural effusion
    - Usually unilateral, R>L
    - A serum to pleural albumin gradient >11 suggests HH
  - Confers a poor prognosis in hospitalized patients (74% mortality in 90 days), despite low MELD score

- May be complicated by
  - Spontaneous bacterial empyema
  - Progressive respiratory failure
  - Trapped lung, and
  - Complications of thoracentesis
- First-line therapy of HH consists of dietary sodium restriction and diuretics plus thoracentesis as required.
  - If ascites is present, then additionally perform LVP with IV albumin
- TIPS can be considered in selected patients as a second-line treatment for refractory hepatic hypothorax (HH).
- Do **not** insert
  - Chest tube for HH (chest tubes associated with high morbidity and mortality), but
  - Consider indwelling tunneled catheters in carefully selected patients who do **not** respond to medical therapy and are not candidates for TIPS.
  - Indwelling tunneled catheters have ↓ infections, ↓ fluid reaccumulating and ↓ need for pleurodesis
- Patients with HH should be considered for LT
  - For MELD exception documentation, should include the following:
    - ≥ 1 thoracentesis >1 L weekly in the last 4 wk (record date and volume)
    - Proof of transudative fluid
    - No evidence of heart failure
    - Pleural fluid culture negative on 2 separate occasions
    - Pleural fluid cytology is benign on 2 separate occasions
    - There is contraindication to TIPS
    - Diuretic refractory

- **Abdominal Hernia**
  - Elective hernia repair in cirrhosis is best performed via a multidisciplinary approach after ascites has been controlled and the patient's overall condition, including nutritional status, has been optimized.
    - Optimal fluid control with diuretics, appropriate nutrition and conservative management with binders may improve hernias
    - LVP may paradoxically cause incarceration
    - Hernia prosthetic mesh reduces recurrence but may increase risk of infection
  - Consider TIPS insertion prior to elective hernia repair, or
    - After an emergent operation in patients with cirrhosis and uncontrolled ascites.
    - Ascites ↓ wound healing, and ↑ risks of spontaneous bacterial peritonitis (SBP)

- **Spontaneous Bacterial Peritonitis** (SBP)
  - One-third of admitted for cirrhosis have bacterial infections including:
    - Spontaneous - SBP, bacteremia and spontaneous bacterial empyema accounting for 36% of infections
    - Urinary tract infection (UTI) (22%)
    - PNA (19%)
    - Skin/soft tissue infections (8%)
  - The ascitic fluid should be cultured at the bedside in aerobic and anaerobic blood culture bottles before initiation of antibiotics.
    - Start empiric antibiotics after paracentesis if high suspicion for infection
    - Mortality increases by ~10% every hour without antibiotics in cirrhotics with septic shock
    - Most commonly Escherichia coli, followed by Klebsiella pneumoniae, Staphylococcus aureus, Enterococcus faecalis, and Enterococcus faecium
  - Patients with ascites due to cirrhosis emergently admitted to the hospital should undergo a diagnostic abdominal paracentesis to rule out SBP even in the absence of symptoms/signs of infection.
  - Patients with ascites who develop signs, symptoms, or laboratory abnormalities suggestive of infection should undergo workup for infection plus a diagnostic abdominal paracentesis (for cell count and bacteriological culture).
    - If the workup is negative and the patient has a pleural effusion
      - The patient should undergo a diagnostic thoracentesis.
    - Suggestive signs: fever, chills, localizing symptoms or deterioration with HE, AKI and/or jaundice
    - Paracentesis should be performed for any cirrhotic patient with ascites who is hospitalized for any reason
  - The diagnosis of SBP or spontaneous bacterial empyema (SBE) is established with a fluid Polymorphonuclear (PMN) leukocyte count >250/mm^3.
    - If positive ascites culture but PMN < 250/mm^3, do **not** treat
  - IV antibiotics should be started empirically in all patients with an ascites/pleural fluid PMN count >250/mm^3•
  - First-line empirical antibiotic therapy for community-acquired SBP/SBE is IV third-generation cephalosporin.
  - Empirical therapy with broad-spectrum antibiotics should be initiated as the first line of treatment in patients with
    - A health care-associated or nosocomial infection, or
    - Recent exposure to broad spectrum antibiotics, or
    - Who are admitted with sepsis or septic shock,
    - Carbapenem as first line for critically ill or nosocomial patients leads to higher resolution of SBP
    - Assess for history of multi-drug resistant organisms or recent antibiotic exposure

- Response to empirical antibiotic therapy may be assessed by repeating diagnostic paracentesis/thoracentesis 2 days after initiation.
  - A ↓ fluid PMN <25% from baseline indicates lack of response → broaden antibiotic coverage and
    - Further evaluation to rule out secondary bacterial peritonitis.
  - Unnecessary if organism is
    - Isolated
    - Susceptible to the antibiotics, or
    - Patient is improving clinically
- Patients with SBP should be treated with IV albumin in addition to antibiotics (1.5 g/kg at day 1 and 1 g/kg at day 3).
  - Patients with AKI and/or jaundice at time of diagnosis of SBP are more likely to benefit from albumin.
  - IV albumin expands intracellular volume, ↓ risk of AKI, and ↑ survival
- NSBBs should be temporarily held in patients with SBP who develop hypotension (mean arterial pressure < 65 mmHg) or AKI.
- Patients who have recovered from an episode of SBP should receive long-term prophylaxis with daily norfloxacin (poor evidence for use of Septra DS). In settings where norfloxacin is unavailable, oral ciprofloxacin is acceptable.
- Antibiotic prophylaxis for SBP should be instituted in all patients with cirrhosis and upper GI hemorrhage.
  - IV ceftriaxone 1 g / 24 h is the antibiotic of choice, and should be used for a maximum of 7 days.
  - Continue until hemorrhage resolves and vasoactive drugs are discontinued
  - Prophylaxis reduces SBP recurrence, but not 3-mon survival
  - Short term treatment prior to LT suggested
- In patients with cirrhosis and low protein (<1.5 g/L) ascites
  - Use primary SBP prophylaxis in selected patients with
    - Renal dysfunction (severe serum creatinine level >1.2 mg/dL), or
    - Blood urea nitrogen level >25 mg/dL, or
    - Serum sodium level <130 mEq/L), or
    - Liver failure (Child Pugh-Turcotte score >9 and bilirubin >3 mg/dL)
    - ↓ ascitic complement levels and opsonic activities → ↑ SBP risk

➢ Treatment

Spontaneous Bacterial Peritonitis (SBP) in persons with Cirrhosis; Antibiotics Prophylaxis

Komolafe O, et al. Antibiotic prophylaxis to prevent spontaneous bacterial peritonitis in people with liver cirrhosis: a network meta-analysis. Cochrane Database of Systematic Reviews 2020, Issue 1. Art. No.: CD013125. DOI: 10.1002/14651858.CD013125.pub2

- There were 23 randomized clinical trials of from 1 to 12 mon, of 2587 participants; 9 antibiotic regimens (ciprofloxacin, neomycin, norfloxacin, norfloxacin plus neomycin, norfloxacin plus rifaximin, rifaximin, rufloxacin, sparfloxacin, sulfamethoxazole plus trimethoprim), no active intervention in the review of people with cirrhosis due to varied etiology, with or without other features of decompensation, and having ascites with low protein or previous history of spontaneous bacterial peritonitis.
  - About 10% of the patients developed SBP, and 15% of the trial participants died
  - No difference between antibiotics or no antibiotics for prophylaxis of SBP in terms of

Outcome
Development of SBP
Liver transplantation
Mortality
Any adverse events (AEs)
Serious AEs
Number of compensation events

Certainty evidence for all of above, very low

- No evidence of any differences in the subgroup analyses (performed when possible) based in whether the prophylaxis was primary or secondary.

	RR, 95%CI	Certainty of Evidence
Lowest rate of AEs		
Norfloxacin	RR, 0.74; 95%CI: 0.59 to 0.94	Low
Sulfamethoxazole plus trimethoprim	RR, 0.19; 95%CI: 0.02 to 0.81	Low
Lowest rate of other decompensation events		
Rifaximin	RR, 0.61; 95%CI: 0.46 to 0.80	Low
Norfloxacin plus neomycin	RR, 0.06; 95%CI: 0.00 to 0.33	Low

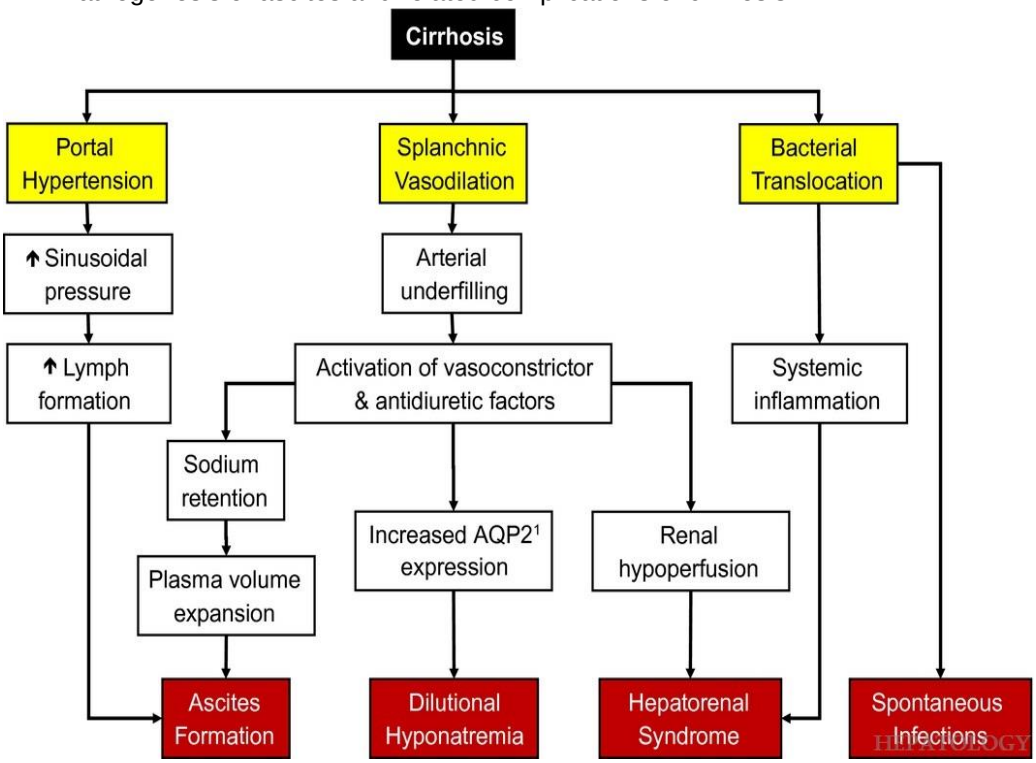
❖ **Hepatorenal Syndrome** (HRS-AKI)

➢ Demography

- AKI very common is hospitalized patients with cirrhosis and ascites (27%-52%)
- Development of AKI associated with ↑ 30-day mortality of 29% to 44%

- Pathophysiology
  - ↓ renal perfusion secondary to renal vasoconstriction, mediated by ↑ activities of
    - Sympathetic nervous system
    - Renin-angiotensin-aldosterone system (RAAS)
    - Vasopressin system
  - ↓ renal autoregulation
  - ↓ cardiac output from cirrhosis-associated cardiomyopathy
  - Immune mediated from systemic inflammation

- Pathogenesis of ascites and related complications of cirrhosis



  - The central event consists of ↓ effective arterial volume (EAV)
  - Splanchnic vasodilation leading to → activation of vasoconstrictor (e.g., renin-angiotensin) and antidiuretic (e.g., arginine vasopressin) factors → portal hypertension → ↑ sinusoidal hydrostatic pressure / ↑gut permeability → bacterial translocation, contributes further to the pathogenesis of complications associated with ascites, including hyponatremia, AKI, HRS, and spontaneous bacterial infections.

Abbreviation: AQP21, Aquaporin-

Printed with permission: Biggins SW, et al. Hepatology 2021;74(2):1014-1048 (Figure 1).

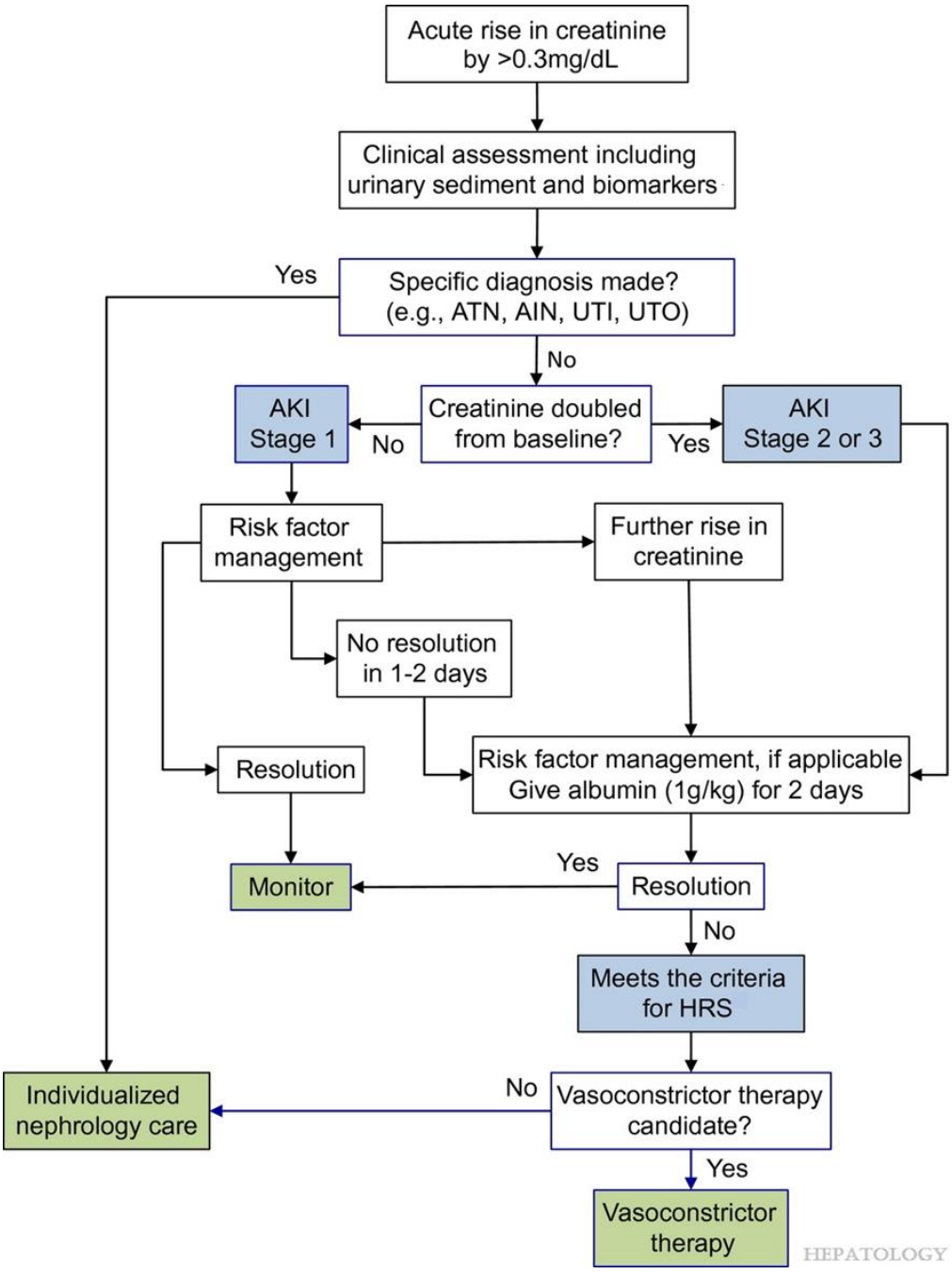
- Stages of AKI
  - Stage 1 - ↑Cr_s >26.5 µmol/L to 2-fold of baseline
  - Stage 2 - ↑Cr_s between 2-fold to 3-fold of baseline
  - Stage 3 - ↑Cr_s >3-fold of baseline or Cr_s >353.6 µmol/L plus an acute increase >26.5 µmol/L, or initiation of renal replacement therapy (dialysis)
  - Once AKI is diagnosed, treat precipitating factors:
    - Fluid losses
    - Bacterial infections
    - Hemodynamic instability, and
    - Potentially nephrotoxic agents (e.g., particularly nonsteroidal anti-inflammatory drugs [NSAIDs]).
    - Main causes in cirrhotics are
      - Pre-renal AKI (hypovolemia or HRS), and
      - Acute kidney injury (ATN)
    - Investigations: urine sediment, fractional excretion of sodium or urea, and urine sodium in patients receiving diuretics
  - Hypovolemia-induced AKI should be managed with
    - Fluid replacement therapy
    - Correction of the cause that led to volume depletion, and
    - Diuretic withdrawal
    - Withhold NSBBs in hypotensive patients (SBP <90 mmHg)
  - Differential diagnosis of AKI, HRS, and ATN is challenging and should follow the consensus criteria presented in the algorithm.
    - Diagnosis of HRS-AKI requires:
      - Cirrhosis with ascites
      - ↑Cr_s >26.5 umol/L from baseline within 48 h, or a percent increase in Cr_s >50% which is known or presumed to have occurred within the preceding 7 days
      - Absence of shock
      - No current or recent nephrotoxic drugs
      - No structural kidney disease indicated by proteinuria (>500 mg/day), microhematuria (>50 RBC/hpf) and/or normal renal US

- Treatment
  - The treatment of choice is vasoconstrictor drugs plus albumin.
    - The preferred drug is terlipressin, administered either as IV bolus or continuous IV infusion.
    - Terlipressin not available in US or Canada
    - Give albumin 1 g/kg on day 1, then 40-50 g/day

- In settings where terlipressin is not available, give norepinephrine (NorEpi).
  - If neither can be administered, a trial of oral midodrine (5 to 15 mg po every 8 h) in combination with octreotide (100 to 200 µg every 8 h or 50 µg/h IV) may be considered, yet the efficacy is low.
  - NorEpi given as an infusion at 0.5 mg/h up to 3 mg/h to ↑ mean arterial pressure (MAP) by 10 mmHg and ↑ urine output >200 mL over 4 h
  - Do **not** use TIPS (insufficient studies)

- Patients should be closely monitored for the possible development of side effects of vasoconstrictors and albumin, including
  - Ischemic complications (fingers, skin, intestines, or heart), and
  - Pulmonary edema.
  - Abdominal pain (ischemia)
- Response to terlipressin or norepinephrine is defined by
  - Cr_s decreasing to <132.6 µmol/L or
  - Return to within 26.5 µmol/L of baseline over a maximum of 14 days
  - In patients whose creatinine remains at or above the pre-treatment level for > 4 days with the maximum tolerated doses of the vasoconstrictor, therapy may be discontinued.
  - Cases with very high pre-treatment Cr_s may need longer treatment than 14 days
- Recurrence may occur after treatment discontinuation, and should be retreated.
- All cirrhosis patients with AKI should be considered for urgent LT evaluation given the high short-term mortality even in responders to vasoconstrictors.
  - Improvement in MELD score after treating HRS does not correlate with ↑ survival
- Use renal replacement therapy (RRT) in liver transplant (LT) candidates with
  - ↑renal function, or
  - Electrolyte disturbances, or
  - ↑ volume overload unresponsive to vasoconstrictor therapy
- Initiation of RRT in patients who are not candidates for LT must be made with a clear endpoint in mind.
  - Mortality rates extremely high in patients on RRT not listed for LT despite the cause
- In patients with suspected HRS-AKI, decisions about management including initiation of vasoconstrictor therapy and RRT should be made, if possible, by multidisciplinary teams including specialists in hepatology, nephrology, critical care, and transplant surgery.
- Simultaneous liver-kidney transplantation may be necessary for patients who are not expected to recover kidney function post transplantation.
  - Risk factors for poor renal recovery include CKD, diabetes, unrecognized renal disease, unexpected intraoperative events, and post-transplant immunosuppression.
  - Eligibility criteria for simultaneous liver-kidney transplant:
    - AKI >6 wk with RRT (dialysis) and/or eGFR/CrCL <25 mL/min
    - CKD with eGFR <60 mL/min for >90 days with ESRD or eGFR <30 mL/min
    - Metabolic diseases
    - Safety net: Increased priority for patients on kidney waitlist between 60-365 days after liver transplantation, and is on dialysis or eGFR < 20 mL/min

- Proposed algorithm for the diagnosis and management of AKI in patients with cirrhosis.



Printed with permission: Biggins SW, et al. Hepatology 2021;74(2):1014-1048 (Figure 4).

- The key diagnostic steps include
  - (1) clinical assessment and examination of urinary sediments and biomarkers,
  - (2) response to risk factor management, and
  - (3) response to albumin infusion.
  - Clinical assessment includes
    - Evaluation for prerenal (e.g., overdiuresis, dehydration), or structural (e.g., shock, nephrotoxins, obstructive uropathy) etiologies.
- Urinary sediments and biomarkers (particularly NGAL) may indicate ATN, whereas
  - Fractional excretion of sodium <1% may suggest HRS.
- Risk factor management includes
  - The withdrawal of nephrotoxic drugs
  - Reduction or withdrawal of diuretics
  - Detection/treatment of infections, if present, and
  - Volume replacement (if severely volume-depleted) using 5% albumin or crystalloids.
- Patients experiencing a further rise in serum creatinine despite risk factor management may immediately proceed to albumin challenge (some members of the writing group advocate taking into account the absolute creatinine value in addition to the change in creatinine to expedite this step to allow earlier institution of vasoconstrictors in patients with a high (e.g., >1.5 mg/dL) creatinine).
- These patients are expected to have
  - Ascites, commonly refractory, and almost always hyponatremia

Abbreviations: AIN, acute interstitial nephritis; UTI, urinary tract infection; UTO, urinary tract obstruction

- Ascites in cirrhosis in children
  - Diagnosis of ascites and its cause in children requires a comprehensive evaluation of clinical history, examination, and diagnostic testing including abdominal ultrasound.
  - Common causes in children include biliary atresia, PSC, autoimmune hepatitis, cholestatic genetic disorders, Wilson's, A1AT, and other genetic disorders
    - In newborns causes include
      - Congenital infections
      - Mitochondrial disorders
      - Tyrosinemia
      - Biliary atresia

- Children with cirrhosis and ascites should be referred for evaluation for LT.
- Ascites in children is initially managed with
  - Restricted sodium intake to < 2 mmol/kg per day and
  - Administration of spironolactone (1-4 mg/kg per day) and furosemide (1-Jmg/kg per day in divided doses).
  - Water restriction recommended when Na^{+}_{s} is <125 mEq/L
- Symptomatic children with grade 3 ascites, or treatment resistant ascites (RA) should usually undergo
  - Therapeutic paracentesis, although
    - The indications, risks, and benefits of this procedure in children have not been fully defined.
  - Will require general anesthesia or deep sedation for paracentesis
- Children undergoing LVP should receive 25% albumin infusion of 0.5-1.0 g/kg, or 6-8 g per liter of ascites removed.
- Diagnostic paracentesis should be performed in children with ascites and fever, abdominal pain, or clinical deterioration. The risks and benefits of this procedure for use in all children with new ascites but without these symptoms have not been defined.
  - SBP defined by PMN >250/mm^3
- Children with proven or suspected SBP should be treated with broad-spectrum antibiotic cover against both Gram-positive and Gram-negative organisms.
- No recommendation can be given for the management of AKI and HRS in children with cirrhosis because of the absence of relevant definitions and lack of data on treatment and outcomes

EASL Clinical Practice Guidelines on the Management of Ascites, Spontaneous Bacterial Peritonitis, And Hepatorenal Syndrome in Cirrhosis

European Association for the Study of the Liver. J Hepatol 2010;53(3):397-417.

❖ Ascites / Spontaneous Bacterial Peritonitis (SBP)

- Paracentesis
  - Diagnostic
    - Indications
      - All new onset ascites grade 2/3 ascites
      - All patients hospitalized for
        - ↑ ascites
        - Any complications of cirrhosis
    - Laboratory
      - Diagnostic paracentesis "…should be carried out in all patients with cirrhosis and ascites at hospital admission to rule out spontaneous bacterial peritonitis (SBP)"
    - Tests
      - WBC, including polymorphonuclear cells (PMN; neutrophils)
      - Protein < 15 g/L
        - ↑ risk of spontaneous bacterial peritonitis (SBP)
        - Consider prophylactic antibiotics
      - Culture/sensitivity
      - Lipase/amylase
      - Serum ascites albumin gradient (SAAG)
        - Diagnose
          - Cirrhosis
          - Different causes of cirrhosis

➢ Treatment

- Low salt diet
  - "No added salt" diet
  - No pre-prepared meals
- Do **not** restrict water intake unless (Na^+_s) (serum sodium concentration) < 120 mmol/L
  - Contraindications
    - ↑↓ K^+_s
    - ↓ Na^+_s
    - ↑ Cr
- Diuretics
  - First correct serum potassium (K^+_s) before initiating diuretics
  - Aldosterone 100 mg po od, increasing in increments of 100 mg to maximum of 400 mg/day
  - If no/inadequate response to salt retention plus aldosterone 400 mg/day → add furosemide 40 mg/d po, increasing by increments of 400 mg up to maximum of 100 mg/d

- Maintain salt respiration plus diuretic in lowest dose needed to maintain patients with no ascites

- Frequent measurement of electrolytes
- Target weight loss in patients with ascites
  - No edema, 0.5 kg per ay
  - Edema, 1 kg per day

Laboratory Alert

- Stop diuretics if
  - K^+_s
    - < 3 mmol/L (furosemide)
    - > 6 mmol/L (aldosterone)
  - Na^+_s < 120 mmol/L
  - Muscle cramps
    - Drugs

  - Drugs to avoid in patients with ascites
    - NSAIDs
    - ACEIs, ARBs, α1-adrenergic receptor blocker
    - Aminoglycosides
    - Contrast material
    - PPIs (↑ risk of SBP)

MCQ Alert

- Give the mechanism of the benefit of giving albumin infusion in patient having paracentesis.
  - Albumin IV is a plasma expands which ↓ risk of post-paracentesis circulating dysfunction (which may ↑ risk of SBP/HRS)

- Large volume paracentesis (LVP)
  - Failed first line therapy
  - Predose with albumin
  - Prevent reaccumulation of ascites by using low dose diuretics

- If patient reaccumulates ascites despite
  - ↓ salt intake / diuretics
  - Consider
    - Repeat therapeutic paracentesis
    - TIPS procedure
    - Assessment for liver transplantation

- Definition and diagnostic criteria for refractory ascites in cirrhosis.
  - Diuretic-resistant ascites
    - Ascites that cannot be mobilized or the early recurrence of which cannot be prevented because of a lack of response to sodium restriction and diuretic treatment
  - Diuretic-intractable ascites
    - Ascites that cannot be mobilized or the early recurrence of which cannot be prevented because of the development of diuretic-induced complications that preclude the use of an effective diuretic dosage
  - Requisites
    - Treatment duration
      - Patients must be on intensive diuretic therapy (spironolactone 400 mg/day and furosemide 160 mg/day) for at least 1 wk and on a salt-restricted diet of less than 90 mmol/day
    - Lack of response
      - Mean weight loss of <0.8 kg over 4 days and urinary sodium output less than the sodium intake
    - Early ascites recurrence
      - Reappearance of grade 2 or 3 ascites within 4 wk of initial mobilization
    - Diuretic-induced complications
      - Diuretic-induced hepatic encephalopathy is the development of encephalopathy in the absence of any other precipitating factor
      - Diuretic-induced renal impairment is an increase of serum creatinine by >100% to a value >2 mg/dL (177 µmol/L) in patients with ascites responding to treatment
      - Diuretic-induced hyponatremia is defined as a decrease of serum sodium by >10 mmol/L to a serum sodium of <125 mmol/L
      - Diuretic-induced hypo- or hyperkalemia is defined as a change in serum potassium to <3 mmol/L or >6 mmol/L despite appropriate measures

Printed with permission: European Association for the Study of the Liver. J Hepatol 2010;53(3):397-417 (Table 3).

Therapeutic Alert

- Do **not** use TIPS when
  - CP score > 11
  - HE
    - Current ≥ grade 2
    - Chronic
  - Laboratory
    - Bilirubin > 5 mg/dL
    - INR > 2
  - Comorbidities
    - Infection, active
    - Renal failure (↑ Cr_s)
    - Cardiopulmonary disease, severe

Clinical Gem

- In patients with symptomatic, non-response hepatic hydrothorax
  - TIPS might be of benefit

Abbreviations: ACEI, angiotensin counting enzyme inhibitors; ARBs, angiotensin receptor blockers; Cr_s, serum creatinine; ECF, extracellular fluid; HE, hepatic encephalopathy; HRS, hepatorenal syndrome; K^+_s, serum potassium concentration; LVP, large volume paracentesis; MELD, Model for End Stage Liver Disease; Na^+_s, serum sodium concentration; NSAIDs, non-steroidal anti-inflammatory drugs; SAAG, serum albumin ascites gradient; SBP, spontaneous bacterial peritonitis; SBP, systolic blood pressure; SBPEs, spontaneous bacterial pleural enzymes; TIPS, transjugular intrahepatic portal shunt

❖ Spontaneous Bacterial Peritonitis (SBP)

➢ Laboratory

- Diagnostic paracentesis "…should be carried out in all patients with cirrhosis and ascites at hospital admission to rule out spontaneous bacterial peritonitis (SBP)"

- Clinical suspicion of SBP
  - New onset ascites
  - Worsening ascites
  - Worsening failure liver +/- kidney function
  - Hepatic encephalopathy (HE)
  - GI bleeding [not necessarily esophageal variceal bleeding (EVB)
  - Hypotension / shock
  - Pulmonary hydrothorax (spontaneous bacterial pleural empyema a possible complication, and associated with SBP)
  - Fever

  - Diagnosis of SBP
    - PMN > 250/mm^3
    - Culture of ascitic fluid /blood (in the event of bacteremia but negative culture of SBP) perform total protein (if ↑, then ↑ risk of SBP, complications)
    - Bacterial ascites is a form of SBP
      - Ascitic fluids PMN < 250 mm^3, but
      - Ascitic culture positive
      - Repeat paracentesis, and treat if
        - Second culture is positive
        - Second PMN again
          < 250/mm^3 → follow but no antibiotic
          > 250/mm^3 → antibiotics

Clinical Pearl

- SBP → hepatic hydrothorax may develop into spontaneous bacterial empyema (SBPE)
- "Diagnostic thoracentesis should be performed in patients with pleural effusion and suspected infection with vasculation of fluid into blood culture bottles
- Diagnosis
  - Pleural fluid PMNs
    > 250/mm^3 plus positive culture
    < 250/mm^3 plus negative culture
- Treat SBPE the same as SBP

➢ Diagnosis imaging

- CT scan of abdomen id secondary bacterial peritonitis is suspected

➢ Treatment

- Antibiotics
  - Immediately upon diagnosing SBP (and before culture results available (affective in ~90%)
    - Cephalosporins e.g., ceftriaxone
    - Amoxycillin/clavulanic acid
    - Ciprofloxacin

MCQ Trick

- Give the circumstance under which quinolones such as ciprofloxacin would not be used empirically to treat CBP.
  - Do **not** use a quinolone for first-line therapy for SBP if the patient was previously taking a quinolone for prophylaxis for recurrence of a previous episode of SBP.
    - Other contraindication
      - Nosocomial SBP
      - High community presence of bacterial resistance to quinolones

  - Repeat paracentesis after 48 h of antibiotics
    - Empirical regimen, as shown above, effective in 90%
    - "effective" defined as
      - PMN < 250/mm^3, and
      - Ascitic fluid culture negative
      - ↓ symptoms / signs e.g., fever

        ↓
    - If organisms on culture not sensitive to empirical antibiotics, and
      - Secondary bacterial peritonitis excluded (multiple organisms)
      - "…antibiotics should be changed according to in vitro susceptibility of isolated organisms, or modified to alternative empiric blood spectrum agents"
  - Albumin infusions
    - 1.5 g/kg at diagnosis of SBP, then on day 3 give second albumin infusion of 1.0 g/kg
      - The addition of albumin to antibiotics →
        - ↓ HRS frequency
        - ↓ mortality

➢ Prophylaxis against SBP

- Patient with chronic liver disease / cirrhosis plus
  - GI bleeding (no previous SBP)
  - Compensated → norfloxacin 400 mg/d po
  - Decompensated → ceftriaxone IV
  - Ascitic fluid total protein < 15 g/L and
    - No prior SBP
    - Previous SBP

    } Norfloxacin 400 mg/d po
- Other antibiotics for SBP prophylaxis
  - Norfloxacin 400 mg po od: ciprofloxacin 750 mg po per wk, or
  - Clotrimazole (800 mg sulfamethoxazole plus 160 mg trimethoprim po od)
- Patients who recover from SBP have a poor long-term survival and should be considered for liver transplantation.

❖ Hepatorenal syndrome (HRS)

- Renal failure in cirrhosis is associated with SBP, even when treated with appropriate antibiotics and albumin infusions (in 30%)
- Suspect non-HRS associated parenchymal renal disease in patient with cirrhosis and renal dysfunction if this is
  - Urinalysis
    - Proteinuria / albuminemia
    - Microhematuria
  - Ultrasound
    - Abnormalities in size of kidneys
- For practical therapeutic purpose, HRS is diagnosed "…only when serum creatinine increases > 133 µmol/L (1.5 mg/dL)"
  - "Repeat measurement of serum creatinine [concentration] is helpful in the early identification of HRS"

➢ Monitoring/Screening

- Renal function
  - Blood
    - Serum creatinine
  - Urine
    - Urine output per day, fluid balance
  - Vital signs, including antral blood pressure
- Infection
  - Blood, urine, ascitic fluid cultures
    - Continue prophylactic antibiotics for SBP, and treat other infections by early diagnosis, cultures and empirical antibiotics

❖ Hyponatremia

- Hypovolemic hyponatremia
  - ↓ Na^+_s with no associated ascites/edema
- Hypervolemic hyponatremia
  - ↓ Na^+_s with ascites / edema
    - Thought to be due to "…prolonged negative sodium balance with marked loss of extracellular fluid"
- Treatment
  - Treat underlying disease
  - Fluid restriction to ~1000 mL/d only if Na^+_s < 125 mmol/L
    - Avoid increasing Na^+_s by > 8 mmol/d (to prevent osmotic demyelination syndrome)
  - Limit data on use of albumin IV
  - Tolvaptan po
    - Initial po fluid restriction or IV saline
    - Avoid drugs with ↑ CYP3A
- Terlipressin (vasoconstrictor therapy)
  - 1 mg q4-6 h IV bolus plus albumin may be used in type 1 HRS to slowly ↓ Cr_s to < 133 µmol/L (1.5 mg/dL)
  - Dose may be ↑ to maximum of 2 mg/4h
  - Adverse effects
    - Ischemia
      - Heart (coronary arteries)
      - Splanchnic circulation
      - Fingers
    - Fluid overload
- Renal replacement therapy (RRT)
- Liver transplantation (LT)
  - Exception MELD points for HRS
  - Optimize treatment of HRS before LT for type I/II HRS
  - Consider combined liver plus kidney transplantation in persons with HRS who required renal replacement therapy for > 12 wk

• Prevention of HRS

- Treat SBP → ↓ risk of HRS (antibiotics, albumin)
- ↓ risk of SBP
  - Alcohol hepatitis
    - Pentoxifylline
  - Cirrhosis
    - Pentoxifylline, norfloxacin

- Grading Ascites

Grade	Definition	Treatment
1	− Diagnosed by abdominal ultrasound	▪ None
2	− Moderate symmetrical distention of abdomen	▪ ↓ salt intake to 2 g/d ▪ Diuretics
3	− Gross ascites /marked abdominal distention	▪ Add large volume paracentesis to ↓ salt intake plus diuretics

- Investigation

Recommendations

- Perform diagnostic abdominal paracentesis
  - Consider LT assessment of ascites 2/3 development
  - New onset ascites grade 2/3 (Level A1)
  - Hospitalization
    - ↑ ascites
    - Any complication of cirrhosis (Level A1)

- Laboratory measurements of ascitic fluid
  - Neutrophil count
  - Albumin / total protein concentration < 15 g/L indicates ↑ risk of SBP (SAAG gradient) (Level A-1)

- Treatment

Recommendations

Grade 2/3 Ascites

- ↓ salt intake to 2 g/d (no added salt, no pre0prepared needs) (Level B1)
  - Do **not** restrict water intake unless hyponatremia of Na^{+}_{s} < 100 mmol/L
- Do **not** direct bed rest for patient (Level B1)

- Diuretics
  - Aldosterone 100 mg po / d, ↑ dose 100 mg q7d until response to maximum of 400 mg/d
    - If body weight of patient is < 2 kg/wk, or
    - If hyperkalemia develops

    } Begin furosemide 40 mg/d po, increasing to maximum of 160 mg/d depending upon weight response (Level A1)
  - Continue 2g/d salt diet
  - Monitor body weight and serum electrolytes frequently, especially during first month
  - Adjust to dose of diuretics to the lowest possible to resolve ascites (Level B1)
- Caution when starting diuretics
  - Do **not** use in patient with hepatic encephalopathy (Level B1)
  - Correct serum K+s concentration first
  - Slowly ↑ dose of presence of
    - Hyponatremia
    - ↑ Cr_s (renal dysfunction)
- Stopping rules for diuretics (level B1)
  - Na^+_s < 120 mmol/L
  - ↑ Cr_s (serum creatinine)
  - ↑ HE (hepatic encephalopathy)
  - Severe muscle cramps
  - Stop
    - Aldactone if K+s > 6 mmol/L
    - Furosemide K+s < 3 mmol/L

  (Level B1)

- Recurrent Ascites
  - Use combination of Aldactone plus furosemide in ratio of 4:1, in increasing doses depending upon patient's response (Level A1)
    - Continue 2 g/d salt diet
  - Maximum recommended weight loss per day while patient is on diuretics
    - No edema, 0.5 kg/day
    - With edema, 1.0 kg/day

    (Level A1)

- Grade 2 Ascites
  - Large volume paracentesis (LVP) is the treatment of choice, plus
    - Albumin 8 g per litre (L) ascitic fluid removed (Level A1)
      - Do **not** substitute other plasma expanders to prevent post-paracentesis circulatory dysfunction, and give the albumin for all LVTs used for grade 3 ascites, regardless of the volume removed (Level B1)
  - Following LVP plus albumin
    - Use lowest effective dose of diuretics to prevent recurrence of ascites

- Contraindications in patients with ascites

Drug Class	Adverse Effects
– NSAIDs	▪ ↑ Na^+ retention, ↓ Na^+_s, ↑ Cr_s
– ACEI/ARPs	▪ ↑Cr_s (renal impairment)
– Aminoglycosides	▪ ↑ Cr_s (renal impairment)

  - Contrast material for diagnostic imaging
    - Use guidelines for cautious use
    - ↑Cr_s (renal impairment)

    (Level A1)
  - PPIs
    - Avoid unless absolutely necessary

- Refractory Ascites
  - Effectiveness (weight loss) of diuretic therapy plus 2 g salt diet must be monitored when the patient is stable, e.g., hemorrhage, infection (Level B1)
  - Consider patient for liver transplant (LT) if they develop refractory ascites (Level B1)
  - Subtypes

➢ Treatment of grade 3 ascites

- LVP plus albumin plus low salt diet plus diuretics
  - Stop diuretics if Na^+< 30 mmol while patient is on diuretics
- TIPS
  - Indications
    - Requirement for frequent LVPs
    - Ineffective LVP (loculated ascites) (Level B1)
    - Selected patients with symptomatic recurrent hepatic hydrothorax
  - Problems
    - ↑ risk of hepatic encephalopathy onset / worsening
    - Lack of improvement of survival rate (Level A1)
    - Slow benefit and requirement to continue low salt diet and diuretics (Level B1)
  - Contraindications
    - Laboratory
      - Serum bilirubin > 5 mg/dL
      - INR > 2
    - Hepatic encephalopathy (HE)
      - Current HE ≥ grade 2
      - Chronic HE
    - Child-Pugh score > 11
    - Active infection
    - Renal failure, progressive
    - Cardiopulmonary disease, severe (Level B1)

- Spontaneous Bacterial Peritonitis (SBP)
  - Indications for diagnostic paracentesis
    - All patients with cirrhosis plus ascites
    - GI/Liver
      - GI bleeding
      - GI symptoms
      - Hepatic encephalopathy
      - ↓ing hepatic function
    - Kidney
      - ↑ Cr_S (↓ renal function)
    - Systemic inflammation/infection

    (Level A1)
  - Laboratory
    - Diagnostic: PMN (neutrophils) > 250 / mm^3 on microscopy of ascitic fluid (Level A1)
    - Blood / ascitic fluid cultures before starting empirical antibodies
    - A positive urine culture is not necessary to diagnose SBP (Level A1)
    - A positive ascitic fluid but negative PMN count (bacterial ascites)

      → Antibiotics if patients have signs of systemic infection / inflammation (Level A1)

      → Repeat diagnostic paracentesis
        - If PMN > 250/mm^3 → antibiotic
        - If PMN < 250/mm^3 → follow

        (Level B1)
  - Treatment
    - Empirical antibiotics against gram-negative aerobic bacteria
      - Third-generation cephalosporins
      - Amoxycillin/clavulanic acid
      - Quinolones (do **not** use for acute SBP if patient already taking quinolones for prophylaxis against a previous episode of SBP)
    - Repeat diagnostic paracentesis after 48 h of antibiotics, and perform PMN count, culture of ascitic fluid (if initial culture at time zero was positive) (Level A1)
      - Alter antibiotics depending on result of first diagnostic paracentesis
      - Assess for possible LT

      (Level A1)

  - SBP must be treated with both antibiotics plus albumin infusion
    - Hospitalization
    - Albumin

      → ↓ risk of SBP progressing to HRS

      → ↑ survival

- Failed antibiotics treatment (10%)
  - Suspicion
    - Clinical
      - Symptoms/signs
    - Laboratory
      - PMN on second vs. first paracentesis
        - Increasing, or
        - Faling to decrease (Level A1)
  - Exclude secondary patients
    - Mild organisms
    - CT scanning (possible perforation)
    - Alter empirical antibiotics / adjust antibiotics depending upon in vitro sensitivity of organisms isolated from initial paracentesis (Level A1)

- Follow up after successful treatment of SBP
  - Antibiotics long term prophylaxis
    - Norfloxacin 400 mg po per day
    - 2nd choices
      - Clotrimazole (800 mg sulfamethoxazole plus 160 mg trimethoprim)
      - Ciprofloxacin 750 mg po q wk
  - Unique considerations for SBP prophylaxis
    - Severe liver disease, GI bleeding
      - Use ceftriaxone for prophylaxis
    - Mild liver disease, alternate to quinolone
      - Norfloxacin (Level A1)
  - Severe liver disease
    - Ascitic fluid protein < 15 g/L even without previous SBP
      - Norfloxacin (Level A1)

- Spontaneous bacterial pleural emphysema
  - Complication of hepatic hydrothorax / pleural effusion
  - Perform diagnostic thoracentesis
  - Laboratory diagnosis on pleural fluid
    - PMN > 250/mm^3, culture positive
    - PMN > 500/mm^3, culture negative

- Hyponatremia (↓ Na^+_s)
    - Hypovolemic
        - Caused by ↓ extracellular fluid (ECF) / total body ↓ Na^+ in absence of ascites/edema
        - Treat underlying cause (e.g., excessive diuretics), plus 0.9% normal saline solution (Level A1)
    - Hypervolemic
        - Causes by ↓ renal excretion of "free water", ↑ ECF / ↑ total body Na^+, usually with ascites / edema
        - Treat underlying cause, plus fluid restriction of 1000 mL/d only when Na^+_s < 230 mmol/L
            - Albumin infusion may be useful in some patients
        - Vaptans, without concomitant fluid restriction or IV saline
            - Slow ↑ Na^+_s (< 100 mm/day, close monitoring to prevent osmotic demyelination syndrome
            - Do **not** use with other drugs which are metabolized by CYP3A (Level B1)

- Hepatorenal Syndrome (HRS)

➢ Definition
- Renal failure [↑ Cr_s > 133 µmol/L, or ↑ing Cr_s; Level B1] in the patients with
    - Advanced liver disease (cirrhosis plus ascites)
    - No identified renal disease
    - No hypovolemia / shock
    - No nephrotoxic drugs

➢ Diagnostic criteria

Criteria for diagnosis of hepatorenal syndrome in cirrhosis.

- Cirrhosis with ascites
    - Serum creatinine >1.5 mg/dl (133 µmol/L)
- Absence of shock
- Absence of hypovolemia as defined by
    - No sustained improvement of renal function (creatinine decreasing to <133 µmol/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 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. J Hepatol 2010;53(3):397-417 (Table 8).

- Suspect primary renal disease if
  - Proteinuria > 500 mg/d
  - Microhematuria > 50 RBCs / hpf
  - Abnormal renal ultrasound
    - Renal biopsy not be required (normal in HRS)

➢ Types of HRS

- Type 1
  - Rapid / progression renal dysfunction
    - ↑ Cr_s ≥ 100% compared with baseline, and
    - Cr_s > 2.5 mg/dL in < 2 wk
- Type 2
  - Slower ↑ Cr_s, or stable ↑ Cr_s

(Level A1)

➢ Treatment

- Type 1
  - Monitor
    - Vital signs / arterial pressure
    - Fluid balance / urine output
    - ICU admission and
    - Consider measurement of central venous pressure (CVP) to manage fluid / electrolyte balance without fluid overload (Level A1)
  - Investigate / treat infection e.g., SBP
    - If SBP previously diagnosed, continue antibiotics (Level C1)
  - Ascites grade 3 (tense ascites)
    - LVP plus albumin infusion (↓ patients discomfort from distention)
  - Furosemide
    - To maintain urine output
    - To reduce central volume overload

(Level A1)

} Otherwise stop diuretics when HRS is diagnosed

- Vasoconstrictors (vasopressin), plus albumin
  - Midodrine, terlipressin plus octreotide, norepinephrine → target Cr_s to < 133 µmol/L
  - If < 25% ↓ Cr_s after 3 d − ↑ dose
  - If Cr_s not < 133 µmol/L – stop vasoconstrictor plus albumin
  - Failure of above therapy
    - Consider renal replacement therapy
    - For subgroup who require renal support for > 12 → liver plus kidney transplantations (Level B2)
  - Contraindications/complications
    - Cardiac − Ischemia / arrhythmias
    - GI − Splanchnic ischemia
    - Skin − Digital ischemia
  - Liver transplantation with/without response to vasoconstrictors plus albumin
  - Recurrence of HRS Type 1
    - Repeat treatment outlined above (Level A1)
  - TIPS procedure
    - Not yet sufficiently supported by data to recommend

- Type 2
  - Vasoconstrictor plus albumin effective in ~65%
    - Liver transplantation

- Prevention of HRS
  - Treat SBP
  - Severe alcoholic hepatitis
    - Pentoxifylline
  - Advanced cirrhosis
    - Norfloxacin (even without SBP)

(Level B)

Abbreviations: Cr_s, serum creatinine; GI, gastrointestinal; HRS, hepatorenal syndrome; LVP, large volume paracentesis; SBP, spontaneous bacterial peritonitis

PORTAL HYPERTENSION

Risk Stratification and Management of Portal Hypertension and Varices in Patients with Cirrhosis: AASLD Practise Guidance (2023)

Kaplan DE, et al. Hepatology. 2023 Oct 23. doi: 10.1097/HEP.0000000000000647. Epub ahead of print. PMID: 37870298.

Most significant changes to this guideline (compared to 2017)

- Recognition of the concept of compensated advanced chronic liver disease (shifting away from requirement of histological or radiological diagnosis of cirrhosis for initial risk stratification.
- Codification of methodology to use non-invasive assessments to identify clinically significant portal hypertension (CSPH)
- Endorsement of a change in paradigm with the recommendation of early utilization of non-selective beta blocker (NSBB) therapy when CSPH is identified in order to decrease risk of decompensation
- Further explores pharmacotherapy for portal hypertension (PH)
- Clarifies role of redemptive TIPS in acute variceal hemorrhage
- Discusses recent data related to management of cardiofundal varices
- Addresses portal hypertensive gastropathy (PHG) and endoscopy prior to TEE and antineoplastic therapy

❖ Context of Portal Hypertension (PH) in Patients with Cirrhosis

➢ Definition

- Portal vein (PV) pressure is proportional to
  - Splanchnic blood inflow
  - The resistance opposing this flow
- PV pressure = PV (inflow to liver) flow – inferior vena cava (IVC) flow (outflow from liver)
  - Measured as a gradient rather than absolute, to reduce influence in change from the intraabdominal pressure
  - NORMAL PV PRESSURE→ 1-5 mm Hg
- PH in cirrhosis >5 mm Hg

➢ Pathogenesis

- ↑ resistance to portal flow followed by and ↑ portal venous inflow
- Site of ↑ resistance forms the basis of the classification of PH into
  - Prehepatic → occurring in PV prior to entering liver
  - Intrahepatic → occurring within the liver
  - Post hepatic → occurring when blood exits the liver through hepatic veins

Classification	Level	Examples
○ Prehepatic (in PV, prior to entering the liver)	− PV and branches	▪ PVT
○ Intrahepatic (occurring in the liver)	− Presinusoidal (portal triads)	▪ EtOH-associated hepatitis ▪ PBC ▪ Porto-sinusoidal vascular disorder ▪ Sarcoidosis ▪ Schistosomiasis
	− Sinusoidal	▪ Cirrhosis (all causes)
	− Post-sinusoidal (central veins)	▪ Sinusoidal obstruction syndrome (SOS)
○ Post-hepatic (occurring when blood exits the liver through the hepatic vein	− Hepatic veins − IVC	▪ Budd-Chiari syndrome, congestive hepatopathy

Abbreviations: PV, portal hypertension; PVT, portal vein thrombosis

Printed with permission: Kaplan DE, et al. Hepatology. 2023 Oct 23. doi: 10.1097/HEP.0000000000000647. Epub ahead of print. PMID: 37870298. (Table 1).

❖ Cirrhosis, Decompensated

➢ Definition

- The development of clinically overt complications of PH, specifically overt ascites, variceal hemorrhage, or overt hepatic encephalopathy (HE)
  - Usually when portal pressure gradients > 10 mm Hg (CSPH)
- Mean survival in
  - Compensated patient, 12 yr
  - Decompensated patient, < 1.5 yr
- Patients with decompensated cirrhosis develop successive complications:
  - Recurrent variceal hemorrhage
  - Refractory ascites
  - HE
  - Hepatorenal syndrome
  - Spontaneous bacterial peritonitis (SBP)
  - Jaundice

➢ Determining the Stage of Cirrhosis

- Liver biopsy has historically been used for diagnosis of cirrhosis and/or performing HVPG measurements to establish the presence of CSPH
  - This is invasive and not universally available—non-invasive tests to identify cirrhosis and/or CSPH have been explored

- “Advanced chronic liver disease” (ACLD) → a new entity, describes a patient who (without liver biopsy) is likely to be close to cirrhosis based on liver stiffness measurements (LSM) and platelet count
  - Can be applied widely as a surrogate for advanced fibrosis/cirrhosis
  - If the patient does not have prior decompensation→ cACLD
- LSM by transient elastography cut offs (validated, references in guideline):
  - <10 kPa rules out cACLD
  - ≥ 15 kPa rules in cACLD
  - > 25 kPa rules in CSPH
- Platelet counts used to determine whether the patient is likely to have CSPH in those with intermediate LSM values
- In persons with intermediate values of LSM
  - <10 kPa rules out cACLD
  - Use platelet count < 150 K/mm^3 to determine if patient likely CSPH

The Stages of Cirrhosis and Advanced Chronic Liver Disease (ACLD)

A

Stages of chronic liver disease	No cirrhosis	Compensated cirrhosis		Decompensated cirrhosis	
		Lower risk of decompensation	Higher risk of decompensation	First decompensation	Further decompensation
Clinical features (ascites, VH or HE)	None	None	None	One event	>1 event or complication of event*
Histological diagnosis	F0-F2	F3/F4 (thin septa)	F4 (thick septa)	Clinical	Clinical
Hemodynamic features (HVPG mmHg)	3-5	5-10	>10 (CSPH)	>20 worse outcomes in VH	>20 worse outcomes in VH
Endoscopic features	None	No varices	± Varices	± Varices	± Varices

Risk of death

B

Non-invasive staging of chronic liver disease	No cACLD	Possible cACLD	Highly suggestive of cACLD	cACLD	
Liver stiffness (kPa)	<10	10-15	15-20	20-25	>25
Platelet count (K/mm³)	NR	NR	If <110 = CSPH	If <150 = CSPH	CSPH**

Risk of decompensation

- (A) Clinical features, histologic findings, hepatic venous pressure gradients (HVPG), and endoscopic features typical of
  - Compensated cirrhosis +/- significant portal hypertension (CSPH)
  - Decompensated cirrhosis, and
  - Development of further decompensated cirrhosis
  - Relative risk of death is indicated in the purple dashed line
- (B) Liver stiffness measurements and platelet counts used to characterize
  - Compensated advanced chronic liver disease (cACLD) and
  - CSPH, using non-invasive, non-histological criteria.

Abbreviations: HE, hepatic encephalopathy; VH, variceal hemorrhage

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➢ Pathophysiological Basis of Pharmacotherapy

- Overview
  - Accumulation of fibrous tissue and nodule formation and vascular distortion → ↑ vascular resistance and ↑ portal pressures
    - Splanchnic vasodilation → blood flow → further ↑ portal pressure
    - ↓ nitric oxide bioavailability → ↓ intrahepatic vascular tone → ↑ hepatic resistance
- Optimal NSBB for PH
  - NSBBs → ↓ portal pressure through decreased cardiac output (β-1 blockade) and splanchnic arterial vasoconstriction (β-2 blockade)
  - Carvedilol also has anti-alpha-1 adrenergic activity → ↓ HVPG
    - Metabolized in liver therefore used at lower doses than for heart failure (see table)
    - Better reduction of portal pressures in head-to-head trials with traditional NSBBs → preferred agent

Therapy	Mechanism of Action	Starting Dose	Titration	Maximum dose	Goal	Common Adverse Effects	Maintenance
○ Propranolol	- ↓ HR / contractility → ↓ CO	20-40 mg b.i.d.	↑ dose q2-3 days, until reach treatment goal	– Without ascites, 320 mg/day – With ascites, 160 mg/day	▪ HR of 55-60 bpm if tolerated ▪ SBP ≥ 90 mm Hg	– Bradycardia – Constipation – Dyspnea – Fatigue, – Hypotension – Orthostasis	▪ Indefinitely or until TIPS or liver transplant ▪ No indication for routine upper endoscopy
○ Nadolol	- ↑ splanchnic arterial vasoconstriction (beta-2) → - Unopposed ↑ alpha-adrenergic constriction	20-40 mg at bedtime		– Without ascites, 160 mg/day – With ascites, 80 mg/day			
○ Carvedilol	- Above plus ↓ intrahepatic vascular resistance from anti-alpha-adrenergic activity	6.25 mg daily	↑ to 6.25 mg b.i.d. after 3 days	– 12.5 mg/day (higher doses can be considered for non-hepatic causes)	▪ No HR goal ▪ Maintain SBP ≥ 90 mm Hg		

Abbreviations: b.i.d., twice a day; HR, heart rate; SBP, systolic blood pressure

Adapted from: Kaplan DE, et al. Hepatology. 2023 Oct 23. doi: 10.1097/HEP.0000000000000647. Epub ahead of print. PMID: 37870298. (Table 3)

Recommendations

Other Treatments	Action: Target Abnormality Mechanism of ↑ hepatic Vascular Resistance	Splanchnic Vasodilation	Gut-Liver Axis	Collaterals and Varices
○ Antifibrotic	+			
○ Anticoagulants	+			
○ Antioxidants	+			
○ Antiangiogenics				+
○ Antibiotics			+	
○ Balloon tamponade				+
○ BRTO				+
○ Collateral embolization				+
○ Endoscopic therapy				+
○ Esophageal stents				+
○ Fecal transplantation			+	
○ Probiotics			+	
○ PARTO				+
○ Somatostatin		+		
○ Statins	+			
○ Terlipressin		+		
○ TIPS	+			

Target	Treatments
○ ↑ hepatic vascular resistance	− Anticoagulants − Antifibrotic agents (experimental) − Antioxidants − Carvedilol − Statins − TIPS
○ Splanchnic vasodilation	− Somatostatin and analogs − Terlipressin
○ Gut-liver axis	− Fecal transplantation − Probiotics, antibiotics
○ Collaterals and varices	− Antiangiogenics (experimental) − Collateral embolization, BRTO, PARTO, esophageal stents, balloon tamponade NSBB and carvedilol − Endoscopic therapy

- Experimental pharmacological targets
  - Novel therapeutic agents being explored to prevent PH or treat PH:
    - Anticoagulants
    - Anti-inflammatory agents
    - cGT activators/stimulators
    - Statins
      - Phase 2 studies have shown significant effects of HBPG reduction
      - RCT showed improved mortality with the addition of simvastatin to standard secondary prophylaxis after variceal bleeding
      - Retrospective studies decreased rate of progression to cirrhosis, decompensation, death, greater reduction in HCC risk
      - Simvastatin 20 mg daily; atorvastatin metabolism altered in cirrhosis therefore low doses recommended pending additional data

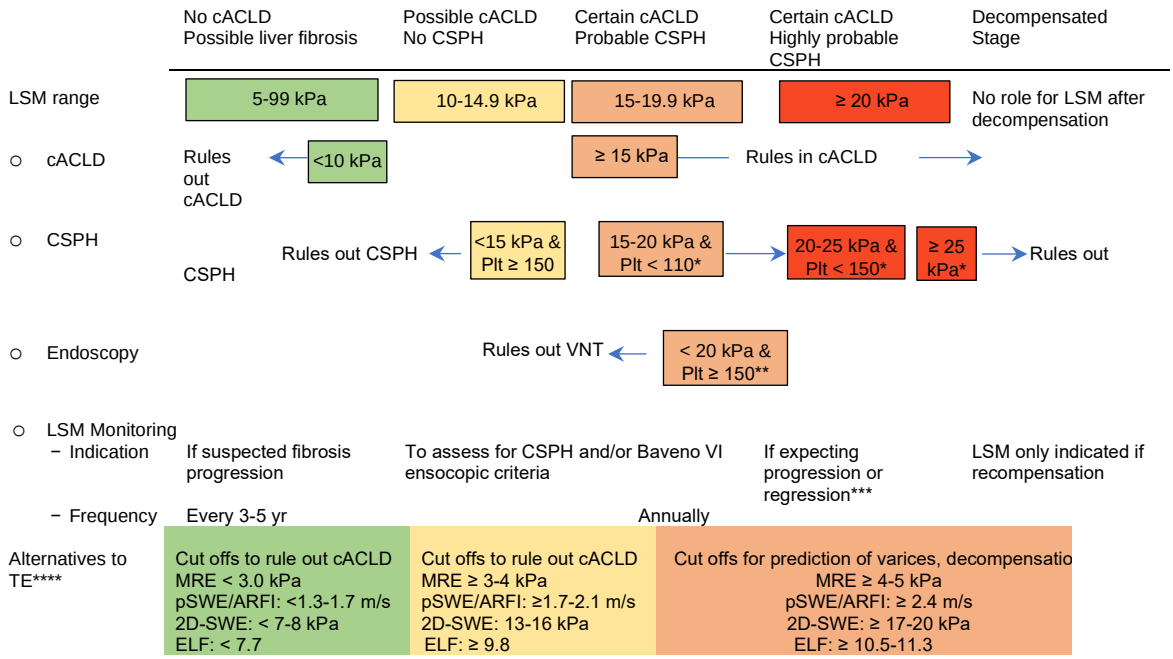
- Diagnosis
  - Portal pressure is indirectly determined by measuring liver sinusoidal pressure by a transjugular catheter placed into a hepatic vein
    - "Wedging" of the catheter to occlude the hepatic vein lumen (usually with a balloon) equals the sinusoidal pressure
    - The wedged hepatic vein pressure is equivalent to the portal vein pressure in patients with cirrhosis because intersinusoidal communications are closed due to nodules and fibrous septa
  - Wedged hepatic vein pressure – free hepatic vein pressure
    - Free hepatic vein pressure is the unwedged pressure measurement
  - HVPG provides prognostic information in compensated and decompensated cirrhosis at baseline, in response to vasoactive drugs (i.e., NSBB), after elimination of cirrhosis, prior to resection for HCC, prior to any major OR in patients with cirrhosis
  - Moderately invasive, carries procedural risks, and requires local expertise

- Non-invasive Liver Disease Assessment (NILDA)
  - Three scenarios where using NILDA is relevant:
    - Monitoring progression in patients with LSM 5-10 kPa (repeat q2-3 yr)
    - Confirming an initial LSM suggestive of cACLD to reduce false positive findings
    - Monitoring progression in patients with initial LSM diagnostic of cACLD without CSPH (repeat LSM q1yr)
  - ≥ 20% increase/decrease appears to correlate with clinically relevant deterioration or improvement
  - No role for baseline or serial LSM in decompensated cACLD (by definition with CSPH) unless clinical recompensation has occurred and discontinuation of NSBB is being considered
  - Importance of diagnosing CSPH
    - ↑ risk of varices / variceal hemorrhage
      - Need to begin use pf prophylactic NSBB

- Non-invasive detection of CSPH
  - CT/MR/US have limited but defined role in identifying CSPH
    - Collaterals (varices, recanalization of umbilical vein, splenorenal shunt)
    - Presence of ascites
  - The best validated non-invasive staging system for compensated cirrhosis is based on LSM (transient elastography) and platelet count

- “RULE OF FIVE”
  - Purpose
    - To quantify ↑ relative risk of decompensation and liver-related mortality and
    - To define cACLD, CSPH, and the threshold for screening upper endoscopy
  - Insufficient data to support use of serological markers alone (i.e., PLT, ELF) to exclude CPSH and eliminate need for endoscopy

Abbreviations: CSPA, clinically significant portal hypertension; EGD, esophagogastroduodenoscopy; ELF, enhanced liver fibrosis; PLT, platelet counts



*ANTICIPATE model for HBV, HCV, alcohol-associated liver disease, and lean NAFLD (body mass index < 30 kg/m^2). Positive predictive value (PPV) > 90% for LSM ≥ 25 kPa; PPV > 60% for the LSM + platelet criteria.
**Baveno VI criteria for variceal screening.
***≥20% change accepted as clinically significant.
****Cutoffs for non-TE elastography methods and laboratory-based tests are not solidly validated, and the cutoffs listed here should therefore be interpreted with caution. The green box to rule out compensated ACLD (cACLD) are derived from normal range values and/or cutoffs for F0 vs. F1–4.

Abbreviations: 2D-SWE, two-dimensional shear wave elastography; ARFI; Acoustic Radiation Force Impulse Imaging; BMI, body mass index; ELF, enhanced liver fibrosis; MRE, magnetic resonance elastography; Plt: platelet count; TE: transient elastography

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- Spleen stiffness measurements (SSM) by transient elastography when HPVG >10 mm Hg show a stronger correlation with HVPG than LSM
  - SSM ≤ 46 kPa may be suited for ruling out varices needing treatment and eliminating need for endoscopy in patients who would otherwise be selected using the Baveno VI criteria (LSM ≥ 20 kPa, PLT <150)
  - Still needs validation because:
    - Studies have only included viral hepatitis patients, thus limiting generalizability to patients with ALD and MASLD
    - High technical failure rates (15-27%)
    - Need for validation of a novel spleen-dedicated probe
- Non-transient elastography methods→ MRE, point shear wave elastography (pSWE), two-dimensional shear wave elastography
  - Less well validated
  - Manufacturer variability
- Non-invasive liver disease assessments (NILDA) are
  - Best calibrated for chronic viral hepatitis and/or ALD but tend to
  - Overestimate CSPH in patients with obesity and MASLD
  - Imaging-based NILDA > blood-based NILDA in this population

Abbreviations: ALD, alcoholic liver disease; MASLD, metabolism associated liver disease; MRE, magnetic resonance elastography; NILDA, non-invasive liver disease assessments

➢ Patients with cACLP

- Perform a non-invasive liver disease assessment (NILDA) to diagnose CSPH
  - The presence of a CSPH signal needs to initiate prophylactic therapy vs. acute variceal hemorrhage
- Techniques to identify high risk of CSPH, decompensation, and variceal hemorrhage
  - Liver biopsy
    - Fibrous septa
    - Small nodules
  - NILDA
    - Need to begin use pf prophylactic NSBB
    - HVPG ≥ 10 mm Hg
    - LSM ≥ 20 to 25 kPa
    - SSM ≥ 40-45 kPa
  - Laboratory
    - Platelets < 150 K/mm^3
    - rNF-AG > 315%
    - APRI > 0.876
    - ELF ≥ 11.1
    - ICE-r ≥ 16.7%

Abbreviations: APRI, AST/platelet ratio index; ELF, enhanced liver fibrosis; LSM, liver stiffness measurement; SSM, spleen stiffness measurement

Guidance Statements

- HVPG measurement is the gold-standard method to assess portal pressure in patients with cirrhosis
- CSPH is defined as HVPG ≥ 10 mm Hg
- HVPG may underestimate portal pressure in some patients with obesity and MASH-related cirrhosis
- Presence of clinical decompensation, gastroesophageal varices on EGD, portosystemic collaterals or hepatofugal flow on imaging is sufficient to diagnose CSPH
- CSPH can be non-invasively identified by LSM and platelet count
  - CSPH diagnosed with LSM ≥ 25 kPa irrespective of PLT
  - CSPH diagnosed with LSM 20-24.9 with PLT <150
  - CSPH diagnosed with LSM 15-19.9 with PLT <110
- Performing annual LSM by transient elastography (TE) and serum PLT may provide prognostic information in patients with cACLD without baseline CSPH in whom the underlying etiologies of cirrhosis remain controlled

➢ Treatment of patients with compensated cirrhosis

- All patients with compensated cirrhosis should have imaging q6mon to screen for
  - Hepatocellular cancer (HCC), and for
  - Portal vein thrombosis (PVT)
- Evidence indicating development of CSPH
  - Collaterals and flow reversal
  - Varices
  - Ascites
  - IF PRESENT→ has CSPH□NSBB can be initiated
- If use of NSBB is contraindicated/not tolerated, use LSM and PLT criteria as per Baveno VI criteria (LSM <20 kPa, PLT >150) to r/o likelihood of high-risk varices can avoid EGD
  - Re-evaluate annually
- Perform esophagogastroduodenoscopy (EGD) if LSM not available
- NSBB in compensated cirrhosis without CSPH
  - No reduction of incidence of new varices, variceal bleeding, clinical decompensation

Guidance statements

- Use of NSBB in patients with cirrhosis WITHOUT CSPH is not recommended for prevention of decompensation
- Lifestyle modification and treatment of underlying liver disease should be prioritized to prevent progression

- Compensated cirrhosis proven likely CSPH (HVPG ≥ 10 mm hg)
  - These patients are at increased risk of decompensation
  - Data from two prospective trials support initiation of NSBB to prevent decompensation in cACLD with CSPH without high-risk varices
    - 2-year follow up showed pts on NSBB had significantly lower risk of decompensation
  - In the absence of imaging-surrogates for CSPH and transient elastography not available
    - Patients with cACLD should undergo EGD
      - q2yr if no varices, but liver injury is ongoing
      - q3yr if no varices, but liver injury is controlled

Guidance Statements

- In patients with compensated cirrhosis and CSPH goal of therapy is to prevent the development of clinical decompensation
- NSBBs (preferably carvedilol) should be considered in patients with cACLD and CSPH to prevent decompensation
- Screening endoscopy in patients with compensated or decompensated disease on NSBB; the need for screening endoscopy can be obviated in some patients on a selective BB by switching to NSBB after discussion with prescriber
- Patients with cACLD and CSPH (by TE, HVPG, or imaging) who are candidates for NSBB should be treated to prevent hepatic decompensation
- Where transient elastography is unavailable to diagnose CSPH, when empiric NSBB contraindicated or not considered due to prior intolerance, endoscopic surveillance of all patients is recommended. If no varice repeat EGD q2yr (if ongoing insult to liver) or q3yr (if insult removed/treated). Repeat endoscopy if decompensation occurs

Abbreviations: ACLD, advanced chronic liver disease; b.i.d., twice per day; bpm, beats per minute; BRTO, balloon-occluded retrograde transvenous obliteration; cACLD, compensated advanced chronic liver disease; CO, cardiac output; CSPH, clinically significant portal hypertension; HE, hepatic encephalopathy; HR, heart rate; HRS, hepatorenal syndrome; HVPG, hepatovenous pressure gradient; IVC, inferior vena cava; LSM, liver stiffness measurement; NO, nitric oxide; NSBB, non-selective beta blocker; PARTO, plug-assisted retrograde transvenous obliteration; PH, portal hypertension; PV, portal vein; SBP, spontaneous peritonitis; SBP, systolic blood pressure; TE, transient elastography; TIPS, transjugular intrahepatic portosystemic shunt; VH, variceal hemorrhage;

Portal Hypertensive (Esophageal) **Bleeding in Patients with Cirrhosis: AASLD Guidelines** (2017)

Garcia-Tsao G, et al. Hepatology 2017: 65; 310-335

- Definition
  - Portal hypertension (PH) is defined as a hepatic venous pressure gradient (HVPG) > 12 mmHg
    - Varices develop at the rate of 10% to 15% per year
      - At any time, about 50% of persons with cirrhosis have varices

- Classification of cirrhosis

Terminology	HVPG, mmHg	Clinical Decompensation*	Histological Cirrhosis
Compensated cirrhosis (CC)			
− Mild pH	> 5, < 10	-	-
− Clinically significant portal hypertension (CSPH)	> 10	+	+
▪ Without GEV** (60%)	> 10	-	+
▪ With GEV* (40%)	> 10	+/-	+
Decompensated cirrhosis* (GEV in 85%)			

*ascites, VH, HE, post-surgical decompensation, HCC

** Note the distinction between the presence of gastroesophageal varices (GEV) vs. variceal hemorrhage (VH):
- GEV appears in 40% of patients in compensated cirrhosis, but with bleeding from GEV (VH), the portal pressure (PP) will be > 12 mm Hg.
  - The patient is now classified as having decompensated cirrhosis.

Prognosis of terminology	Cirrhosis, yr
− Stage	
▪ Compensated	> 12
▪ Decompensated	~ 1.8

Variceal Hemorrhage (VH)	5 yr mortality rate
− Isolated	20%
− Associated with other clinical features of decompensation	80%

Abbreviations: AASLD, American Association for the Study of Liver Diseases; BRTO, balloon-occluded retrograde transvenous obliteration; CACLD, compensated advanced chronic liver disease; CC, compensated cirrhosis; CSPH, clinically significant portal hypertension; CTP, Child-Turcotte-Pugh classification; GEV, gastroesophageal varices; HCC, hepatocellular cancer; HE, hepatic encephalopathy; LS, liver stiffness; NIT, non-invasive test; NSBB, non-specific beta blocker; PP, portal pressure; SWE, shear wave elastography; TE, transient elastography; TIPS, transjugular intrahepatic portal hypertension; VH, variceal hemorrhage; VP; vasopressin

- GEV will be present overall in
  - CC, 60% (CC, GEV+)
  - CC, GEV → CC GEV+, 8% per year
  - Decompensated cirrhosis 85% have GEV
    - DC + GEV → VH, 15% per yr
    - VH, initial bleed 6 wk mortality rate, 15% - 25%
    - Recurrent bleed (untreated GEV), 60% in 1-2 yr
  - Prognosis of EGV depends on progression to large GEV (10% per yr)
    - Rate depends on
      - Severity of liver disease
      - Size of GEV
      - Red wale
      - HVPG > 20 mmHg marks

➢ Pathophysiology

- Fibrosis of tissue
- Vessel
  - Distortion from regenerative noodles
  - Microthombi
  - ↓ endothelial no bioavailability

↓

↑ vascular tone

↓

↑ portal pressure (PP)

↓

↑ no production

↓

Splanchnic vasodilation

↓

↑ collateral circulation

↓

↑ gut blood flow

↓

GEV

- ↑ intrahepatic resistance to portal flow → ↑ portal

- ↑ PP
  - ↑ intrahepatic resistance to portal flow due to
    - Structural
      - Fibrosis
      - Regenerative membrane
    - Functional
      - ↑ intrahepatic vascular tone (activation of vasoactive systems)
  - Splanchnic vasodilation
    → ↑ blood flow into gut (portal venous system)
    → ↑ retention of Na^+/H_2O / ↑ blood volume / ↑ blood volume / ↑ cardiac output (hyperdynamic circulation)
    → ↑ portal venous inflow
  - ↑ portosystemic collaterals

- The pathogenesis of portal hypertension includes
  - ↑ intrahepatic vascular resistance as the result of changes in intrahepatic morphology
  - ↑ blood flow in splanchnic circulation as the result of
    - Imbalance of vasoactive agents, angiotensin II, antidiuretic hormone, endothelin, norepinephrine, nitric oxide
    - Neogenesis
  - Development of collateral veins as the result of neoangiogenesis as
    - Dilation of portosplenic collateral veins
- Targets for pharmacotherapies
  - Structural
    - Anti-fibrotics
    - Anti-coagulants
  - Functional (vasodilatory)
    - α-adrenergic antagonists
    - Angiotensin-2 blockers
    - Nitrates
    - Statins
    - Diuretics / Na+ restriction
  - Splanchnic vasoconstriction
    - Non-selective beta blockers (NSBB) → B1 blocking → ↓ CO
    - Vasopressin (VP) → B2 blocking → splanchnic vasoconstriction
    - Somatostatin/ octreotide
- Procedural therapies
  - Esophageal variceal ligation (EVL, aka esophageal variceal band ligation [EVBL])
  - Injection
    - Sclerosants
    - Balloon occluded retrograde transmission (BRTO, L. renal vein →gastro- / splenorenal collateral)
  - Transjugular intrahepatic portosystemic shunt (TIPS)
  - Corrects hypertensive: PV to normotensive (bypass site of ↑ resistance)
- Types of surgical shunts
  - Selective: divert all portal blood
  - Non-selective: divert some portal blood
    - Portocaval shunts (PV to IVC)
    - Mesocaval shunts (SMV to NC)
    - Proximal splenorenal shunt PSV to LRV
    - H-graft polytetrafluoroethylene ≥ 16 mm grafts
    - Target diameter TIPS

  Into systemic circulation
- Distal splenorenal shunt (blood in splenic vein flows into the left renal vein)
- H-graft polytetrafluoroethylene reinforced grafts (8 mm, 10 mm 1D, correcting SMV/PV → IVC
- Small diameter TIPS
  - Risk of hepatic encephalopathy from shunts
    - Selective 10% to 20%
    - Non-selective, 40% to 80%

Procedure	HE	Variceal Rebleeding
○ Surgical shunt		
− Non-selective	40% to 80%	
− Selective	10% to 80%	
○ TIPS		
− 10 mm	40%	13% to 17%
− 8 mm*	18% to 27%	7% to 16%

* required more re-interventions

❖ First/repeat acute esophageal variceal bleeding

- ○ PRBC transfusion target to initiate PRBCs and to maintain hemoglobin (Hb) concentration to 7 d/dL
- ○ Vasoactive drugs
  - − Octreotide/somatostatin, or
  - − Vasopressin / terlipressin

} For 2-5 d

Drug	Recommended Dose
− Octreotide (SMT analogue)	▪ Initial IV bolus of 50 µg (can be repeated in first hour if ongoing bleeding) ▪ Continuous IV infusion of 50 µg/h
− Vasopressin (VP)	▪ Continuous IV infusion: 0.2-0.4 U/min; can be increased to 0.8 U/min, plus ▪ IV nitroglycerin at a starting dose of 40 µg/min (can be increased to maximum of 400 µg/min, adjusted to maintain a systolic blood pressure 90 mm Hg)
− Somatostatin (SMT)	▪ Initial IV bolus 250 µg (can be repeated in the first hour if ongoing bleeding) ▪ Continuous IV infusion of 250-500 µg/h
− Terlipressin (VP analogue)	▪ Initial 48 h: 2 mg IV q4h until control of bleeding ▪ Maintenance: 1 mg IV q4h to prevent rebleeding

Abbreviations: IV, intravenous; SMT, somatostatin; VP, vasopressin

- ○ Ceftriaxone 1 g / 24 h IV for 7 d, or when blood stops / vasoactive drug is stopped
- ○ EGD when patient is stable, and within 12 h, EBL for EVB
- ○ TIPS procedure within 72 h of SGD for EVB/EVL for following inductions, as long as no contraindications
  - − Failure of EBL
  - − High risk of rebleeding cirrhosis
    - ▪ Child-Pugh class C, or
    - ▪ Class B with active bleeding on EGD
    - ▪ Once TIPS is successful placed, stop IV vasoactive drug

❖ Secondary prophylaxis (after recovery from acute EVB)

- Maintenance
  - NSBB
    - Continue nadolol or propranolol (but not carvedilol) at dose and durations, as suggested in table of treatment of primary prophylaxis, or
    - Continue EGD plus EBL q1-4 wk to obliterate RV
    - Then after EV obliterate, then repeat EGD + EVL at 3 to 6 mon, then q6-12mon
  - If TIPS performed, no NSBB + EVL required
  - If TIPS placed, no NSBB/EVL required

- Secondary prevention (prevention of rebleeding)
  - Effectiveness of pharmacological/endoscopic methods to stop variceal bleeding, ~80%
    - For those who continue to bleed / have rebleeding
    - Decompressive shunts between hypertensive portal and normotensive systemic veins

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➢ Diagnostic Imaging

- Abdominal ultrasound (US) of the liver is recommended for persons with cirrhosis, and even some without cirrhosis and advanced fibrosis (F2/F3) to detect early HCC.

- Give the features on diagnostic imaging which suggest the presence of portal hypertension (PHT).
  - Portal collateral circulation (100% specific for CSPH)
    - Umbilical vein recanalized
    - Spontaneous splenorenal circulation
    - Left/short gastric vein dilation
    - Reversal of flow in portal system
  - Portal (congestion)
    - Dilation > 5 mm PV
    - ↓ velocity of flow

Clinical Tip

- The absence of physical signs associated with chronic liver disease (such as palmar erythema, spider nevi, caput medusa (visible abdominal portosystemic collaterals) does exclude the presence of clinically significant portal hypertension (CSPH; HVPG ≥ 10 mmHg).

MCQ Tricks

- Give the values of HVPG (mmHg) at which the following occur.
  - GEV — 10
  - Risk of VH — ≥ 12
  - ↑ mortality rate — ≥ 16
  - Failure to control bleeding/death (during acute VH) early rebleeding — ≥ 20
  - ↓ risk of complications — < 12, or 20% ↓ from baseline
    - VH
    - HE
    - Ascites
    - Death
  - The HVPG is correlated with Child-Pugh score / MELD score (Model for end-stage liver disease)
    - These are predictions of risk of
      - Rebleeding
      - Death
  - 3% increase in mortality rate, in patients awaiting liver transplantation — ↑ of 1

- Give the "backbone of non-invasive [diagnostic tests] of portal hypertension (PH).
  - MR elastography (MRE) to access liver stiffness (LS)
  - Transient elastography (TE; FibroScan®)
    - LS/TE ≥ 21 kDa and HVPG ≥ 10 mm Hg are equally effective in predicting decompensation"

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- Give non-invasive tools (NITs) in addition to TE to predict the value of CSPH, the changes in HVPG, or the absence of ↑ HVPG (< 150,000/mm^3).
  - Shear wave elastography (SWE)
    - Two dimensional real-time SWE
  - Magnetic resonance elastography (MRE)
  - Liver/spleen stiffness / platelet count
  - Spleen stiffness (SS) > 54 kPa in the presence splenomegaly
  - ↓ platelet count plus another unrelated NITs

❖ NSBBs and primary/secondary prevention of VH

- Some authors suggest that the "optimal [therapeutic] response" to NSBBs is
  - Pulse rate
    - ↓ 50-55 bpm
    - ↓ 20% from baseline
  - The problem is "…that changes in heart rate do **not** correlate with changes in HVPG, and that non-invasive tolls (NITs) are not useful in assessing changes in HVPG".
- Problems with use of NSBBs
  - Contraindications, 15%
  - Dose ↓ / discontinuation, 15%
    - Carvedilol 3.125 mg b.i.d. → max 6.25 mg b.i.d.

➢ Treatment

It is generally believed that small esophageal varices (EV) have a low risk for VH.

- Give the exceptions, when small EV have a high risk of VH.
  - Red wale marks, signaling thinning of venous wall.
  - Any size of EV in a patient who is CTP-C stage.
  - The value of the INR is "…. Not a reliable indicator of coagulation status in [patients with] cirrhosis".
  - Give Ceftriaxone 1 g / 24 h for maximum of 7 d in patients with VH in order to
    - ↓ infection (e.g., spontaneous bacterial peritonitis [SBP])
    - ↓ recurrent variceal hemorrhage (VH)
    - ↓ death
  - The commonest cause of upper GI bleeding (UGIB) in patients with cirrhosis is peptic ulcer disease.
    - However, because the patient with liver disease has the risk of UGIB from esophageal/gastric varices, until the diagnosis of bleeding varices or ulcer is established by EGD, the patient must be triaged with the assumption that the more serious condition is bleeding (EV/GV) and to treat this appropriately.

- Give how to be certain that a patient with cirrhosis and UGIB and VH has in fact bleed from the varices.
  - Visualize the active bleeding from varix/varices
  - Red wale sign
  - White nipple sign
  - When varices are the only lesion seen on EGD, and blood is in the stomach on EGD.
  - EGD performed > 24 h after UGIB, and there is no active bleeding, and just varices are seen on EGD.
  - Non-cirrhotic prehepatic portal hypertension occurs in adults in some parts of the world and may be associated with varices.

➢ Management of Esophageal Varices in Patients with Cirrhosis

Findings	Management
○ No varices	− EGD q3yr, unless decompensation develops, or patient coming to surgery or planned pregnancy
○ Varices	
− Small varices < 5 mm	− As above
▪ With red wale marks (erythematous raised areas)	− Non-selective β-blocker therapy (NSBBs): (propranolol, nadolol, or carvedilol)
− Large varices (> 5 mm)	− Start NSBB or endoscopic variceal band ligation (EVBL)
− Varices in patients unable to tolerate β blockers	− EVBL
− Bleeding varices	− EVBL

Poterucha J. MKSAP® 18 Gastroenterology and Hepatology. American College of Physicians – MKSAP

Food Impaction

❖ Non-endoscopic pharmacological management of esophageal soft food bolus impaction

Conservative management of oesophageal soft food bolus impaction (John Hardman J, et al. Cochrane Database Syst Rev. 2020 May; 2020(5): CD007352. DOI: 10.1002/14651858.CD007352.pub3)

- Definitive management is with endoscopic intervention, recommended within 24 hours.
- Prior to endoscopy, many patients undergo a period of observation, awaiting spontaneous disimpaction, or may undergo enteral or parenteral treatments to attempt to dislodge the bolus.
- There is little consensus as to which of these conservative strategies is safe and effective to be used in this initial period, before resorting to definitive endoscopic management for persistent impaction.
- Intravenous (IV) diazepam followed by glucagon was compared with IV placebo on rates of disimpaction intervention.
  - The rates of disimpaction were small and insufficient, 38% vs 32% (RR, 1.19; 95%CI, 0.51 to 2.75, P = 0.69)
- There is currently inadequate data to recommend the use of any enteral or parenteral treatments in the management of acute oesophageal soft food bolus impaction.
  - There is also inadequate data regarding potential adverse events from the use of these treatments, or from potential delays in definitive endoscopic management.
    - Caution should be exercised when using any conservative management strategies in these patients.

Transjugular Intrahepatic Portosystemic Stent-Shunt (TIPSS) **in the Management of Portal Hypertension**

Tripathi D, et al. Gut 2020;69(7):1173-92.

*In some of the medical literature, TIPSS is referred to as TIPs, transjugular intrahepatic portosystemic stent.

➢ Indications to use TIPSS

Recommendation

- TIPSS for bleeding EV vs. endoscopic hemostatic therapy (EHT) +/- drug therapy
  - ↓ rebleeding (no difference at 6 wk)
  - ↑ Hepatic encephalopathy (HE)
  - **No** difference in survival
- Active EVB, Child's B/C
  - Early TIPSS (≤ 72 h of EHT-controlled esophageal variceal bleed (EVB)
    - 12 mon transplant-free survival
      Early vs. later TIPSS (86% vs. 61%, P = 0.001; ARR 25%; 95% CI, 2 to 48; NNT, 4 (95% CI, 2.1 to 50)
    - Early TIPSS also gives superior transplant-free survival at 6 wk/1 yr (HR, 0.50; 95%CI, 0.25 to 0.98; P = 0.04)
    - Early TIPSS gives better control of bleeding/rebleeding (HR, 0.26; 95%CI, 0.12 to 0.55; P < 0.0001)
  - Early TIPSS beneficial for patients with MELD ≥ 19

Recommendations

- **Bleeding**
  - All persons being considered for TIPSS
    - Screen for convert/overt hepatic encephalopathy (HE) (Strong recommendation, high-quality evidence)
  - EGV bleeding refractory to pharmacological/endoscopic therapy (Baven, 6 criteria) (strong recommendation, moderate-quality evidence)
    - When CPS (C10-13) / MELD ≥ 19, hemodynamically stable, EV/EBV ½ bleeding (weak recommendation, moderate quality of evidence)
    - When Child-Pugh Score (CPS) > 13
      - Do **not** do TIPSS
      (Strong recommendation, low quality of evidence)
  - Secondary prevention of bleeding EV, failed SBB/EVBL, "…careful patient selection to minimize hepatic encephalopathy (HE) (weak recommendation, moderate quality evidence).
    - It is not yet known if there is a role for TIPSS for first-line therapy in secondary prevention (strong recommendation, low quality of evidence).

- Secondary prevention of bleeding GV, rebleeding despite endoscopic injection therapy
  - TIPSS +/- embolization
- Secondary prevention of selected patients, large/multiple GV
  - TIPSS +/- embolization may be used as first-line therapy (Strong recommendation, moderate-quality evidence)
- Bleeding stomal varices
  - Covered stents useful to ↓ rebleeding
- Bleeding ectopic variceal, refractory to NSBB / local therapy
  - TIPSS +/- embolization
- Portal hypertensive gastropathy (PHG) bleeding, refractory to NSBB +/- local therapy
  - TIPSS

  (Weak recommendation, low-quality evidence)
- Acute EV bleeding, renal dysfunction
  - Undertake TIPSS

  (Weak recommendation, very low-level evidence)
- Patient with gastric antral vascular ectasia (GAVE)
  - Do **not** use TIPSS (no benefit)
  - Management of GAVE
    - Pharmacological
      - Tranexamic acid
    - Endoscopy
      - Band ligation
      - Argon frequency dilation (RFA)
      - Surgery

- **Ascites**

Recommendations

- TIPSS is superior to repeated large volume paracentesis (LVP) for patients with refractory/recurrent ascites
  - ↑ control of ascites
  - ↑ survival
    - ↑ transplant-free survival, ↓ renal failure, but
    - ↑ HE (except when using covered stents for TIPSS)
  - Patient with refractory/recurrent ascites may also be considered for liver transplantation (LT)
- Assessment of severity of liver disease with regards for appropriateness of using tips
  - Child-Pugh score (CPS)
  - Model for End Stage Liver Disease (MELD) score
  - BSG Guideline recommended scoring system for TIPSS

- ↑ risk patient, advanced liver disease, assessment for use of TIPSS
  - Clinical
    - Liver
      - Current HE
    - Heart
      - Systolic/diastolic
      - Dysfunction, severe
    - Lung
      - Severe pulmonary hypertension
  - Laboratory
    - Lung
      - Clinically significant pulmonary hypertension on catheter studies
- Patient who is awaiting liver transplant (LT)
  - Use TIPSS for ascites only after discussion with multidisciplinary LT program personnel (Strong recommendation, very low-quality evidence)
- Refractory/recurrent ascites
  - Selected patients for treatment of TIPSS provided no contraindications to the procedure

  (Strong recommendation, high-quality evidence)
  - Contraindications
    - Bilirubin > 50 µm/L
    - Platelets < 75 x 10^9
    - Previous HE
    - Infection
    - Heart failure
    - Pulmonary hypertension, severe

  (Strong recommendation, moderate quality evidence).

- **Hydrothorax**

➢ Definition (refractory hepatic hydrothorax)

- "…failure to control symptomatic fluid accumulation through optimization of sodium intake and diuretic treatment".

➢ Demography

- End stage liver disease (ESLD), 10%

➢ Treatment

- Thoracentesis for symptoms
- Repeated hepatic hydrothorax
  - TIPSS

Recommendation

- TIPSS for refractory hepatic hydrothorax (Strong recommendation, moderate-quality evidence).

- **Hepatorenal syndrome** (HRS)
  - Renal dysfunction associated with portal hypertension
    - Improves with TIPSS, but
      - ↑ risk of HE (~50%)
      - Cirrhotic cardiomyopathy
  - Treatment is focused on the improving function of the liver transplantation may be required.
  - ↑ Cr_s in patient with indication for acute TIPSS → proceed with procedure
  - ↑ Cr_s elective TIPSS
    - ↑ risk of
      - ↑ post-TIPSS mortality
      - ↑ HE
      - ↓ natriuretic effect of TIPSS
    - RCT cut-off for ↑ Cr_s and TIPSS
      - Exclude patients with intrinsic renal disease, or mean basal Cr_s 70-124 µmol/L

Recommendation

  - TIPSS for HRS type 1 or 2 do **not** do (consider experimental) (Weak recommendation, very low level of evidence).

- **Budd-Chiari Syndrome** (BCS)

➢ Definition

  - "…obstruction of the hepatic venous outflow from the level of the [hepatic] sinusoids to the inferior vena cava"

➢ Causes/associations

  - Primary
    - 50% have JAK2 positive myeloproliferative neoplasm
    - With procoagulant conditions may be associated with BCS

➢ Treatment

  - All patients
    - Anticoagulation
  - Symptomatic
    - Hepatic vein (HV) interactions (HVI)

- Unsuccessful/technically impossible HVI
  ↓
  TIPSS
- Acute BCS (small vessel BCS)
  → TIPSS
  → Assess for possible eligibility for liver transplantation (LT)
- Not all HV obstructed
- TIPSS in BCS
  - Technically challenging
  - Benefit
    - Symptom relief 70%
    - 5 yr survival rate 70%
- If all HV occluded → do a direct intrahepatic portocaval shunt (DIPS) (IVC to liver to portal vein).
- HE with TIPSS/DIPS ~15%
- Poor prognosis estimated using Rotterdam Class III patients, early TIPSS in BCS patients
  - BCS TIPS score > 7
    ↓
  Consider these patients for liver transplant

Recommendations

- Manage patient with BCS in Centre of Excellence, preferentially LT centre (Strong recommendation, very low-quality evidence).
- Perform TIPSS in BCS patients when failure to respond to
  - Anticoagulation
  - Hepatic vein procedures (including when hepatic vein interactions are not technically feasible) (weak recommendation, low-quality evidence).
- In persons with BCS, failed anti-coagulation / hepatic vein interventions, and a poor prognosis assess for liver transplantation (Strong recommendation, moderate-quality evidence).

- Prophylactic TIPSS before non-hepatic surgery
  - TIPSS prior to non-hepatic surgery in patients with portal hypertension / idiopathic non-cirrhotic portal hypertension (INCPH)
    - Do **not** perform because no difference in post-operative
      - Morbidity
      - Mortality

Looking Forward

- There is evidence to support that hepatic venous pressure gradient (HVPG) < 10 mm Hg predicts that the patient with liver disease is unlikely to decompensate after surgery.

Recommendation

- Do **not** perform TIPSS before non-hepatic surgery
  - Possible exception
    - Curative surgery for cancer

(Weak recommendation, low-quality evidence).

- **Idiopathic non-cirrhotic portal hypertension** (INCPH; aka portosinusoidal vascular liver disease

➢ Histopathology

- Sclerosis, hepatoportal
- Nodular regenerative hyperplasia (NRH)

➢ Prognosis

- Better than cirrhosis
  - ↑ 5 yr survival rate
    - ↑ risk of mortality
      - Ascites
      - ↑ Cr_s (serum creatinine)
      - Portal vein cavernoma
      - Comorbidities, non-hepatic

Recommendations

- Use same selective criteria as for patients with cirrhosis
  - Careful consideration to risk factor for hepatic encephalopathy
  - Use covered stents

- **Portal vein thrombosis** (PVT)

➢ Indications (for TIPSS in PVT)

- Acute PVT with ischemic bowel
- EVB, cirrhosis with PVT
- Extent of PVT prevents LT
- Traditionally PVT was considered to be a contraindication for TIPSS

- Give factors which predict successful placement of TIPSS.
  - Anatomy
    - Intrahepatic PVT branches
    - Local thrombosis (possibility for thrombolysis)
    - Transjugular local thrombolysis
    - Transplenic transhepatic rendezvous
    - Portal pressure guided stent placement

➢ Outcomes

- Successful TIPSS ~85%
- HE, 25%
- ↓EVB, compared to NSBB plus EVBL → rebleeding
  - 1 yr, 15% vs. 45%
  - 2 yr, 25% vs. 50%

Recommendation

- MDT discussion
  - Acute PVT
  - Cirrhosis, PVT, EVB
  - Sometimes contraindicated
  - ↑ risk of failure if cavernoma present

- **Hepatic encephalopathy**
  - Identify patient at risk of post-TIPSS hepatic encephalopathy (HE)
    - Patient-related
      - Age > 65 yr
      - Liver
        - Previous HE / covert HE
        - PV cavernoma
        - Sensitivity
          - MELD > 15 to 18
          - CP > 10

- Kidney
  - −Severe intrinsic renal disease stage 4/5
    - Be awake of diabetes, associated renal/vascular disease, and ↓ renal handling of NH_3
- Heart
  - −Systolic dysfunction
- Muscle
  - −Sarcopenia (↑ risk of post-TIPSS HE)

− Shunt
- ↓ size
- Bare

Severity of Encephalopathy	Description	Findings
○ Minimal	− Only on neuropsychiatric testing	
○ Grade 1 (AS)	− ↓ awareness − ↓ sleep	▪ Disoriented to time, place ▪ Psychomotor slowing ▪ Asterixis
○ Grade 2 (DLP)	− Disoriented − Personality change	
○ Grade 3	− Somnolence − Confusion − ↑ disorientation	▪ Disoriented to time, place, and situation, with asterixis
○ Grade 4	− Coma	▪ No response even to painful stimuli

Recommendations

○ TIPSS → ↑ risk of HE / ↑ pre-existing HE

○ Screen all persons being considered for TIPSS for covert/overt HE (Strong recommendation, high-quality evidence).

○ Screen with ≥ 2 of the following methods
- − Critical Flicker Frequency (CFF)
- − Enhanced/quantitative; spectral enhanced
- − Psychometric hepatic encephalopathy score (PHES)
- − Stroop testing

(Strong recommendation, moderate-quality evidence).

○ Do **not** do TIPSS in present of covert HE (relative contraindication) (Weak recommendation, low-quality evidence).

○ Carefully consider doing TIPSS in person → 65 yr (possible ↑ risk of HE) (Weak recommendation, low-quality evidence).

- HE develops, consider
  - Guideline-based best practise for treatment of HE
  - ↓ shunted blood flow in TIPSS
    - Shunt reduction, embolization, or occlusion

  (Weak recommendation, low-quality evidence).

- **Cardiac disease**

- Cardiovascular abnormalities associated with cirrhosis.
  - Cirrhotic cardiomyopathy
    - EGG prolonged QT interval
    - Myocardium
      - Hypertrophy
      - ↓ compliance
      - ↓ systolic (and possibly ↓ diastolic) dysfunction
      - ↑ cardiac output (CO) 50% ↑
      - ↑ right atrial pressure (RAP) 100% ↑
    - Pro BNP (pro-B-type naturetic peptide > 125 pg/mL
      - Predicts post-TIPSS development of
        - Heart failure (HF) (decompensation) in persons with cirrhosis
        - Perioperative cardiac events in patients having non-cardiac surgery having non-cardiac surgery
        - QTc interval (and risk of dysrhythmia)
    - Also predicts
      - Severity of liver disease

Recommendations

- Do **not** do elective TIPSS in persons with severe
  - Left ventricular dysfunction / ↓ ejection fraction
  - Pulmonary hypertension

  (Strong recommendation, moderate- quality evidence).

- **Service Delivery**
  - Minimum number if TIPSS performed per yr by facility providing TIPSS service, 10/yr (Strong recommendation, moderate quality of evidence).
    - Complex patients/procedure recipients
      - Liver transplantation 20 cases/yr
      - HV/PV thrombosed

    (Strong recommendation, moderate quality of evidence)
      - Emergency TIPSS Prioritize for transfer

    (Strong recommendation, low quality of evidence)

- **Perform appropriate pre-TIPSS elective evaluation**
    - Cardiac
        - Multidisciplinary team discussion
        - Laboratory
            - NT-pro BNP (N-terminal pro-B-type naturetic peptide)
            - ECG
                - 12 lead

      (Strong recommendation, moderate-quality evidence).

        - Echocardiogram, cardiology examination as appropriate in patients with severe left ventricular dysfunction or severe pulmonary hypertension (strong recommendation, moderate- quality evidence).
        - If patient with acute EV bleeding, cardiac history and potential need for echocardiogram → ECHO may be inaccurate, so perform emergent TIPSS (Strong recommendation, low-quality evidence).

- **Nutrition**

Recommendations

- For elective TIPSS
    - Functional/nutritional

  (Weak recommendation, low-level evidence)

- **Cross-sectional imaging**
    - Sarcopenia on CT scan seen pre-TIPSS products
        - Sarcopenia continuing post TIPSS
        - ↓ effectiveness of TIPSS

  (Strong recommendation, very low level of evidence)

    - Informed consent (Strong recommendation, high level of evidence)
    - Anaesthetic / deep sedation (Strong recommendation, very low level of evidence)
    - Prophylactic antibiotics only if bleeding varices (Strong recommendation, very low level of evidence).
    - Anticoagulation
        - Platelet transfusion for < 50 x 10^5 /L (Weak recommendation, very low level of evidence).
        - Thromboelastographic (instead of INR to determine coagulation status) (Strong recommendation, moderate level of evidence).

- Access all persons being considered for TIPSS to be assessed for covert / subclinical / minimal HE
  - Avoid TIPSS if ≥ 2 tests positive
    - Psychometric testing
      - Psychometric hepatic encephalopathy score (PHES)
      - Patient with refractory ascites
      - Probability of no HE after TIPSS in the normal PHES 90%
    - Critical flicker frequency (CFF)
      - HE → ↓ CFF
      - If CFF > 34 Hg in patient with no history of HE before TIPSS – risk of post-TIPSS over HE 0% (NPV, 100%)
    - Stroop testing
    - EEG, spectral enhanced (P 3-4 lead) or quantitative EEG < 8 Hg is abnormal

- Usually accepted contraindications for TIPSS
  - Heart
    - Failure / ↓ ejection fraction
    - Recent myocardial infarction
    - Cardiac valve insufficiency
  - Lung
    - Pulmonary hypertension, severe
  - Kidney
    - Liver failure, rapidly progressive
    - Malignancy of liver, Hepatocellular cancer (HCC) / Cholangiocarcinoma metastatic
    - Polycystic liver disease
    - Bile duct obstruction
  - Infection/sepsis

- TIPSS procedure

Recommendations

- Use PTFE (covered) stents (Strong recommendation, high level of evidence).
- Measure portal pressure gradient (PPG) (portal pressure – IVC pressure) (Strong recommendation, moderate level of evidence)
- Targeted PPG
  - Variceal bleeding < 12 mmHg
  - No bleeding ≥ 20% of baseline

  (Strong recommendation, high level of evidence).

- Embolization
  - Individualize decision
    - Portography (PPG)
    - Cross-sectional imaging

  (Weak recommendation, low level of evidence).

- Post-TIPSS, at 1 wk
  - Prothrombotic (e.g., BCS)
    - Doppler ultrasound plus discussion with interventional radiologist re need for TIPSS venography
  - Not prothrombotic
    - Doppler ultrasound needed only when dysfunction of the TIPSS is suspected

    (Strong recommendation, low level of evidence).
  - Otherwise no need for routine venography (Strong recommendation, low level of evidence)
  - Perform further follow-up Doppler ultrasound q6-12mon, or
  - If patient with TIPSS is under surveillance for HCC development

Abbreviations: aka, also known as; APC, argon plasma coagulation; BCS, Budd-Chiari syndrome; BSG, British Society of Gastroenterology; CCA, cholangiocarcinoma; CFF, critical flicker frequency; CO, cardiac output; CP, Child Pugh; Cr_s, serum creatinine; EEG, electroencephalogram; EHT, endoscopic homeostatic therapy; EV, esophageal variceal; EVB, esophageal variceal bleeding; EVBL, esophageal variceal band ligation; GAVE, gastric antral vascular ectasia; HCC, hepatocellular cancer; HE, hepatic encephalopathy; HR, heart rate; HRS, hepatorenal syndrome; HV, hepatic vein; INCPH, idiopathic non-cirrhotic portal hypertension; LT, liver transplantation; MELD, Model of End Stage Liver Disease; NNT, number needed to treat; NPV, negative predictive value; NSBB, non-specific beta blocker; NT-pro-BNP, pro-B type naturetic peptide; P, probability value; PHES, psychometric hepatic encephalopathy score; PHG, portal hypertension gastropathy; PV, portal vein; PVT, portal vein thrombosis; RAP, right atrial pressure; RCT, randomized controlled trial; RFA, radiofrequency dilation; TIPS, transjugular intrahepatic portosystemic shunt; TIPSS, transjugular intrahepatic portosystemic stent shunt; yoa, years of age

COMPLICATIONS OF DISEASES OF THE LIVER

Clinical Malnutrition in Patients with Liver Disease: ESPEN Guidelines (2018)

Plauth M, et al. Practice Guideline Clin Nutr 2019;38(2):485-521.

- Demography of malnutrition
  - Cirrhosis
    - High prevalence of malnutrition (↑ risk of ascites, hepatorenal syndrome)
    - Deficiencies
      - Protein
      - Fat soluble and B vitamins
      - K^+, Mg^{2+}, PO_4^{2-}
      - Trace elements

    (Strong consensus (100% agreement)

  - The prevalence/severity of these are related to the clinical stage of the liver disease
    - Compensated 20%
    - Advanced 60%

- **Alcoholic steatohepatitis** (ASH)

Recommendations

- Some recommendations are stated as “GPP”, which is used to represent “Good practice points/expert consensus: Recommended best practise based on the clinical experience of the guideline development group.
- The strength of the consensus is based on the % of the participants who have agreed with the statement
  - 90%; consensus, > 75% − 90%; majority, > 50% −75%; no consensus, < 50% “
- In patients with liver cirrhosis, anticipate progressive ↓ carbohydrate, protein and lipid metabolism with ↓ glycogen, ↓ non-oxidative glucose metabolism and ↓ albumin synthesis (Strong consensus, 100% agreement).
- In patients with ASH, deficiency of trace elements and vitamins is common (Strong consensus, 100% agreement)
- In patients with acute liver failure (ALF), due to subtotal loss of hepatocellular function and ensuring multi-organ failure, a hyper-aminoacidemia and hyper-aminoacidemia (Strong consensus, 100% agreement)
- In patients with acute liver failure (ALF), alcoholic hepatitis, there is ↑ resting energy expenditure (REE), but
  - REE is normal in NAFLD (consensus, 90% agreement)

- Use spontaneous ad lib eating/feeding as long as the following are present:
  - Intake cough/swallow reflexes
  - Adequate intake of energy/protein

  (Grade of recommendation, good practice points (GPP) – Strong consensus [100% agreement])
- Use individualized nutrition counselling (Grade of recommendation, GPP – Strong consensus [100% agreement])
- Use oral nutrition supplements, such as late evening/nightly if oral nutrition is not sufficient to achieve feeding goals (Grade of recommendations GPP – Strong consensus [100% agreement])
- Use enteral nutrition (EN) when patients with severe ASH cannot reach their calorie requirements by food / oral nutritional supplements (ONS) (Grade of recommendation B – Strong consensus [100% agreement])
  - This provides ↑ survival / ↓resolution of infection, especially in those with ASW who have moderate malnutrition
    - This does not ↑ risk of hepatic encephalopathy (HE)
    - This use of EN is as effective as the use of corticosteroids
    - In persons given EN for 4 wk, there is ↓ mortality over the next year (Grade B – Consensus [85% agreement])
- Use formula with ↑ energy density, ≥ 1.5 kcal per mL (Grade of recommendation GPP – Strong consensus [92% agreement])
- Use parenteral nutrition (PN) if oral/EN fail to provide sufficient nutrition for malnutrition for malnourished patients with NASH (Grade of recommendation, GPP – Strong consensus [100% agreement])
  - No ↑ survival, but ↓ infection / ↓ HE, and ↓ fatty infiltration in persons with moderately but not severe ASH.
  - Use PN if po/EN do **not** provide sufficient energy/protein if patient is hypermetabolic (after correction for urinary creatinine as a measure if lean body mass)
    - ↓ cough/swallow reflexes
    - Unprotected airway
    - Hepatic encephalopathy
- Supplement with appropriate electrolytes, trace elements, vitamins (Grade of recommendation GPP – Strong consensus [100% agreement])
  - Ensure that supplementation includes possible deficiencies in thiamin, folate, pyridoxin, zinc)
- Use formulas with ↑ energy density, ≥ 1.5 kcal per mL (Grade of recommendation, GPP – Strong consensus [92% agreement]
- If po/EN stopped at any time ≥ 12 h, give IV glucose 2-3 g/kg body weight per day.
- If lasts > 72 h (even if IV glucose is given) → total parenteral nutrition (Grade of recommendation, GPP – Strong consensus [100% agreement])

❖ **Non-alcoholic Fatty Liver Disease** (NAFLD)

- In patients with NAFLD/NASH, the associated metabolic syndrome plays an important role in comorbidity (Strong consensus, 100% agreement)
- In obese patients with NAFLD/NASH fail to ↓ body weight with changes in diet/lifestyle, consider bariatric surgery (Strong consensus, 100% agreement) may
  - ↓ body weight
  - ↓ steatosis NASH/fibrosis
  - ↓ insulin resistance

➢ Treatment

Recommendations

- Diet and exercise
  - Targets for patients with non-alcoholic steatohepatitis (NAFLD/NASH) plus big overweight/obese
    - To ↓ steatosis / ↓ ALT / ↓ AST 7-10%
    - To ↓ fibrosis > 10% (and sometimes full resolution of NASH
  - Weight loss after gastric bariatric surgery and improvement in hepatic histopathology

	Mean	95% CI
– ↓/resolution		
▪ Steatosis	81%	62-95%
▪ Fibrosis	66%	38-88%
– Resolution of NASH	75%	42-91%

  - First-line therapy
    - Hypocaloric diet (including fructose sweetened soft drinks) plus ↑ physical activity (Grade of recommendation A – Strong consensus [100% agreement])
  - Follow current obesity guidelines irrespective of the macronutrient composition (Grade recommendation A – Strong consensus [93% agreement])
  - Use a “Mediterranean diet” to improve steatosis and insulin sensitivity (Grade of recommendation B – Strong consensus [100% agreement])
  - In a person with NAFLD/NASH who is suffering a severe intercurrent illness and oral nutrition testing is “adequate/impossible/contraindicated”
    - Give EN/PN (Grade of recommendation, good practice points [GPP] – Strong consensus [96% agreement])
    - When PN is indicated in NAFL/NASH patients with BMI < 30 kg/m^2, give EN +/-PN, ≥ 1.5 kcal/mL with correction of deficiencies in electrolytes, vitamins, trace elements
    - When PN is indicated in NAFL/NASH patients with BMI > 30 mg/m^2 , target intakes of energy, 25 kcal/kg per day; perform 2.0-2.5 g/kg ideal body weight (IBW) per d (Grade of recommendation, GPP – Majority agreement [71% agreement])

- Exercise → ↓ steatosis
  - No data of effects upon hepatic steatohepatitis

  (Grade of recommendation A – Strong consensus [100% agreement])
- Alcohol
  - Abstain from any/all alcohol (Grade of recommendation A – Strong consensus [100% agreement])
  - There is a "...threshold for morbidity from cirrhosis but not for mortality regardless of gender"
  - "Once there are signs of liver disease of any etiology…abstain [from alcohol] due to the high relative risks for any consumption associated with mortality"

- NAFL/NASH plus celiac disease
  - Follow current guidelines in terms of treating celiac disease with treatment of any associated nutrient deficiencies and comorbidities, strict gluten-free diet for life, family screening when indicated, periodically surveillance for ↓ bone mineral density (DEXA scan), maintaining vaccinations up to date, and age-appropriate screening for cancer (e.g., breast, cervix, colorectum) (Grade of recommendation B – Strong consensus [96%])
  - Liver disease in celiac disease
    - ↑ ALT, ↑ AST at time of diagnosis of celiac disease (CD) 40%
  - Celiac disease in liver disease ("chronic unexplained elevation of transaminases ~9%)
    - In persons with hepatic cirrhosis ↑ risk of CD (2x)
    - Hazard ratio (HR) for NAFL/NASH in CD, 2.8 (95% CI, 2.0 – 3.8)
  - ↑ ALT / ↑ AST (transaminitis) in persons with CD
    - Improves on a gluten free diet in > 75%
    - Some patients with NAFL/NASH plus CD who are on the liver transplant list may improve sufficiently (↓ MELD score) that they can be delisted
    - A gluten free diet → ↓ complications in persons with associated autoimmune hepatitis (AIH), primary biliary cholangitis (PBC)

- Vitamin E (α-tocopherol)
  - In persons with NASH proven on liver biopsy, and who have no evidence of diabetes, give vitamin E (800 IU α-tocopherol daily (Grade recommendation B – Strong consensus (100% agreement)
    - Improvement
      - ↓ ALT / ↓ AST
      - ↓ abnormal NAFL/NASH histopathology
      - Vitamin E intake ↑ benefit of weight loss ≥ 2 kg (↓ ALT, ↓ NPS, ↓ fibrosis scores)
    - Caution for men with history of prostate cancer
      - Vitamin E may ↑ risk of prostate cancer
    - Safety (Cochrane meta-analysis) "no significant effect of antioxidants [including vitamin E) on all cause mortality or liver-related mortality"

- Do **not** use other antioxidants to treat patients with NAFL/NASH (e.g., anthocyanin, bayberries, resveratrol, vitamin C) (Grade of recommendation 0 – Strong consensus [100% agreement])
- Note
  - Vitamin C intake may be ↓ in NAFLD patients
    - Correct intake of vitamin C, but do **not** otherwise administer routinely
  - Preliminary data suggest benefit to ↑ the use of
    - L-carnitine
    - Omega-3 fatty acids

    } – Not currently recommended (Grade of recommendation 0 – Strong consensus [100% agreement])

- Probiotics/symbiotic
  - Use to improve liver enzymes in NAFL/NASH patients (Grade of recommendation 0 – consensus [89% agreement])
    - No specific dose/type of probiotics/symbiotics recommended
  - Usually ↓ ALT, ↓ AST, ↓ GGT, and in some studies even included ↓ hepatic triglycerides.

- Bariatric surgery
  - Use in non-cirrhotic patients with NAFL/NASH who have failed hypocaloric diet and exercise (Grade of recommendation B – Strong consensus [100% agreement])

A Sad Statistic

- Even with a multidisciplinary team encouraging dieting and exercising
  - < 10% of obese persons lose > 10% of their body weight

- Bariatric surgery improves NAFL/NASH

Histopathology	Bariatric Surgery
– NAFLD	92%
– NASH	81%
– Fibrosis*	66%
– Complete resolution of NASH	70%

*additional intraoperative findings of fibrosis in 47%, and cirrhosis in 4% of patients

- Perioperative mortality rate of NAFL/NASH patients from bariatric surgery
  - No cirrhosis, 0.3%
  - Cirrhosis
    - Compensated, 0.9%
    - Decompensated, 16%

- ↑ insulin sensitivity, ↓ need for antidiabetic medication (Strong consensus [100% agreement])

❖ Cirrhosis

Recommendations

- In patients with cirrhosis, a high prevalence of malnutrition, protein depletion and trace element deficiency should be anticipated" (Strong consensus, 100% agreement)
- Multidisciplinary team
  - Nutritional counselling/care (Grade of recommendation, GPP – Strong consensus [100% agreement]
  - Monitor nutritional states / guide nutritional goals (Grade recommendation GPP – Strong consensus [100% agreement])
- Nutritional intervention
  - Use current guidelines as for non-cirrhotic patients (Grade of recommendation A – Consensus [89% agreement]
  - Use EN/PN for potential clinical benefit without an increase in adverse effects

  (Grade of recommendation, GPP – Strong consensus [100% agreement])

- Nutrient requirements
  - Energy
    - ↑ energy expenditure
      - Malnutrition
      - Fasting/starvation
      - Overweight/obese
  - Protein/energy
    - Non-malnourished
      - 1.2 g/kg per day

      Grade of recommendation A – Strong consensus (100% agreement)
    - Malnourished +/- sarcopenia
      - 1.5 g/kg per day, plus
      - 30-35 kcal/kg per day

      (Grade of recommendation B – Strong consensus [100% agreement])
    - Persons who are intolerant to ↑ protein intake → provide adequate protein intake by using vegetable proteins, or branched chain amino acids (BCAA) 0.25 g/kg per day
      - BCAA may also be given in persons with advanced cirrhosis to
        - ↑ event-free survival
        - ↑ quality of life

      (Grade of recommendation B – Consensus (89% agreement)

- If energy/protein targets cannot be met by oral intake of food
  - Provide EN (Grade of recommendation B – Strong consensus [100% agreement])
  - Insert nasogastric tube to provide EN if no presence of esophageal varices (Grade of recommendation 0 – Strong consensus [100% agreement])
  - Only place a percutaneous endoscopic gastrostomy (PEG) tube in "exceptional cases" (↑ complications of severe ascites, INR > 1.5, PTT > 50s)

- Micronutrients
  - Correct clinically suspected/confirmed deficiency (Grade of recommendation, GPP – Strong consensus [100% agreement])
  - ↓ salt intake in persons with ascites, but balance the ↓ salt intake with the potential to ↓ food intake (and thereby ↓ intake of energy/protein) (Grade of recommendation GPP – Consensus [78% agreement])

- Obesity
  - In overweight persons
    - ↓ body weight by 5 kg plus supervised physical activity for 16 wk → ↓ HPVG
  - Use PN if EN/oral intake not effective/feasible (Grade of recommendation B – Strong consensus [100% agreement])

- After LT, there is ↑ risk of sarcopenic obesity and metabolic syndrome
  - Target early/rapid restoration of total body protein and muscle function (Strong consensus, 100% agreement)

- In ALF patients with ASH, deficiency of trace elements and vitamins is common (Strong consensus, 100% agreement)

- In ALF patients plus obesity, there is ↑ risk of
  - Death
  - Need for transplantation
  - ↓Mortality post-transplantation

  (Strong consensus, 100% agreement)

- In ASH/cirrhotic patients who are malnourished, there is ↓ survival (Strong consensus, 100% agreement).

❖ Surgery (elective, including listed for liver transplantation)

- Screen for malnutrition → correct energy/protein intake (Grade of recommendation B – Strong consensus [100% agreement]), as per the given recommendations for persons with cirrhosis (Grade of recommendation, GPP – Strong consensus [100% agreement]).

- Use the "ERAS" approach (Grade of recommendation good practice points [GPP] – Strong consensus [100% agreement])

- Use standard nutrition requirements (Grade of recommendation A – Strong consensus [100% agreement])

- Non-obese
  - Energy
    - 30-35 kcal/kg per day
  - Protein
    - 1.2-1.5 g/kg per day

  (Grade of recommendation, GPP – Strong consensus [100% Strong consensus [100% agreement])

- Obese
  - Energy
    - 25 kcal/kg per day
  - Protein
    - 20-25 g/kg per day

  } May use EN/PN if necessary to reach targets

  (Grade of recommendation, GPP – Strong consensus [93% agreement])
  - Manage nutrition as per recommendations given previously for NASH (Grade of recommendation, GPP – Strong consensus [100% agreement])

- Post-operatively
  - Within 24 h
    - Normal food intake/EN (Grade of recommendation B – Strong [100% Agreement])
      - For early post-operative EN, use NG/NG feeling tubes (as in non-liver disease surgery (Grade of recommendation B – Strong consensus [100% agreement])
      - EN nutrition formula may be given with selected probiotics (Grade of recommendation B – Consensus [86% agreement])
      - If the patient who requires EN has HE, use BCAA-enriched formulars (Grade of recommendation – Majority agreement [79%])
    - Manage according to the ERAS protocol (Grade of recommendation, GPP – Strong consensus [100% agreement])
    - Use PN
      - When normal food intake/EN not possible/practice → PN (↓ length of ventilation / ↓ length of hospital stay [LOS] in ICU) (Grade of recommendation B – Consensus [86% agreement])
      - When EN not possible/practical
      - When HE present, plus unprotected airway
      - ↓ cough/swallowing reflexes (Grade of recommendation GPP – Strong consensus [100% agreement])

- Donor of liver explant
  - There are **no** recommendations for nutritional regimes for the donor, e.g. arginine, glutamine (to ↓ risk of ischemic/reperfusion injury) (Grade of recommendation GPP – Strong consensus [100% agreement])

- Nutrition-associated liver injury (NALI)
  - Malnutrition
    - Results in a wide range of hepatic dysfunction, as well as severe fatty liver (String consensus [100% agreement])
  - Overnutrition
    - May also cause NAFL/NASH (Strong consensus [100% agreement])
  - In patients with parenteral nutrition associated liver disease (NAFLD) it may be difficult to distinguish between the PN and sepsis / extensive small bowel resection (Strong consensus, 100% agreement)
  - Parenteral nutrition-associated cholestasis (PNAC)
    - Incidence and mortality are variable (0 to 50%, and 0 to 22%, respectively)
    - Other causes of cholestasis need to be excluded before blaming the PN, e.g., sepsis, or extensive resection of the small bowel (NAFLD, intestinal failure associated liver disease, ↓ choline, ↑ Mg (toxicity) (Strong consensus, 100% agreement)
    - When PNAC progresses, small bowel transplantation may be necessary
    - Use an infusion of a mixture of fish-oil emulsion (the fermentation of ↓ Nl/N3 rate may reverse biopsy demonstration changes of PNAC) (Grade of recommendation B – Strong consensus [92% agreement]

Abbreviations: ALF, acute liver failure; ASH, alcohol steatohepatitis; BM, biomedical endpoint; CD, celiac disease; CI, confidence interval; DM, decision making endpoint; DMT, diabetes mellitus; EN, enteral nutrition; GGT, gamma glutamyl transferase; GPP, good practice points; HE, hepatic encephalopathy; HEE, Health economic endpoint; IBW, ideal body weight; IE, integration of classical and patient-reported endpoint; INR< international normalized ratio; K^+, potassium ion; LT, liver transplant; Mg^{2+}, magnesium ion; NAFL, non-alcoholic fatty liver; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; NH_3, ammonia; PNAC, parenteral nutrition associated cholestasis; po, by mouth; PO_4^{2-}, phosphate ion; PTT, partial thromboplastin time; QALYs, quality adjusted health years; RFH-NPT, Royal Free Hospital – Nutrition Prioritization

Malnutrition, Frailty, and Sarcopenia in Patients with Cirrhosis: AASLD Practice Guidelines (2021)

Lai JC, et al. Hepatology 2021; 74: 1611-1635

➢ Definition

- Malnutrition
  - "A spectrum of nutritional disorders across the entire body mass index (BMI)"…resulting in…"a clinical syndrome that results from an imbalance (deficiency or excess) of nutrients that causes measurable adverse effects on tissue/body from (body shapes, size, composition) or function, and/or clinical outcome"

➢ Pathophysiology

- ↓ intake, digestion, absorption
- Contributing factors in persons with chronic liver disease
  - Liver accelerated starvation / hypermetabolism
    - ↓ glycogen synthesis. storage
    - ↑ gluconeogenesis
    - ↑ fatty acid oxidation
    - ↑ body protein breakdown, especially branched-chain amino acids
  - Muscle myotoxic effects of ↑ ammonia (NH_3) posttranslational changes of muscle contractile proteins → ↓ muscle mass / function
- Contributing factors
  - Alcohol use disorder (AuD)
  - NAFLD
    - Insulin resistance → adipocyte system → inflammation
    - ↑ markers of inflammation: IL-1, -6, -10, c-reactive protein (CRP), tumour necrosis factor (TNF-α)
  - ↑ BMI / obesity (associated with ↓ skeletal muscle index (SMI)
  - HCV infection
  - Alterations in gut microbiome
  - ↓ testosterone, growth hormone secretion / sensitivity

➢ Measurement

- Frailty
  - "Impaired muscle contractile function" which results in "…decreased physical function, decreased functional performance, and disability"
  - Assess global or individual components
    - Many subjective tools, such as
      - Activities of daily living (ADLs)
      - Karnofsky Performance Status (KPS)
      - Liver Frailty Index (LPI)

➢ Prevalence

- Varies by measurement tool used
  - In general, ↑ frailty with ↑ severity of liver disease
  - Examples: cirrhosis patients, hospitalized
    - Hepatic encephalopathy (HE), 38%
    - No HE, 18%

Guidance Statement

- Assess all patients with cirrhosis for frailty at baseline and longitudinally q1yr if cirrhosis compensated and q3-6 mon if decompensated
  - No one specific assessment tool is recommended
- "All patients with cirrhosis should be counselled on the risk and adverse clinical consequences of frailty regardless of their baseline status"

➢ Outcomes

- Frailty improves in 90% after liver transplantation
- Improvement in frailty associated with
  - ↓ mortality, ↓ disability
  - ↑ quality of life (QoL)

• Sarcopenia

- "The phenotypic manifestation of loss of muscle mass"
  - Associated with ↑ mortality
  - Above three functions are clinically interrelated
- Progressive with ↑ severity of liver disease

➢ Measurement

- Clinical
  - Mid arm muscle circumference (MMC)
  - Triceps skin fold thickness (TSFT)
  - Body mass index (BMI)
- Physiological
  - Bioelectric impedance analysis (BIA)
    - Phase angle measurements useful in presence of ascites
- Diagnostic imaging
  - Ultrasound
  - MRI
  - CT
    - "gold standard" for diagnosis of sarcopenia, using quantitative morphomics software
  - DEXA (dual energy X-ray absorption) scan

- Prevalence
  - Sarcopenia patients with cirrhosis
    - Men, 59%
      - Correlated with severity of liver disease
    - Women, 21%

- Outcomes
  - Sarcopenia predicts outcomes before/after liver transplantation (LT) with/without HCC
    - Mortality: e.g., predicting mortality on LT waitlist
      - Cut-off points, cm^2/m^2
      - Men, < 50
      - Women, < 39
    - Development of WE
    - Infection
    - Length of hospital stay

SO YOU WANT TO BE A GASTROENTEROLOGIST!

- Define "Sarcopenic Obesity" (↓ SMI, ↑ BMI)
  - A low sex-adjusted SMI, and ↑ BMI of ≥ 25 kg/m^2
    - With sarcopenic obesity in NAFLD, ↑ progression to cirrhosis

- Screening

Guidance Statements

- Perform objective measurements of muscle loss at baseline and longitudinally in patients with cirrhosis (prognostication, intervention)
  - Preferred method is SMI measurement by CT image analysis
    - Do **not** do CT just for determination of SMI when CT performed for other purposes
  - MRI not yet validated to assess muscle mass in persons with cirrhosis
    - There are no bedside tools
- Testing for sarcopenia may be substituted for assessment of frailty in persons who are too sick or are not able to complete frailty testing
- In research studies if possible, assess both frailty and sarcopenia
- Screen for frailty/sarcopenia
- Multidisciplinary team (MDT)
- Educate patient and family

- Nutritional assessment and management
  - Energy, protein, vitamins
- Identify/treat contributing factors, including dietary intervals, inadequate exercise, comorbidities, complications of liver disease (ascites, HE)
- Possible hormone treatment
- Use TIPS/LT for standard indications, but **not** specifically for frailty / sarcopenia.
- The patient listed for LT with frailty
  - Treat before LT (LT reduces frailty, but the rates of improvement are related to the pre-LT frailty)
  - Frailty / sarcopenia by themselves are not absolute contraindications to LT

Guidance Statements

- Treat all the conditions associated with cirrhosis and to complications in order to manage any associated malnutrition, frailty and sarcopenia.
- If TIPS is indicated for ascites or for acute variceal bleeding it may improve the above conditions, but do **not** use a TIPS for primary treat if malnutrition, frailty and sarcopenia.
- Do **not** consider frailty or sarcopenia as absolute contraindications for LT.

➢ Nutritional Care

Guidance Statements

- Provide personalized, intensive nutritional support, including educational resources and counseling
  - Tailor the patient's need and include consideration of their personalized habits around nutrition

❖ Outpatients

- Energy
  - Calculate the patient's resting energy expenditure (REE)
    - Indirect calorimetry (metabolic cart)
    - Predictive equations
      - Harris-Benedict
      - Mifflin-St. Jeor

- Recommended calorie intake for patients with cirrhosis
  - No fluid retention – 35 kcal/kg per day
  - With fluid retention, estimate the patient's dry weight
    - + post-paracentesis, or
    - + estimate severity of fluid excess, and subtract a percentage of the patient's body weight to find the "dry-weight"
      - Mild, 5%
      - Moderate, 10%
      - Severe, 15%
      - If bilateral pedal edema present to the knees, add an extra 5%
  - BMI corrections (after correction for excess water)

BMI kg/m^2	Energy Intake (kcal/kg per day)
30-40	25-35
≥ 40	20-25

  - Na^+ reduction to 2 g Na+ may lead to ↓ undesirable calorie intake
    - Suggestion: liberalization of sodium restriction should be considered if the patient is unable to maintain nutritional targets because of diet unpalatability

Guidance Statements

- If indirect colorimetry is not available to measure the cirrhotic patient's REE, use
  - Predictive equation, e.g., Harris-Benedict
  - Weight-based equations using patient's ideal body weight
  - Kcal/kg per day
    - Non-obese, at least 35 kcal/kg per day
    - Obese (non-hospitalized, clinically stable)

BMI kg/m^2	Energy Intake (kcal/kg per day)
30-40	25-35
≥ 40	20-25

- If patient has cirrhosis plus frailty or sarcopenia while on a salt-restricted intake, consider liberalizing sodium intake

- Protein Intake
  - Recommended daily protein intake in patients with cirrhosis, 1.2-1.5 g/kg
  - Use ideal body weight (based on height) for "prognostic reasons"
  - No need to use branched-chain amino acid (BCAA; valine, leucine, isoleucine)
    - No evidence for benefit of supplementation with individual amino acids

Guidance Statements

- For patients with cirrhosis, give 1.2-1.5 g/kg ideal body weight per day
  - If patient is critically will, increase protein intake to 1.2-2.0 g/kg per day
- Use multiple sources of protein, with no need to supplement protein intake with BCAA or individual amino acids
- Do **not** decrease daily protein intake in cirrhotic patients with hepatic encephalopathy

- Timing of Food Intake
  - Avoid prolonged fasting
    - Give attention to multiple tests requiring fasting
  - Use 3 meals per day plus snacks q3-4 h while patient is awake

Guidance Statements

- Minimize fasting times while patient is awake, nutritional intake should be q3-4 h
- Reduce the nocturnal fasting time, provide an early breakfast and a late evening snack (~150 to 700 kcal)

- Methods of Feeding
  - If patient cannot meet their dietary intake of calorie/proteins, consider carefully whether enteral nutritional supplementation would be useful +/- safe
    - There is evidence that placement of an enteric feeding tube in a patient with cirrhosis and from esophageal varices is associated with upper GI bleeding within 48 h in 15% of patients
    - In patients with esophageal varices (EV), which stop bleeding and an enteral tube is inserted for nutritional purpose, EV rebleeding within 48 h occurs in 15%
    - The MELD-Na score predicted the ↑ risk of bleeding (a second study did **not** confirm the risk of bleeding)
  - Do **not** use a percutaneous gastrectomy tube to provide feeding
    - ↑ complications
    - ↑ mortality
    - This risk is particularly if there is ascites or portal hypertension resulting in collate vessels developing, such as in the anterior abdominal wall (Caput medusa)

Guidance Statements

- When nutritional requirements of the patient with cirrhosis are not satisfied by oral intake, consider inserting a feeding tube
  - Do **not** place a percutaneous gastroscopy tube in the patient with cirrhosis plus ascites

- Cirrhosis, Frailty/Sarcopenia and Obesity
    - Overweight/obese patients with cirrhosis weight loss of only 5% - 10% →
        - ↓ portal hypertension
        - ↓ progression of liver disease
        - If this obese patient also has frailty/sarcopenia, a multidisciplinary team (MDT) is recommended so that the ↓ energy intake does not affect the required protein intake of 1.2-1.5 g/kg per day to help correct the sarcopenia/frailty

Guidance Statements

- Special must be taken to attempt to reduce obese patients' body weight when she/he has decompensated cirrhosis
    - Use required/recommended adequate intake of protein and stress the importance of an exercise program to decrease the excess body fat without reducing the muscle mass/function with severe acute alcoholic hepatitis

❖ Inpatients

- One randomized controlled trail (RCT) of hospitalized patients with severe acute alcoholic hepatitis showed that energy intake of ≥ 2.2 kcal/kg per day → ↓ mortality 67%, regardless how the calories were provided
    - A meta-analyzes of nutritional supplementation in hospitalized patients with all causes of cirrhosis did not show a benefit of nutritional support on mortality
    - Critically ill hospitalized patients with cirrhosis, at targets
        - 21.5 kcal/kg per day of protein
        - 1.2-2.0 g/kg per day of protein
    - This may ↓ mortality by
        - ↑ hyperglycemia
        - ↑ sepsis

Guidance Statements

- For hospitalized patients with cirrhosis, obtain a professional dietary consultation with 24 h implement a feeding program to ↓ fasting intervals/duration, including when a patent is fasting for procedures.
    - Advance NPD diet when no longer necessary
- Use oral nutritional supplementation for hospitalized patients who cannot meet their energy needs "…through volitional intake alone"
    - If volitional intake and oral nutritional supplement do **not** achieve nutritional targets
        - Provide enteral nutritional support
    - Only use parenteral nutrition if enteral nutrition and oral intake
        - If absolutely necessary use parenteral nutrition in patients with decompensated cirrhosis

- When providing enteral nutritional support, take care to avoid
  - Pulmonary aspiration
  - Hyperglycemia
  - Bleeding from esophageal varices, including recurrent bleeding treated with banding of EV
- Micronutrient deficiencies
  - Assess at least q1yr
  - Provide oral multivitamin supplement when appropriate

❖ Physical activity

Guidance Statement

- Provide both aerobic and resistance training to ↑ muscle mass / ↑ muscle contractile function
  - Moderate / vigorous intensity, 150-300 mm per wk
  - Muscle strengthening exercise, 2 d/wk
  - Tailor the above based upon each patients' baseline and follow up assessment of frailty and sarcopenia, based on standard tools

❖ Hormone replacement

Guidance Statements

- If blood testosterone concentrations are low, consider testosterone replacement therapy (TRT)
  - Low testosterone levels
    - Total < 12 nmol/L
    - Free < 230 pmol/L
  - Do **not** give TRT if the man has
    - HCC/history of HCC or malignancies
    - History of thrombosis

Reproductive Health in Patients with Liver Disease: AASLD Practice Guidance (2021)

Sarkar M, et al. Hepatology 2021; 73; 318-364.

❖ **Sexual Function in Patients with Chronic Liver Disease** (CLD)

➢ Suggestion

- In the patient with CLD, always inquire about sexual dysfunction (SD)
  - If SD present, investigate and treat as appropriate.

➢ Background

- Women with CLD
  - Abnormal hypothalamic-pituitary axis (HPA) → ↓ FSH (follicle-stimulating hormone) / ↓ LH (luteinizing hormone) →
    - Anovulation
    - Amenorrhea (25%)
    - ↑ fertility
    - ↓ libido
    - ↑ dyspareunia
- ↑ severity of CLD in pregnancy/postpartum/breastfeeding
  - ↑ complications
    - Obstetrical
    - Perinatal
    - From medication

Clinical Alert

- Although female fertility is reduced in patients with CLD, even those with decompensated liver disease or liver transplantation may become pregnant.
  - The key: use effective contraception plus planned parenthood

- Men with CLD
  - Hypogonadotropic hypogonadism
  - ↑ estrogens
    - ↑ peripheral conversion of androgens to estrogen
    - ↑ SHBG (sex hormone-binding globulin) → ↓ free testosterone
    - ↓ HPA function
  - Male sexual dysfunction

- Risk factors for ↑ sexual dysfunction in females/males with CLD
  - Drugs/toxins
    - Alcohol
    - Beta blockers
    - Spironolactone
  - Psychological factors
  - Cause of CLD
    - Hemochromatosis → hypogonadism
    - Diabetes-associated NALFD → autonomic dysfunction

❖ Planned Parenthood

- Women of reproductive age who have CLD should always be asked about sexual activity and desire to become pregnant.
- Importance
  - Optimize associated CLD
  - Look for and trat any liver-related complications
  - Psychosocial support
  - Where appropriate consultation with
    - Specialties in maternal-fetal medicine)
    - High risk obstetrician
    - No mental-health worker
- Safe contraception for women with

- Combined Hormonal Contraception (CHC)
  - Chemistry
    - Estrogen plus progestin
    - Failure rate, 9%
  - Safety
    - Central nervous system (CNS)
      - Stroke
    - Cardiovascular system (CVS)
      - Venous thromboembolism (VTE)
      - Hypertension (HBP)
    - GI
      - Cholestasis
    - Possible ↑ risk of breast cancer

- Do **not** use OCP if
  - Budd-Chiari syndrome (BCS)
  - Decompensated cirrhosis
  - Graft failure after LT
  - NAFLD (women with multiple cardiovascular risk factors)
  - Use of multiple medications metabolized by the cytochrome P450 system (↑ risk of drug-drug interactions)

- Progestin-only contraception
  - Non-estrogen oral contraceptives
    - Depot medroxyprogesterone acetate (DMPA) injections q12wk
    - Failure rate, 6%
    - ↓ bone mineral density (BMD)
    - Implants of DMPA
      - Long-acting reversible contraceptive (LARC)
      - Failure rate, 0.05%

    } ▪ No estrogen-associated AEs (stroke, HBP, VTE)

Treatment Tip

- Advise women taking hormonal contraception (progestin [P] +/- estrogen [E]) to also use a barrier method because of P/E failure rate of 9%.

- Intrauterine Devices (IUDs)
  - Low failure rates
    - No ↑ risk of pelvic inflammatory disease (PAD)

Clinical Tip

- Immunosuppression: IUDs remain effective (safe in patients with LT, including graft failure)
- The IUDs have the lowest failure rates, are long lasting, and do **not** depend upon the patient remembering to take the medication.

- Contraception in perioperative period
  - Patient already on contraception
    - Continue
  - Patient not on contraception, wish to avoid pregnancy after intercourse ("emergency contraceptive")
    - Copper IUD, or
    - Hormone contraceptive pill
      - Estrogen plus progestin, except not with
        - Budd-Chiari syndrome (BCS)
        - Decompensated cirrhosis
        - LT graft failure
        - Hepatocellular adenomas (HCA)
  - Choice of contraception
    - ↑ risk of unplanned pregnancy (especially adolescents)
      - Use long-acting reversible contraceptive (LARC)
    - Not using LARC
      - Use hormone contraception plus barrier method because of failure rate of oral contraceptive pill (OCP) of 9%
      - Change from use of any teratogenic agents such as mycophenolic acid (MPA)
    - ↑ risk of AEs from estrogens
      - Adenomas (hepatic): BCS, cirrhosis, decompensation, LT plus graft failure (GF)
      - Use other methods of contraception
    - Emergency contraception
    - Always consider young/older women with CLD may benefit from
      - Psychosocial support
      - Maternal-fetal medicine (MFM) specialists

❖ Associated conditions

- Women with CLD have ↑ risk of infertility if their cirrhosis is decompensated (fertility ↓ by 40%) ("…failure to achieve pregnancy within 12 mon of unprotected intercourse, or donor insemination in women younger than 35 yr of age, or 6 mon in women older than 35 yr of age
- After LT
  - Pregnancy may be assisted with in vitro fertilization (success rate ~80%) after 3 cycles
  - Live birth rate in women with CLD plus IVF
    - Mother with CLD but no cirrhosis, 67%
    - Mother with cirrhosis, 50%
- In vitro fertilization is possible in women with cirrhosis or LT

- Preconception counseling for risk stratification is recommended: successful IVF is more likely in Child-Turcotte-Pugh cirrhosis A
  - In women with LT :…stability of graft function should be assessed"

❖ Reproductive Aging

- Menopause (women)
  - Perimenopausal ↓ estrogen
  - Hormone replacement therapy (HRT) → ↓ menopausal symptoms
- Do **not** use HRT for treatment of menopause in women with
  - Budd-Chiari syndrome (BCS)
  - Cirrhosis, decompensated
  - Hepatocellular adenomas (HCAs)

SO YOU WANT TO BE A GASTROENTEROLOGIST!

- Give the effects of CLD on bone health, and give the benefits of estrogen-containing HRT.

Bone Changes in CLD	Benefits of HRT in CLD
○ ↓ Synthesis of new bone ○ ↑ resorption of new bone ○ ↓ muscle mass / ↓ exercise (mobility) ○ ↑ malnutrition	− ↑ activity of hepatic stellate cells/fibrinogenesis − Improve/reverse adverse effects of CLD in bone health

- Andropause (men)
  - Synonyms: testosterone deficiency, or late-onset hypogonadism
  - ↓ testosterone (T) in older men, plus further ↓ T because of CLD
    - The ↓ T usually remains in the normal range
    - The correlation is poor between symptoms of deficiency of T and blood concentration of T
    - Supplementation of ↓ T in CLD →
      - ↓ loss of muscle mass (sarcopenia)
      - ↓ survival (trend)
      - ↑ liver enzymes (LEs), self-limited
  - Testosterone supplementation may be used in men with CLD and hypogonadism

- Transgender Health
  - General approach
    - Welcoming and supportive physician and environment
    - Educated MDs/RNs/Staff

    } ▪ ↓ barriers to care
  - Transgender patients
    - Female → male
      - Screen: polycythemia
      - Treatment: androgen

❖ Laboratory and Diagnostic Testing for possible liver disease in pregnancy

- Physiological and hormonal changes in pregnancy
  - CVS
    - Systemic circulation
      - ↓ resistance
      - ↓ blood pressure
    - Splanchnic circulation
      - ↑ vasodilation
    - ↑ heart rate / ↑ cardiac output (50%. T3)
    - ↑ volume
      - RBC and plasma (blood volume)

    } ▪ Hyperdynamic circulation
  - Gallbladder
    - ↓ GB emptying → ↑ gallstones
  - Liver
    - ↑ portal hypertension → esophageal varices (EV) / EV enlargement
    - ↑ IVC compression e.g., uterus →
    - ↑ collateral blood flow
    - ↓ hepatic metabolism / ↓ clearance of drug
    - Altered liver enzymes (LEs) / liver function tests (LFTs)

Approach to patients with liver dysfunction in pregnancy

- Aminotransferases (ALT, AST), bilirubin (Br), bile acids (BAs) usually normal in pregnancy
- Which LEs/LFTs
  - Stay normal in healthy pregnancy
  - ↑/↓ during pregnancy

- Liver diseases unique to pregnancy

Trimester	Wks	Name
○ T1	0-12	− Hyperemesis gravidarum (HG) − Intrahepatic cholestasis of pregnancy (ICP)
○ T2	13-28	− Pre-eclampsia (>20) − HELLP (> 27)
○ T3	29-4	− ICP (> 30) has occasionally been reported in T1 − Acute fatty liver of pregnancy (AFLP) (> 29)

  - The usual time of onset of liver diseases unique to pregnancy are shown above in brackets
    - If any of these laboratory tests is abnormal in pregnancy → investigate
  - Liver diseases in pregnancy which may ↑ severity in pregnancy
    - Cirrhosis
    - Vascular disease of the liver
    - Gallstones

➢ Suggestions

❖ Diagnostic Imaging

  - Abdominal ultrasound with Doppler (with **no** contrast)
    - Limit Doppler exposure time to assess maternal hepatic vasculature
    - Use MRI/MRCP without gadolinium (contraindicated in pregnancy)
      - Crosses placenta
      - Excreted by fetus into amniotic fluid (↑ fetal exposure)
  - Limit diagnostic imaging using radiation
    - Iodinated contrast
      - During pregnancy
        - May cause neonatal hypothyroidism
      - While breastfeeding
        - Safe
    - Gadolinium
      - Safe to fetus and mother during
        - Pregnancy, **No**
        - Breastfeeding, Yes
  - Elastography
    - Not yet sufficient data to be evaluated for safety in pregnancy

- Suggestions
  - Consider abdominal ultrasound to be safe during pregnancy
  - Unless absolutely necessary in pregnancy, do **not** do diagnostic imaging
    - CT (ionizing radiation)
      - Limit cumulative dose to < 50 mEq
    - MRI with gadolinium
    - Iodinated contrast
    - Elastography (until more safety data is available)
  - MRI/MRCP is done without gadolinium (contraindicated in pregnancy)
    - Preferred to abdominal CT (ionizing radiation) even without contrast

Safety Issue

- During breastfeeding, gadolinium/iodinated contrast are safe to use, but
  - Do **not** use gadolinium or iodination during pregnancy

Treatment of Chronic Liver Disease: Drug Pregnancy and Lactation

- Hepatitis B Virus (HBV)
  - "Chronic HBV [infections] has little influence on the course of pregnancy"
  - Mother, prenatal
    - Test for HBsAg
    - If prenatal mother already on non-TDF antiviral →
      - Switch to TDF anti-viral
      - If considering stopping anti-HBV therapy (~5% to 25%)
    - In women planning pregnancy have advanced fibrosis from HBV infection
    - Do **not** stop therapy (fear of relapse/decompensation)
  - Mother-to-child transmission (MTCT)
    - ↑ ALT/ ↑ AST may occur if anti-viral therapy stopped
    - Vaccinate baby within 12 h of birth
    - The risk of MTCT is very rare if mother's HBV DNA < 200,000 IU/mL
    - If ↑ HBV DNA in mother and mother treated with anti-viral therapy (TDF) in T3, wk 28-32, then MTCT is reduced 70%, from 27% to 8%
    - If HBV DNA ≥ 7 log IU/mL, then because of the ↑ risk of MTCT, stop TDF at time of birth of child
    - MTCT is not reduced by cesarian section (cesarian delivery should be used for obstetrical indications only)
    - If HBV DNA ≥ 7 log IU/mL and amniocentesis early use of HBV antiviral therapy

- Prolonged rupture of the membranes or long duration of labour
  - Give the infant monoprophylaxis
- Breastfeeding
  - Safe even in the presence of cracked or bleeding breast nipples if infants are vaccinated and are given HBIG

➢ Suggestions

- Perform a test for HBsAg
  - If newly HBsAg+, link patient with a clinician knowledgeable in the long-term management of HBV
- For all women who are HBsAg+
  - Inform patient of ↑ risk of CTCT with all invasive pregnancy procedures (e.g., amniocentesis)
  - In T2, measure HBV DNA and if ≥ 200,000 IU/mL
    - Start anti-viral therapy
    - Stop HBV therapy at delivery or up to 3 mon postpartum
  - When anti-viral stopped, or up to 6 mon post-partum
    - Reassess ALT/HBV DNA
- Breastfeeding is recommended ("not contraindicated") either with or without continuation of antiviral therapy

- **Hepatitis C** (HCV) **Infection**
  - Test all pregnant women for HCV infection ("universal screening")
    - If HCV+, refer patient to a clinician who can address the timing of optimal postpartum therapy.
  - ↑ risk of adverse outcome from HCV infection during pregnancy (↑ 1.6x)
    - ↑ risk of intrahepatic cholestasis of pregnancy (ICP)
      - Odds ratio (OR) 20.14; 95%CI: 9.4 to 44.3)
  - Clearance of HCV may occur postpartum in 25%
    - Repeat HCV-RNA testing postpartum
  - Risk of CT
    - HCV, 6%
    - HCV plus HIV, 11%

    } ▪ Intra-/peri-/postpartum
  - HCV+ mother: amniocentesis may be necessary
    - Avoid contact with placenta
      - Invasive monitoring of fetus
      - Episiotomy
      - Prolonged rupture of ruptured membranes (↑ risk of MTCT, OR, 9.3)

- Breastfeeding
  - Considered to be safe, no significant association between breastfeeding and HCV transmission", but
    - Do **not** breastfeed during antiviral therapy
  - However
    - Do **not** breastfeed if mother's nipple is cracked
- Children born to mothers who are HCV+
  - < 18 mon
    - Parents to undertake precautions to ↓ risk of HCV transmission
  - > 18 mon
    - Infants should be tested for anti-HCV

➢ Treatment

- Do **not** start treatment of HCV during pregnancy
  - If mother already on DAA therapy for HCV "… the decision to continue [HCV antiviral} therapy requires careful considerations"
  - Possible special circumstances to continue HCV treatment during pregnancy
    - ↑ risk of virological response
    - ↑ risk of mother-to-child transmission (MTCT)
- Do **not** use ribavirin (RIB)
  - RIB must be stopped by male or female partners with HCV treated with RIB
  - Stop the RIB ≥ 6 mon before planned conception
- If conception not planned, both male and female partners must use "…highly effective contraception"

➢ Suggestions

- Test pregnant women for HCV at each pregnancy
  - If HCV+
    - Begin HCV treatment after delivery and after completion of breastfeeding
- For woman of childbearing age who are HCV+
  - Give preconception antiviral therapy for HCV
- If men or women with HCV require use of ribavirin
  - Use highly effective contraception (HEC; e.g., copper IUD)
  - Stop RIB and continue HEC for ≥ 6 mon
- Inform women who are HCV+ to avoid
  - Invasive pregnancy procedures, such as amniocentesis (may cause MTCT)
  - Invasive fetal monitoring, prolonged rupture of membranes, episiotomies.
- No need to monitor mother for ↑ ALT flares in HCV+ women not necessary

- Breastfeeding can be done safely by mother who is HCV+, except
  - Do **not** so breastfeeding
    - During anti-HCV therapy of mother
    - If skin breakdown plus bleeding of the mother's nipple

- **Wilson disease** (WD)

➢ Pathophysiology

- Genetic mutation of the aminophospholipid transporter synthase (ATPase) copper transporter translocase ATP7B, aka P-type ATPase
  - Abnormal hepatocyte ATP7B leads to accumulation of copper in liver/body

➢ Clinical effect on female fertility

- ↑ amenorrhea/oligomenorrhea
- ↓ fertility
- ↑ spontaneous abortion (less likely if woman maintained on therapy)

➢ Treatment

- The optimal approach for the WD women is to be on double protection against conception, then once excess copper has been mobilized, switch to zinc, stop contraception medications, and continue on zinc.
- Concern that D-penicillamine is teratogenic
  - If pregnant and on D-penicillamine, reduce dose ¼ to ½ of their usual prepregnancy dose
  - After pregnancy, if D-penicillamine dose was reduced during pregnancy then restore the dose to the higher dose used before pregnancy.
- Chelation therapy (D-penicillamine, or trientine) to deplete ↑ copper stores
  - Perform 24-h copper concentration measurement
    - Switch from chelation depletion therapy to oral zinc maintenance therapy once urinary copper in normal range
- Advise women to use double contraception method while on D-penicillamine
  - Plan for conception when ↑ copper stores are depleted, and patient is maintained on zinc po

Treatment Tip

- Do **not** suddenly stop therapy for WD, especially during pregnancy.

- Breastfeeding
  - **No** breastfeeding in mothers with WD

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- Give the reason to discourage breastfeeding of the mother with WD.
  - Normally mother passes copper (Cu) into fetus.
  - In WD
    - The ATP7B is present in the mammary glands to ↓ Cu in mother's milk
    - The drugs used to treat WD are also excreted in mothers' milk and are present in ↑ amounts
      - The effect of ↑ drug in milk and ↓ copper in milk leads to ↓ Cu available to suckling baby → risk of development of Cu-deficiency in child.

➢ Suggestions

- Advise women with WD before conception re
  - Birth control information and instruction
  - Genetic counseling
  - Timing of use of chelation therapy for depletion of Cu, then switching to Zn to maintain Cu balance
- With patient's Cu-stores depleted by chelation therapy, and patients' urinary copper concentration maintained in the normal range on zinc, then continue on zinc and proceed with planned pregnancy
  - If patient continued on D-penicillamine at reduced dose during pregnancy, then postpartum ↑ dose to the prepregnancy level, and monitor 24-h urine copper to determine timing to switch to Zn.
- Do **not** breastfeed the child of a mother treated for WD.

- **Autoimmune Hepatitis** (AIH)
  - ↓ female fertility in patients with AIH, even in the absence of cirrhosis
  - Pregnant women with AIH have
    - ↑ ALT flares, especially in the first 3 mon post-partum (~25%)
      - ↑ risk of flare if
        - < 1 yr of remission before conception
        - Lack of immunosuppression therapy
    - Some have ↓ ALT / spontaneous remission
    - If ↓ immunosuppression dose reduced during pregnancy, ↑ dose early post-partum
  - Corticosteroids, azathioprine are safe to use in pregnancy
    - Do **not** use mycophenolate (MPA): ↑ risk of
      - Congenital malformations
      - Spontaneous abortions

➢ Suggestions

- Advise patient with AIH who is wishing to become pregnant
  - Use double contraceptive protection until AIH well controlled with immunosuppression for ≥ 1 yr
  - Reassure patient that immunosuppression with corticosteroids/azathioprine is safe in pregnancy, but **not** mycophenolate (MPA)
  - Understand that worsening of the AIH and even decompensation is common during pregnancy (~25%)
- Perform LE testing during each of T1, T2 and T3, plus post-partum q2-4 wk for 26 wk

Clinical Gem

- AIH may occur for the first time in the postpartum period.

- **Primary Biliary Cholangitis** (PBC)

➢ Demography

- De novo PBC may occur during pregnancy in (~30% of new diagnoses)

➢ Clinical

- Fertility and maternal outcomes of pregnancy may be worse in PBC
  - IgM/M2 ↓ during pregnancy, returns to baseline postpartum
- Clinical course
  - During pregnancy
    - Stable/improved in 70%
    - Onset ↑ pruritis in ~50%
  - Postpartum ↑ PBC activity in ~70%
- Because the patient with PBC/PSC may also develop intrahepatic cholestasis of pregnancy (ICP), measure serum bile acids in T1 as a baseline for any later change which would suggest ICP.

➢ Treatment

- Ursodeoxycholic acid (UDCA) maintained during/after pregnancy
- Continue UDCA during pregnancy and breastfeeding in patients with PBC, but do **not** use obeticholic acid or fibrate (lack of safety data)

- If pruritis develops
  - Treat symptoms with choice if adding
    - Cholestyramine (4-16 po od)
    - Rifampicin (300-600 mg po od)
    - S-adenosyl-L-methionine (SAMC)
  - Antihistamines
  - If ↑ PBC activity during pregnancy, or if adding cholestyramine to UDCA → ↓vitamin K → ↑ risk of bleeding, requiring supplementation with vitamin K
  - Monitor INR during pregnancy, especially if patient taking UDCA plus cholestyramine

- **Primary Sclerosing Cholangitis** (PSC)
  - PSC and pregnancy
    - Fertility, no effect
    - ↑ preterm births (16% vs. 5% for healthy controls)
    - ↑ cesarian sections (29% vs. 13%)

    } ▪ May be partially the effect of IBD in PSC patient with IBD
  - During pregnancy
    - ↑ de novo pruritis
      - If cholestyramine used, monitor INR
    - ↑ abdominal pain
    - Stability of LE during pregnancy improved with UDCA (67% vs. 13%)
  - Post-partum
    - ↑ LE postpartum in~30% (no clinical change)

MCQ Gem

- Give the differential of ↑ LEs in PSC during pregnancy.
  - Worsening of PSC
  - Underdosing of UDCA
  - Development of PSC-associated tight stricture of biliary tree → cholestasis

➢ Suggestions
  - In PBC/PSC, ICP may develop, unrelated to these two liver conditions
    - Measure serum bile acids in T1 as a baseline to compare if cholestasis worsens later in pregnancy because of ICP.
  - Monitor INR drug pregnancy, and correct with vitamin K po

- **Non-alcoholic fatty liver disease** (NAFLD)
  - Infertility
    - ↑infertility in women with NAFLD plus
      - Obesity
      - Cirrhosis
      - Polycystic ovary syndrome (PCOS)
    - Always inquire if the woman with NAFLD has menstrual irregularity or hirsutism, which suggests PCOS and the ↑ risk of infertility
      - The patient with PCOS plus NAFLD requires specialist referral for therapy of PCOS
  - NAFLD plus pregnancy is associated with ↑ risk of complications in pregnancy when BMI < 30 kg/m^2 at the time of conception
    - Mother
      - Hypertension, OR, 3.1 (95% CI, 2.6-3.8)
      - Postpartum hemorrhage, OR, 1.7 (95% CI, 1.3-2.2)
      - Gestational diabetes mellitus (GDM; depends upon NAFLD, not ↑ BMI or ↑age)
      - ↑ cesarian section (64% vs. 17%)
    - Children
      - Preterm birth, OR, 1.6 (95% CI, 1.3-2.0)
      - Small for gestational age (6% vs. 3%)
  - Women who are overweight (BMI 25-28.9 kg/m^2) or obese (BMI ≥ 30) gain less than normal amounts of weight during pregnancy.
    - Monitor carefully growth of fetus
  - NAFLD in mother may adversely affect the child, whereas breastfeeding and duration of lactation may protect the child from future development of NAFLD.

➢ Suggestions

  - Evaluate symptoms in every woman of reproductive age with NAFLD for polycystic ovary syndrome (PCOS)
    - Preconception
      - Risk of mother and fetus associated with obesity/diabetes
      - Benefit of achieving ideal body weight and correcting obesity-associated complications
  - Breastfeeding is recommended for women with NAFLD →
    - ↓ risk of NAFLD in their children
    - ↓ metabolic complications in mother

- **Alcohol-related Liver Disease** (ArLD)
  - Alcohol use in pregnancy is of risk to fetus
    - ↑ premature birth
    - ↑ small for gestational age
    - ↑ fetal alcohol spectrum disorder (FASD)
  - Screen all pregnant women for their alcohol use
    - Do **not** prescribe disulfiram during pregnancy (↑ fetal abnormalities)
  - Naltrexone is safe to use to treat women with opiate-use disorder

➢ Suggestions

- Screen all pregnant woman for their alcohol use, and treat appropriately.
- If woman has ArLD
  - Suggested delay conception until abstinence is achieved
- Medications used to treat alcohol use disorder during pregnancy "…should be individualized, with careful weighing of the risks of alcohol use vs. those of medication exposure.

- **Hepatocellular Adenomas** (HCAs)
  - About 30% of HCA have estrogen receptors
    - Stop combined estrogen-containing hormonal contraception → regression of HCA
  - HCA < 5 cm diameter
    - ↑ size during pregnancy in > 20% (median increase, 14 mm)
    - No maternal/fetal complications
  - ↑ risk of rupture of HCA during pregnancy when ≥ 6.5 cm diameter
    - Death rate
      - Mother, 44%
      - Fetus, 38%
  - Treatment
    - HCA > 5 cm
      - Blanding embolization
      - Segmental hepatectomy

MCQ Gem

- Give the estrogen sensitive benign hepatic tumours.
  - Hepatocellular adenomas (HCA)
  - Hepatic hemangioma (HH)

- Perform surveillance before, during and after pregnancy
  - Non-pregnant, MRI plus gadolinium
  - Pregnant, MRI (**no** gadolinium) in T2/T3

➢ Suggestions

- Women of reproductive age who have HCAs
  - Possible growth of HCA
  - Possible rupture in pregnancy
- Perform abdominal ultrasound in pregnant women with HCA at T1, T2, T3 plus 3 mon postpartum
- Safety of pregnancy with HCA
  - < 5 cm, yes
  - > 5 cm, perform embolization or resection of HCA before conception

- Hepatic Hemangioma (HH)
  - Common benign liver tumour seen in ~3% of adults
    - May be associated with focal nodular hyperplasia (FNH)
  - A symptomatic until large
    - Pain, bleeding, rupture (< 1%)
  - **Stop** hormonal (estrogen-containing) contraception if HH > 5-10 cm
  - Perform MRI without contrast to determine if size of HH is increasing in pregnancy
    - If ↑ size of HH, intervention may be necessary
  - Pregnant women with HH, previously asymptomatic but now symptomatic → diagnostic imaging to monitor size.

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- Give the cause for the ↑ size of hepatic hemangiomas during pregnancy.
  - ↑ intraabdominal pressure from ↑ size of uterus
  - ↑ circulating blood volume
  - ↑ cytokine producing ↑ growth of hemangioma

- **Focal Nodular Hyperplasia** (FNH)
  - Benign vascular liver tumour seen in ~2% of adults
    - May be associated with other vascular tumours e.g., hepatic hemangiomas in ~20%
    - Hepatic rupture extremely rare (one case report world-wide)
    - Combined estrogen-containing hormonal contraception and pregnancy are safe
      - Do **not** need to monitor size of FNH

- **Budd-Chiari Syndrome** (BCS)
  - ↑ coagulability during pregnancy, plus 8 wk post-partum
  - This ↑ coagulability may unmask an underlying clotting disorder → hepatic vein thrombosis → hepatic outflow obstruction → ↑ hepatic sinusoidal pressure → abdominal pain/ascites
  - Treatment
    - Anti-coagulation
      - Low molecular weight heparin (LMWH, do **not** use vitamin K antagonist)
  - Breastfeeding is safe with LMWH or vitamin K antagonists due to teratogenicity plus ↑ risk of fetal bleeding; little safety data on thrombolytic therapy)
    - TIP (transjugular intrahepatic portohepatic shunt), or liver transplant (LT)
  - In breastfeeding, it is safe to use LMWH or vitamin K antagonists.

➢ Suggestions

  - Diagnose suspected BCS with Doppler ultrasound of the abdomen
  - Treat
    - During pregnancy, with LMWH
    - After pregnancy, during breastfeeding
      - LMWH or vitamin K antagonists

- **Gallstone disease in pregnancy**
  - Prepregnancy ↑ BMI / ↑ serum leptin → ↓ gallbladder motility / ↑ lithogenic bile
  - Diagnosis of gallstones
    - Abdominal ultrasound

➢ Clinical

  - If asked about prevalence of gallbladder disorders in pregnancy, be careful of the wording of the MCQ:
    - Pregnancy plus gallstones, 10%
    - Pregnancy plus gallstones plus symptoms/gallstones-related disease, 0.5-0.8%
    - Cholecystitis has ↑ risk of recurrence whether during/after pregnancy

- Treatment
  - No symptoms
    - Supportive care
  - Recurrent/persistent symptoms of cholecystitis →
    - Cholecystectomy
    - ERCP plus sphincterotomy, depending upon clinical scenario
      - Beware of radiation exposure of fetus – consider ERCP with no fluoroscopy
  - Cholelithiasis may lead to choledocholithiasis, which may lead to cholangitis gallstone, to pancreatitis
    - Gallstone pancreatitis is associated with ↑ risk of fetal death
    - Cholecystectomy for symptomatic gallstones/cholecystitis will ↓ choledocholithiasis
    - Choledocholithiasis treatment with drainage ERCP plus sphincterotomy plus stenting will ↓ risk of gallstone pancreatitis.

➢ Suggestions

- Use abdominal ultrasound to diagnose gallbladder disease during pregnancy
- If cholecystectomy/ERCP plus sphincterotomy/stent are necessary
  - If possible, delay until T2
  - If possible, do without fluoroscopy radiation, or do with use of lead shield to lower abdomen and to pelvis.

❖ **Acute Viral Hepatitis from HEV**

- ↑ complications for symptomatic acute viral hepatitis occurring during pregnancy
  - Spontaneous abortion
  - Prolonged labour
  - Mother-to-child transmission (MTCT)
- Only hepatitis E virus (HEV) and hepatitis C virus (HCV)
  - Associated acute or severe viral hepatitis have ↑ incidence during pregnancy
  - Treat with supportive care
    - For HBV infection associated with HEV infection, use tenofovir disoproxil fumarate (TDF)
- ↑ risk of HEV infection during pregnancy (T2, T3)
  - ↑ risk of severe outcomes
    - Genotype 1
    - Nutritional deficiency, e.g., folate
    - Immunological changes associated with pregnancy
- Death rate
  - Fetus, 33%
  - Neonate, 8%
- MTCT
  - In uterus
  - Peripartum

  } 33% to 100%

➢ Treatment

- No pregnancy − Ribavirin plus interferon
- Pregnancy − Do **not** use above medications (contraindicated during pregnancy)

- **Herpes Simplex Virus** (HSV) **Infection**
  - Must have ↑ suspicion for this rare diagnosis
    - Herpetic rash in 20%
  - Complications
    - Fever, 98%
    - Coagulopathy, 84%
    - Encephalopathy, 80%
  - Treatment
    - Consider using empiric acyclovir IV (no ↑ risk of birth defects)
      - Safe with breastfeeding
    - If severe acute hepatitis progresses to acute liver failure (ALF)
      - Consider liver transplant (LT) during pregnancy (may be life-saving for mother)

➢ Suggestion

- Test the pregnant patient with acute viral hepatitis for HDV and HSV (as well as HAV, HBV)
- Give supportive therapy but
  - **No** ribavirin or interferon
  - Consider
    - Acyclovir for HSV
    - TDF for HBV-associated with HEV

- **Cirrhosis**
  - ↓ frequency of pregnancy in patients with cirrhosis (~1 per 3000-6000 pregnancies)
  - Caution female patient with cirrhosis of ↑ risk of worsening of liver disease during pregnancy
  - Mortality rate in pregnancy < 2%
    - Use Model of End Stage Liver Disease (MELD) score ≥ 10 to predict poor outcome
    - ↑ risk of decompensation during pregnancy
      - Sensitivity, 83%
      - Specificity, 83%
    - Liver-related complications during post-partum ending up to 1 yr after cirrhosis which is
      - Compensated, 1%
      - Decompensated, 13%

      } − ↑ preeclampsia
      − ↑ preterm births
      − ↑ maternal mortality (2% vs. 0%)
      − ↑ fetal mortality (5% vs. 2%), placental abruption ↓ growth

- Uterovaginal bleeding
- Gestational hypertension
- Ascites
- Bleeding

- **Portal Hypertension and Esophageal/Gastric Variceal Bleeding**
  - ↑ risk of bleeding from maternal gastroesophageal varices (GEV), ~5%
    - Maternal mortality rate from hemorrhage from GEV (~20%
    - ↑ risk in T2 (↑ intravascular volume) and during delivery (↑ pressure in IVC from gravid uterus and repeated Valsalva maneuvers)
  - All patients with cirrhosis should have EGD screening for GEV
    - "…all women with cirrhosis" should have variceal screening" … within 12 mon of conception"
  - "If possible, all endoscopic procedure should be deferred until the second trimester of pregnancy" (T2)
  - Large esophageal varices are unlikely if hepatic stiffness on FibroScan® < 20 kPa, and if platelet count is normal.
    - Small varices may be initially present, and may enlarge and bleed pregnancy during pregnancy (30% miss rate by above criteria)
    - Unless EGD done within 12 mon before pregnancy to conform presence/size of GEV, then perform EGD in early second trimester (T2)
    - If EGD done before pregnancy and was negative, then depending upon the time interval, risk factors and whether patient already on primary prophylactic therapy, the EGD may need to be repeated,
    - Reasons to repeat EGD during pregnancy even though prepregnancy EGD did not show varices
      - Continued intake of alcohol
      - Untreated HCV infection
      - New symptoms of hepatic decompensation, i.e.,
        - Ascites
        - Hepatic encephalopathy

➢ Treatment

  - Endoscopy esophagogastroduodenoscopy (EGD) for gastroesophageal varices (GEV)
    - Small
      - Non-specific beta blockers (NSBB)
    - Large
      - Esophageal variceal bond ligation (EVBL)
    - Active bleeding GEV
      - EVBL

- Safety of EGD during pregnancy
  - Perform elective EGD in
    - Early T2
  - Pre-EGD
    - Consult maternal/fetal medicine (MFM) specialist
  - Pre-EGD sedative, use one of
    - Fentanyl
    - Meperidine
    - Propofol
  - **Avoid**
    - Frequent or prolonged procedures
    - EGD in T3

    } To ↓ fetal exposure and to ↓ risk of fetal neurocognitive drugs exposure
- Pharmacotherapy
  - Prophylaxis, primary/secondary
    - Small GEV
      - NSBB, e.g., propranolol
    - Large varices
      - Endoscopic variceal band ligation (EVBL)
  - Active bleeding
    - EVBL
    - Octreotide/somatostatin (do **not** use terlipressin [not available in Canada]; causes ↓ uterine ↓ blood flow)
    - Cephalosporin (prophylaxis against spontaneous bacterial peritonitis [SBP])
    - Consider rescue therapy with transjugular intrahepatic portosystemic shunt (TIPS) if bleeding continues

- Give the adverse effects of splanchnic vasoconstriction therapy given during pregnancy.
  - ↑ contraction of uterus → premature labour
  - ↓ blood flow of uterus → ↑ risk of fetus

  } Balance between ↓ GEV bleeding and safety of fetus

- Management of patient with portal hypertension during delivery
  - Mode of delivery is directed by obstetrical team
    - Vaginal deficiency: suggestions
      - ↓ straining
      - ↓ duration of second stage of labour considerations
    - Cesarian
      - Correct platelet count to > 50,000/mL
      - Avoid injury to abdominal wall (varices)
      - Anticipate possible development of ascites

❖ **Lower GI Bleeding in Pregnancy**

➢ Causes/associations

- Rectal varices, ~55%
- Portal hypertensive colopathy, ~25%
- External hemorrhoids

} − Severe bleeding in < 5%

➢ Sigmoidoscopy during pregnancy

- Bowel preparation
  - − Tap water enemas
  - − Do **not** use polyethylene glycol (safety of PEG in pregnancy is uncertain)

❖ **Splenic Artery Aneurysm** (SAA)

- 50% of SAA presenting with rupture during pregnancy are small (< 2 cm)
- High mortality rate
  - − Fetus, ~15% to 90%
  - − Mother, ~20% to 70%

➢ Suggestions

- Consult MFM specialist before endoscopy regarding coordination of
  - − Fetal monitoring
  - − Sedation of mother
- If preconception EGD not done
  - − If EGD not performed 1 yr before conception
    - ▪ Do EGD in T2
  - − Perform EGD within 1 yr before conception
    - ▪ Ongoing liver injury (alcohol, untreated HCV)
    - ▪ New signs of decompensation (ascites, hepatic encephalopathy [HE])
- Safe sedation for EGD
  - − Fentanyl, meperidine, midazolam, propofol
- Primary/secondary prophylaxis
  - − Small varices
    - ▪ Non-specific β-blocker (NSBB) e.g., propranolol
  - − Large varices
    - ▪ Esophageal variceal band ligation (EVBL)
  - − Active GEV bleeding
    - ▪ Give GEV if bleeding
    - ▪ Octreotide/somatostatin
    - ▪ Cephalosporin (to ↓ risk of SBP)
    - ▪ Do **not** use terlipressin
- Method of delay
  - − An obstetrical decision

❖ **Liver Diseases which are unique to pregnancy**

- **Hyperemesis gravidarum** (HG)

➢ Demography
  - T1
  - ~1% of pregnancies

➢ Risk factors
  - Previous HG

➢ Clinical
  - Vomiting/dehydration
  - ↓ weight > 5% of pregnancy weight

➢ Laboratory
  - ↑ ALT/ ↑ AST in 50% (usually < 1000 U/L)
    - Often normalize with rehydration
  - Abnormal electrolytes
  - Ketonuria
  - Controversy whether associated with gastric infection with Helicobacter pylori

➢ Treatment
  - IV hydration plus thiamine
  - Antiemetic/metoclopramide, ondansetron, promethazine

➢ Prognosis
  - High rate of recurrence in subsequent pregnancies

➢ Suggestions
  - Clinical diagnosis, treated with rehydration IV, correction of electrolyte abnormalities
  - Anti-emetic
  - ↑ ALT / ↑ AST usually corrected with rehydration
    - Persistent ↑ ALT / ↑ AST suggests another etiology

- **Intrahepatic cholestasis of pregnancy** (ICP)

➢ Demography
  - T2, T3 (80% present after wk 30)
  - Prevalence ~5% of pregnancies more common in persons from Sweden, Chile

- Risk factors
  - Previous episodes of IHC (40% to ~90%)
  - ↑ maternal age
  - HCV infection
  - Multiparity
  - Metabolic syndrome
  - ↑ risk
    - Mother
      - Intrahepatic cholestasis
        - Benign, recurrent
        - Familial progressive
      - Progressive liver disease
      - Gallstone/cholangitis
      - Hepatocellular cancer
  - Family history
    - Defects in
      - ATP-binding cassette subfamily B, number 4 (ABC B4, hepatic phospholipid transporter)
      - ABCB1 (bile salt export transporter)
      - ATP8B1

      } – Phospholipid transporter
    - Fetus
      - ↑ risk of intrauterine fetal death (IUFD), estimated from concentration of serum bile acids (BA)
        - Preterm birth
        - Meconium-stained amniotic fluid
        - Respiratory distress/asphyxia

- Clinical
  - Widespread pruritus
    - Worse on palms/soles

- Laboratory
  - ↑ ALT / ↑ AST 2x to 3x ULN (frequent, but not necessary for diagnosis)
  - Total serum bile acid (BA) > 10 µmol/L
    - Distribution of BA concentrations
      - 10-40 µmol/L, 80%
      - ≥ 40 µmol/L, 20%
      - The higher the BA concentration in the mother, the higher the concentration in the fetus, and thus the ↑ risk of severe complications

Abbreviation: ULN, upper limit of normal

- Treatment
  - Ursodeoxycholic acid (UDCA); 10-15 mg/kg
    - Pharmacology
      - Giving UDCA → ↑ UDCA in bile acid pool → ↓ 7α-hydroxylase in hepatocytes → ↓ cholic / ↓ chenic primary bile acids → ↓ pruritic factors (not BA themselves)
  - Antipruritic
    - Antihistamines
    - Cholestyramine
    - Rifampicin
  - Monitor INR, when especially taking cholestyramine for pruritis (may ↓ absorption of vitamin K)
    - Give vitamin K if ↑ INR (to ↓ risk of fetal intracranial bleeding)
  - Monitor patient on the basis of "best obstetrical practice"
  - Delivery at
    - 36-37 wk, or
    - At time of diagnosis if after 37 wk

- Suggestions
  - Pruritis in T2.T3 plus ↑ serum BA > 10 µmol/L makes the diagnosis of ICP
  - ↑ ALT / ↑ AST in ICP
    - But, ↑ ALT / ↑ AST is not necessary to make the diagnosis
  - If ICP suspected, first exclude HCV infection
  - Give UDCA as first-line therapy to ↓ BAs (unknown if ↓ IUFD)
  - Monitor INR for possible development, particularly if patient taking cholestyramine for pruritis
  - If persistent symptoms or ↑ BA / ↑ ALT/AST
    - Look for other diagnosis

- **Preeclampsia/Eclampsia**

- Definition
  - Multisystem disorder usually occurring in late T3 (after wk 20), or immediately postpartum
  - Usually characterized by de novo hypertension plus
    - Maternal organ dysfunction
      - Neurological (seizures)
      - Hepatic
      - Renal (proteinuria is common, but is not necessary for the diagnosis)
      - Hematological

- Demography
  - T3 / immediately postpartum
  - Prevalence ~5% of pregnancies
- Clinical
  - May be associated/overlap with HELLP syndrome (please see below)
- Treatment
  - Perform early delivery
    - Pre-eclampsia, > 37 wk
    - Severe pre-eclampsia, 34 wk

- **Hemolysis, elevated liver enzymes, low platelets** (HELLP) **syndrome**

- Demography
  - T2-T3 (30% between wk 27-37; 20% within 48 h of delivery) prevalence, < 1% of pregnancies
- Risk factors
  - Previous pre-eclampsia/hypertension
  - ↑ age
  - Multiple gestations
  - Diabetes mellitus
- Clinical
  - Hypertension (85%)
  - Abdominal pain / ↑ body weight (65%)
  - Intrahepatic bleeding, rupture, infarction (45%)
  - Jaundice (40%)
  - Nausea/vomiting (35%)
  - Headache, malaise (30%)
  - May be associated with maternal pre-eclampsia +/-
    - Complications of eclampsia
    - Hemolytic anemia
    - Uteroplacental dysfunction
    - Fetal growth retardation

- Laboratory
  - Hemolysis
    - Microangiopathic hemolytic anemia
      - Schistocytes
      - Spherocytes
      - Reticulocytes
    - ↑ uric acid
    - ↑ LDH > 600 U/L
  - ↑ ALT / ↑ AST > 500 U/L
  - Platelets < 50 to 150 x 10^9 /L
    - Disseminated intravascular coagulopathy (DIC)
  - Proteinuria

- Pathophysiology

- ↓ placental perfusion
  - ↓ endothelial function
    ↓
  - Platelet aggregation

- ↑ release of fibrin
  ↓
  - ↑ cross-linked networks in small blood vessels
    ↓
  - Microangiopathic hemolytic anemia

  - ↑ fibrin in hepatic sinusoids
    ↓
  - Obstruction of sinusoids
    ↓
  - Hepatic ischemia

  - Subcapsular hematomas
  - Rupture

- Treatment
  - Immediate delivery of fetus, once maternal stabilization has been achieved
  - For intrahepatic bleeding, rupture, infarction
    - Red blood cell (RBC) transfusion
    - Coagulation (platelet infusion if appropriate)
    - Angiography / hepatic artery
      - Embolization
      - Ligation
    - Hepatic resection

- Suggestions
  - Pre-eclampsia
    - Closely monitor for development of
      - Eclampsia
      - HELLP syndrome
    - Deliver by wk 37

- Eclampsia, HELLP syndrome
- Abdominal ultrasound to exclude
  - HELLP syndromes
  - Hamartoma
  - Infarction
  - Intrahepatic hemorrhage
  - Rupture
    - Arteriographic treatment
    - Surgery
  - Acute liver failure
  - Possible liver transplantation

❖ **Acute Fatty Liver of Pregnancy** (AFLP)

➢ Demography
- T3, postpartum
- Prevalence ~1/10^5 pregnancies
- ↑ mortality
  - Perinatal
  - Maternal, 10%; high if AFLP progresses to acute liver failure (ALF)

➢ Risk factors
- First child
- Male/twins

➢ Pathophysiology
- ↓ fetal long-chain 3-hydroxyacyl CoA dehydrogenase (LCHAD) → ↑ LCHAD metabolites which pass from fetal to

➢ Clinical
- Similar to pre-eclampsia
  - Headache/malaise
  - Nausea/vomiting
  - Abdominal pain
  - Jaundice
- Associated complications
  - Liver
    - Ascites/edema
    - Hepatic encephalopathy, ↑INR ("coagulopathy"), acute liver failure (ALF), intrahepatic hemorrhage/rupture (2%)
  - Genitourinary (GU)
    - Renal failure
    - Vaginal bleeding
    - Polyuria/polydipsia
  - Cardiovascular system (CVS)
    - Hypertension
  - Metabolic
    - Hypoglycemia/hyperuricemia

- Laboratory
  - ↑ ALT/ ↑ AST 300-1000
  - ↑ INR, ↓ fibrinogen / ↓ antithrombin III
  - ↑ LDH, ↑ bilirubin
  - ↓ platelets < 100,000 x 10^9 /L
  - Disseminated intravascular coagulopathy (DIC)

- Diagnosis (Swansen criteria), ≥ 6 of the following, with no etiology other than AFLP (high sensitivity, low specificity)
  - Clinical
    - Abdominal pain
    - Encephalopathy
    - Vomiting
    - Polyuria/polydipsia
  - Laboratory
    - ↑ AST / ↑ ALT > 42 IU/L
    - ↑ bilirubin > 0.8 mg/dL
    - ↑ WBC (leucocytosis) ≥ 11 x 106 /L
    - ↑ INR (PT > 14 sec, or PTT > 34 sec)
    - ↑ NH3 (ammonia) > 42 IU/L
    - ↑ uric acid > 5.7 mg/dL
    - ↓ blood sugar < 72 mg/dL
  - Diagnostic imaging
    - Ascites / bright on ultrasound

- Histopathology (usually not available or necessary)
  - Microvascular steatosis

- Treatment
  - Maternal stabilization
  - Urgent delivery
  - If ALF
    - Transfer mother to specialized liver failure unit

- Suggestions
  - If AFLP is suspected
    - Maternal stabilization
    - Urgent delivery
  - Make diagnosis of AFLP, using clinical/laboratory features
    - Liver biopsy **not** necessary

- Perform abdominal ultrasound
  - If intrahepatic hemorrhage or infarction → assess for possible rupture
    - If hepatic rupture
    - If acute liver failure

    } ▪ Urgent referral to liver transplant centre

➢ Screening

- Screen all newborns of mother for LCHAD deficiency (or ↓ in other fatty acid oxidation defects)
  - Introduce appropriate diet for child with LCHAD deficiency to
    - ▪ ↓ morbidity
    - ▪ ↓ mortality

❖ **Recipients of Liver Transplantations** (LT)

- Males
  - ↓ sex hormone concentrations in men with cirrhosis may become normal after LT, with ↑ libido / erectile dysfunction in ~50% after LT.
    - De novo sexual dysfunction may develop post-LT in ~25%
  - Calcineurin inhibitors used post-LT may ↑ sexual dysfunction, but persistent erectile dysfunction occurs in 50%, and ~25% of men post-LT will develop new symptoms of sexual dysfunction, e.g., sirolimus adverse effects on sexual dysfunction
  - Calcineurin inhibitors (CNIs) may cause
    - Dystrophy of tubules
    - ↓ sperm numbers/motility
    - ↓ testosterone
    - ↑ gonadotropic-releasing hormone (GRH)
    - ↑ luteinizing hormone (LH)
    - ↑ follicle stimulating hormone (FSH)
  - Male sexual activity
    - Males with LT and female partners must use effective contraceptive
      - ▪ When using mycophenolate (MPA), use effective contraception
      - ▪ For 90 d after stopping MPA

- Females
  - After LT
    - Mon 1, ovulation may return
    - Mon 12, most women have redeveloped regular menstrual periods
  - Begin planned pregnancy by starting effective contraception (IUD, or implant SC)

- Because pregnancy in a patient with LT is associated with ↑ morbidity / ↑ mortality, delay conception for 1 yr post-LT to ensure women is
  - Stable with no
    - Infection
    - Rejection
  - Good/stable
    - Graft function
    - Immunosuppression
- During pregnancy in post-LT woman
  - Measure trough levels of cyclosporine / tacrolimus q2-4 wks
- Do **not** use mycophenolate (MPA) or mammalian target of rapamycin (mTOR) inhibitors (limited safety data) during pregnancy

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- Give the pharmacological changes which come with pregnancy which lead to the need to monitor trough blood levels of calcineurin inhibitors (CNIs) during pregnancy.
  - Metabolism
    - ↑ cytochrome P450 activity in pregnancy → ↑ CNI metabolism
  - Kidney
    - ↑ glomerular filtration rate (GFR)
    - ↑ p-glycoprotein transporter activity
  - Cardiovascular
    - ↑ blood volume
    - ↑ body water

    } ↓ concentrations / ↓ binding of CNIs

❖ **BREASTFEEDING/LACTATION**

- Safe to use
  - Azathioprine
  - Corticosteroids
  - Cyclosporine
  - Corticosteroids
  - Tacrolimus
- Do **not** use
  - Everolimus
  - Mycophenolate (MPA)
  - Sirolimus
  - mTor

❖ MATERIAL COMPLICATIONS

- Gestational diabetes mellitus (GDM)
  - ↑ GDM x 2 in woman with LT (~10%)
  - Perform glucose tolerance test in T1, and carefully/fully achieve glycemic control
    - Preconception
    - Gestational
    - Pre-eclampsia
      - Risk in LT recipients ~20%

    } ▪ ↑ risk of
      - Preterm delivery
      - Intrauterine growth

- Hypertension
  - Hypertension during pregnancy

- Graft loss
  - Within 2 yr of delivery, 3%
  - Overall, acute/chronic, 4.4-10%

  } – ↑ risk of graft rejection in women who conceive ≤ 1 yr post-LT

  - Recommend that after LT, a woman waits ≥ 1 yr before becoming pregnant

❖ Fetal complications

- Live birth rate, normal
- ↑ preterm births ~ 2.5x
- ↑ low birth rate / ↑ intrauterine growth restriction ~2x
- Beneficial effect of planned vs. unplanned pregnancies
  - ↑ termination ratio
  - ↓ birth defects
  - ↓ infant death rate

Safety First

- "Safe contraception" means IUD or subcutaneous (SC) implants, with failure rates of < 1%
- Normal weight gain during pregnancy is influenced by the patient's baseline weight category
  - Underweight or normal, ~30 lbs
  - Overweight or obese, ~10 lbs

Abbreviations: 6-MP, 6-mercaptopurine; AALD, alcohol-associated liver disease; AASLD, American Association of the Study of Liver Disease; ABCB4, adenosine triphosphate-binding cassette subfamily B4; ABCB11, adenosine triphosphate-binding cassette subfamily B11; AE, adverse effect; AFLP, acute fatty liver of pregnancy; AFP, alpha fetoprotein; AIH, autoimmune hepatitis; ALF, acute liver failure; ALT/AST, transaminases; AP, alkaline phosphatase; ATP8B1, aminophospholipid transporter synthase copper transporting 8B1; BA, bile acids; BCS, Budd-Chiari syndrome; BMD, bone mineral density; BMI, body mass index; Br, bilirubin; CDC, Centres for Disease Control and Prevention; CHC, combined hormonal contraception; CI, confidence interval; CLD, chronic liver disease; CNI, calcineurin inhibitor; CNS, central nervous system; CT, computed tomography; CTP, Child-Turcott Pugh; Cu, copper; CVS, cardiovascular system; DAA, direct acting agent; DIC, disseminated intravascular coagulopathy; DMPA, depot medroxyprogesterone acetate; ED, erectile hormonal contraception; EGD, esophago-gastroduodenoscopy; ERCP, endoscopic retrograde pancreaticogram; EV, esophageal varices; EVL, esophageal variceal ligation; FASD, fetal alcohol spectrum disorder; FDA, Food and Drug Administration; FNH, focal nodular hyperplasia; FSH, follicle stimulating hormone; GDM, gestational diabetes mellitus; GEV, gastroesophageal varices; GI, gastrointestinal; GRH, gonadotropic releasing hormone; GU, genitourinary; HBP, hypertension; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCA, hepatocellular adenoma; HCC, hepatocellular cancer; HCV, hepatitis C virus; HE, hepatic encephalopathy; HELLP, hemolysis, elevated liver; HEV, hepatitis E virus; HG, hyperemesis gravidarum; HH, hepatic hyperplasia; HPA, hypothalamic pituitary axis; h, hour; HSV, herpes simplex virus; IBD, inflammatory bowel disease; ICP, intrahepatic cholestasis of pregnancy; INR, International Normalized Ratio; IUD, intrauterine device; IUFD, intrauterine fetal demise; IV, intravenous; IVC, inferior vena cava; IVF, in vitro fertilization; LARC, long-acting reversible contraception; LCHAD, long-chain 3-hydroxyacyl CoA dehydrogenase; LDH, lactic dehydrogenase; LE, liver enzyme; LFT, liver function test; LH, luteinizing hormone; LMWH, low molecular weight heparin; LT, liver transplant; MCQ, multiple choice question; MEC, Medical Eligibility Criteria; MELD, Model for End Stage Liver Disease; MFM, maternal fetal medicine; mon, month; MPA, mycophenolic acid; MRCP, magnetic resonance cholangiopancreatography; MRI, magnetic resonance imaging; MTCT, mother-to-child transmission; mTOR, mammalian target of rapamycin; N, normal; NAFLD, non-alcoholic fatty liver disease; NH_3, ammonia; NSBB, non-specific beta blockers; OR, odds ratio; PBC, primary biliary cholangitis; PCOS, polycystic ovary syndrome; PHT, portal hypertension; PID, pelvic inflammatory disease; PP, postpartum; PSC, primary sclerosing cholangitis; PT, prothrombin time; PTT, partial thromboplastin; RIB, ribavirin; SAA, splenic artery aneurysm; SAMs, s-adenosyl-L-methionine; SC, subcutaneous; SHBG, sex hormone binding globulin; T, testosterone; T1, trimester 1; T2, trimester 2; T3, trimester 3; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; TIPS, transjugular intrahepatic portal shunt; UDCA, ursodeoxycholic acid; US, ultrasound; VTE, venothrombolus; WBC, white blood cell; WD, Wilson disease; wk, week; yr, year; Zn, zinc

Relative Adrenal Insufficiency (RAI) **in Patients with Cirrhosis**

Wentworth BJ, et al. Am J Gastroenterol 2022; 117: 1889-1893

- Definition
  - Suspicion of possible RAI in patients with cirrhosis
    - Hypotension, refractory to treatment
      - Unexplained/persistent in patient without ARS (in patients with critical illness RAI is called hepatoadrenal syndrome: ↓ serum cortisol-binding globulin)
    - Hyponatremia (< 125 mEq/L)
      - Unexplained
      - No ascites
      - No diuretics (hold)

- Laboratory
  - Confirm
    - Short Synacthen test
      - ACTH 250 µg, threshold of Δ total cortisol < 9 µg/dL

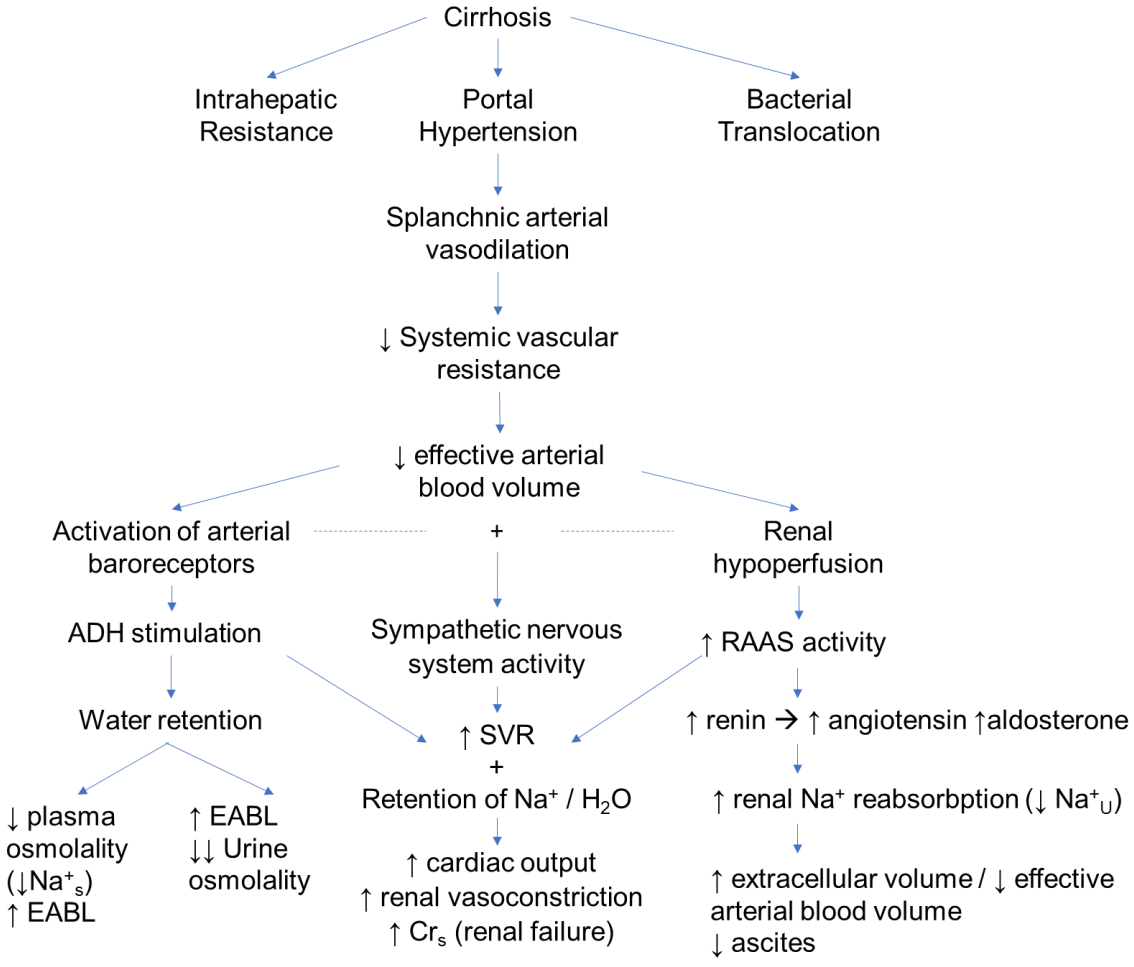
- Prevalence
  - Patient hospitalized
    - Not critically ill, 26-49%
    - Critically ill, 51-82%
  - Outpatient
    - Child-Pugh (C-P)
      - A, 0-44%
      - B, 23-54%
      - C, 57-68%

- Treatment
  - Cautious use of hydrocortisone, but
    - ↑ risk of infection
    - No ↓ mortality rate in out-patients
  - Patient may be a candidate for liver transplantation, depending upon the MELD score

Hepatorenal Syndrome (HRS)

- Definition
  - Inappropriate and intense vasoconstriction leading to ↑ Cr_s (serum creatinine)

- Pathophysiology of HRS: Physiological Effect of Cirrhosis on the Kidney



Revised HRS Nomenclature

Old Classification	New classification	Criteria
○ HRS-1	− HRS-AKI (ICA-AKI) − Exclude other causes of AKI in cirrhosis (HRS is a diagnosis of exclusion)	▪ Absolute increase in Cr_s ≥ 26.5 µmol/L (0.3 mg/dl) within 48 h or ▪ Urinary output ≤0.5 ml/kg B.W. ≥6h* or ▪ % Cr_s ≥50% using the last available value of outpatient Cr_s within 3 mon as the baseline value
○ HRS-2	− HRS-AKD	▪ eGFR <60 mL/min per 1.73 m 2 for <3 mon in the absence of other (structural) causes
	− HRS-CKD	▪ eGFR <60 ml/min per 1.73 m 2 for ≥ 3 mon in the absence of other(structural) causes
	− HRS-NAKI	▪ % Cr_s <50% using the last available value of outpatient Cr_s within 3 mon as the baseline value

Abbreviations: AKD, acute kidney disease; BW, body weight; CRD, chronic kidney disease; Cr_s, creatinine; eGFR, estimated glomerular filtration rate; HRS, hepatorenal syndrome; mon, month; NAKI, non-acute kidney injury;

- ○ Essentially make the diagnosis of HRS
  - − ↑ urine osmolality
  - − ↓ urine sodium
  - − ↓ EABV and renal hypoperfusion

➢ Differential diagnosis of AKI in cirrhosis

Pre-renal	Intra-renal	Post-renal
− Volume depletion	− Acute tubular necrosis (ATN)	− Obstruction
− Hepatorenal syndrome	− Cholemic nephropathy	
− Cirrhotic cardiomyopathy	− Glomerulonephritis (IgA, MPGN)	

➢ Diagnostic criteria for HRS-AKI

- ○ No evidence of glomerular disease (hematuria or significant proteinuria)
- ○ No recent Nephrotoxic mediations (NSAIDs iodinated contrast)
- ○ No shock

- Terlipressin
  - Vasopressin analogue with affinity for both V1 and V2 receptors
    - V1 receptor vascular smooth muscle (systemic, splanchnic, renal and coronary circulations)
    - V2 receptor distal convoluted tubule and medullary collecting ducts in the kidney (regulate aquaporins)
  - Terlipressin (3-12 mg/dL) plus albumin (20-40 g/d) superior to midodrine (7.5-12.5 mg t.i.d.) plus octreotide (100-200 µg t.i.d.) plus albumin 20-40 g/d

Combination	Response	
	Complete	Partial / Complete
Ter +Alb	58	70
Mid+Oct+Alb	5	30

  - Confirm RCT multicentre, prospective, prospective, randomized: Terlipressin (1-2 mg IV q6h plus albumin (20-40 g/d) vs. albumin (20-40 g/d) in Type 1 HRS

	HRS reversal*	Mortality Rate	Required Liver Transplant	Respiratory Failure (adverse effect)
○ Terlipressin (n=199)	32%	51%	23%	14%
○ Placebo (n=101)	17%	45%	29%	5%

*P=0.006
Respiratory failure higher with terlipressin plus total albumin exposure
< 423 g, 12.9%
≥ 423 g, 16.5%

Cavallin M, et al. Hepatology 2015
Wong F, et al. N Eng J Gastroenterol 2021

- Norepinephrine
  - α-/β-agonist
  - Norepinephrine continuous infusion
    - 0.5 mg/h, titrate to maintain MAP ≥ 10 mm Hg maximum dose, plus albumin 20 g/d is non-inferior to terlipressin (0.5-2 mg IV q6h) plus albumin (20 g/d)
  - Norepinephrine has fewer ARs than terlipressin

Nassar Junior AP, et al. PLoS One. 2014;9(9):e107466.

➢ Physiology

When there is no cirrhosis

- Fluid loss
  - Diarrhea
  - GI bleeding
  - Diuresis
  - Serial large volume paracentesis
  - SBP
  - Sepsis

↑ plasma ADH → ↑ production / action → CBV

- EBCV
  - ↓ clearance
  - ↑ activity
  - ↑ ADH regulated water channel
  - Endothelins
  - Kallikreins
  - F2-isoprotanes
  - Lower set point for renal response to ↓ SBP and cardiac output
  - ↑ blood norepinephrine and ↑ plasma renin activity

- Drugs
  - NSAIDs
  - ARBs
  - ACEIs
  - Diuretics
  - Lactulose
  - Nephrotoxic antibiotics
  - Cyclosporine
  - Tacrolimus

- CVS
  - ↓ systemic BP
  - ↑ HR / ↑ cardiac output
  - ↑ SNS activity
  - Hyperdynamic circulation

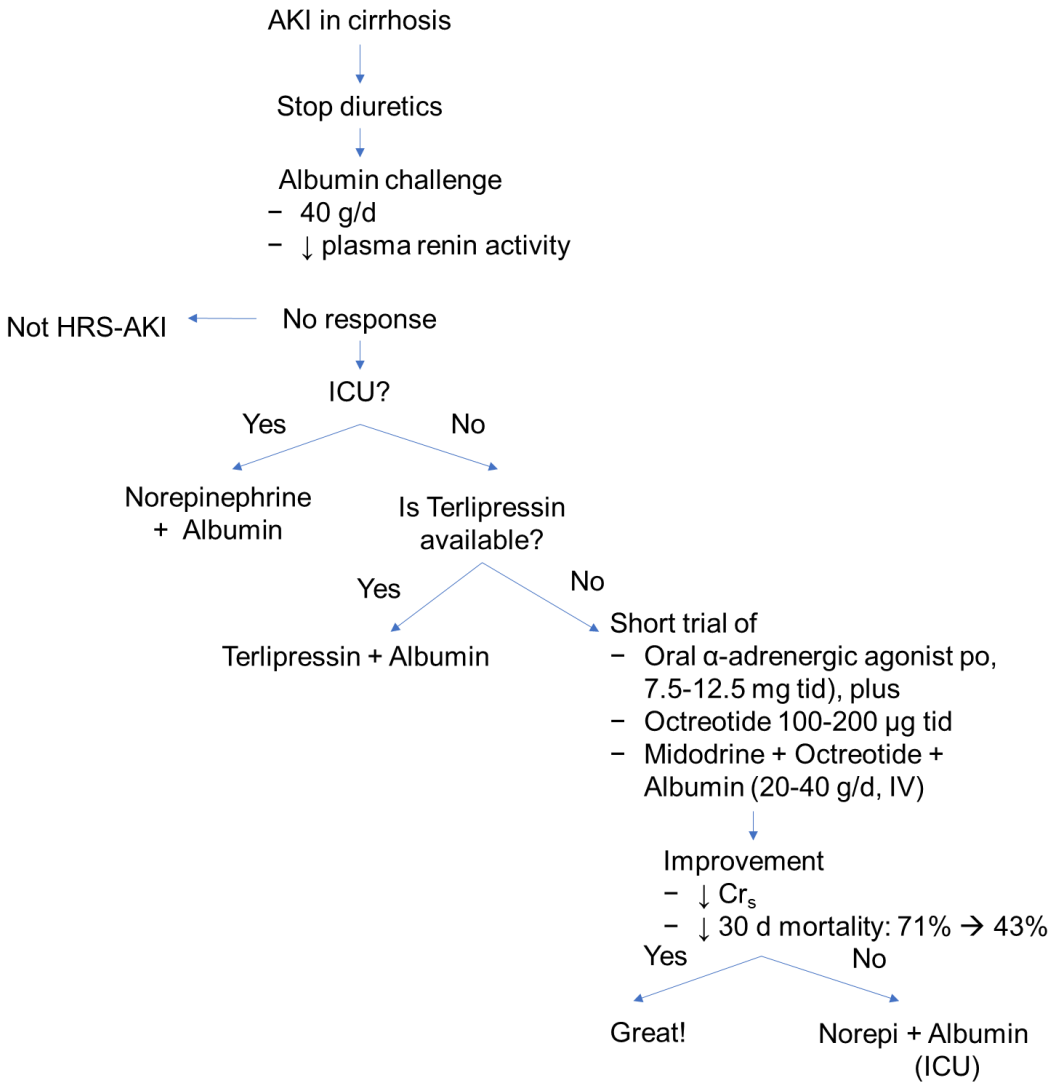
- Renal arterial vasoconstriction

- ↓ GFR
- ↓renal perfusion
- ↓ HRS (inappropriate and intense vasoconstriction)

➢ Pathophysiology

- When there is cirrhosis
  - Infection
  - Inflammation
  - Vasoactive mediators → – ↑ vasodilation, – ↑ NO (nitric oxide), – ↑ CO (carbon monoxide), – ↑ Glucagon, – ↑ prostacyclin, – ↑ adrenomedullin, – ↑ endogenous opiates
  - ↓
  - Splanchnic and peripheral vasodilation
  - ↓
  - CVS
    - ↓ systemic BP
    - ↑ HR / ↑ cardiac output
    - ↑ SNS activity
    - Hyperdynamic circulation
  - ← EBCV
    - ↓ clearance
    - ↑ activity
    - ↑ ADH regulated water channel
    - Endothelins
    - Kallikreins
  - ← Fluid loss
    - Diarrhea
    - GI bleeding
    - Diuresis
    - Serial large volume paracentesis
    - SBP
    - Sepsis
  - Drugs
    - NSAIDs
    - ARBs
    - ACEIs → ↓
    - Diuretics
    - Lactulose
    - Nephrotoxic antibiotics
    - Cyclosporine
  - Tacrolimus
    - F2-isoprotanes
    - Lower setpoint for renal response to ↓ SBP and cardiac output
    - ↑ blood norepinephrine and ↑ plasma renin activity

➢ Treatment


AKI in cirrhosis
Stop diuretics
Albumin challenge
– 40 g/d
– ↓ plasma renin activity
No response
Not HRS-AKI
ICU?
Yes
No
Norepinephrine + Albumin
Is Terlipressin available?
Yes
No
Terlipressin + Albumin
Short trial of
– Oral α-adrenergic agonist po, 7.5-12.5 mg tid), plus
– Octreotide 100-200 µg tid
– Midodrine + Octreotide + Albumin (20-40 g/d, IV)
Improvement
– ↓ Cr_s
– ↓ 30 d mortality: 71% → 43%
Yes
No
Great!
Norepi + Albumin (ICU)

Evaluation and Management of Cirrhotic Patients with Acute Kidney Injury (AKI): **AGA Clinical Practice Update 2022**

Flamm SL, et al. Clin Gastroenterol Hepatol 2022; 20; 2707-2716

➢ Demography

- Cirrhotic with acute kidney injury (AKI)
  - In hospital, 47%
  - Outpatients, 30%
- In these patients with cirrhosis plus AKI, morbidity/mortality rates ↑ 7x

➢ Redefinitions

- Previously, AKI was defined on the basis of serum creatinine concentration, but the Cr_s is reduced in patients with cirrhosis, because of
  - ↓ production of creatine (precursor of creatinine) in liver
  - ↓ muscle mass / female sex
  - ↑ excretion of creatinine by kidney
  - ↑ bilirubin (colorimetric methods)

  ▪ Cr_s in patients with cirrhosis → underestimation of renal function (falsely low Cr_s)

- Acute kidney injury (AKI)
  - Serum creatinine (Cr_s)
    - ↑ within pas 7 d to ≥ 1.5x than baseline
      - When recent Crs not available, use most recent Cr_s within the previous 3 mon
  - Urine volume (U_v) < 0.5 mL/kg per hour for 6 h

- Types of AKI in cirrhosis
  - Hypovolemia
  - Acute tubular necrosis (ATN)
  - Hepatorenal syndrome (HRS)
    - HRS-AKI, cirrhosis plus functional renal dysfunction for < 7 d
    - Non-HRS-AKI, cirrhosis plus functional renal dysfunction > 7 d
    - Urine analysis is normal, but many patients with HRS have histopathological evidence of tubular damage
    - Ultrasound: a normal size

➢ Pathophysiology

- ↑ hepatic NO
  ↓
- Splanchnic vasodilation
  ↓
- ↓ effective arterial blood volume (EABV)
  ↓
- Activation of systemic vasoconstriction pathways
  - ↑ renin-angiotensin-aldosterone system (RAAS)
  - ↑ sympathetic nervous system (SNS)
  - ↑ vasopressin
    ↓
  - ↑ Na^+ reabsorption (Na+ retention)
  - ↓ free H_2O excretion (solute-free water)

  } ▪ Partially restores EABV

- Renal vasoconstriction
  ↓
  - ↓ GFR
    ↓
    - ↓ U_v
    - ↑ Cr_s

- ↑ risk factors
  - Drugs, nephrotoxic, e.g.,
    - ACI/ARBs
    - Diuretics
    - Lactulose
    - NSAIDs
    - NSBB
  - Toxins
    - Alcohol use
  - ↑ loss of fluids / bleeding
    - Vomiting
    - Diarrhea
    - GI bleeding
  - Infection
    - Spontaneous bacterial overgrowth (SBP)
    - Urinary tract infection (UTI)
    - Pulmonary infection (PI)
    - Cellulitis
  - Organ failure
    - Liver
    - Kidney
    - Heart
    - Lungs

- Mechanisms
  - Adrenal dysfunction hepatorenal reflex
  - ↑ intra-abdominal pressure
  - Systemic inflammation

Abbreviations; ACEIs, angiotensin concerting enzyme inhibitor; ARBs, angiotensin II receptor blockers; Cr_s, serum creatinine; EABV, effective arterial blood volume; GFR, glomerular filtration rate; H_2O, water; Na^+, sodium; NO, nitric oxide; NSAIDs, non-steroidal anti-inflammatory drugs; NSBB, non-specific beta blockers; PI, pulmonary infection; RAAS, renin-angiotensin aldosterone system; SBP, spontaneous bacterial peritonitis; SBP, spontaneous bacterial peritonitis; SNS, sympathetic nervous system; UTI, urinary tract infection; U_v, urine volume

- Treatment of AKI in cirrhotic patients
  - Controversial whether long-term infusion of albumin
    - ↓ HRS development, or
    - ↓ 18-mon mortality
  - Determine cause of AKI
    - ATN
    - Hypovolemia
    - HRS
    - Test urine
      - Normal in HRS
      - Abnormal hematuria proteinuria abnormal sediment
    - Fluid challenge
      - Albumin 1 g/kg. maximum of 100 g/d
      - If blood loss-associated AKI. Give RBC transfusion to target of ≥ 8 g/L
      - Monitor Cr_s → ↓ baseline Cr_s to ≤ 0.3 mg/dL hypovolemic
    - Monitoring
      - Urine Na+ excretion
      - Fractional excretion of Na+ (FENa) if patient have ↓ urine output (UO)
      - ↓ FENa (> 1%) = ↓ volume (hypovolemia), or HRS
      - ↑ FENa (> 1%) suggests
        - ATN with renal loss/wasting of renal Na+, or
        - Structural disorders of the kidney
    - Note; recent data questions value of FENa < 1% to distinguish HRS from HTN (no correlation between FENa and the etiology of AKI on kidney biopsy)
    - FENa performance characteristics to diagnose, ↓ volume or HRS
      - Sensitivity (Sn), 100%
      - Specificity (Sp), 14%

- Fractional excretion of urea (FEUrea)
  - Not affect by diuretics
  - Superior to FENa
    - Sn, 75%; Sp, 80%
  - Use FeUrea rather than FENa or urine Na+ concentration to differentiate HRS-AKI from ATN
  - Biomarkers to distinguish structural (ATN / non-HRS from functional [↓ volume or HRS-AKI from ATN])
  - ↑ cystanin C (a low molecular weight) protein from nucleated cells; reflects ↓ GFR
    - It need to be determined whether combination of cystatin C plus for example Cr_s will improve the differentiation of HRS-AKI from ATN-AKI
  - NGAL in the urine useful to distinguish HRS-ATN from ATN, but is not widely available
  - Biomarkers of renal tubular cell damage
    - ↑ a-glutathione S-transferase
    - α1-microglobulin
    - β2-microglobulin
    - ↑ N-acetyl (B-D-glucosaminidase)
    - Kidney injury molecule 1 (KIM-1)
    - Neutrophil gelatinase–associated lipocalin (NGAL)
    - Retinol binding protein

➢ Pharmacological treatment

- Albumin
  - Optimal benefit when serum albumin > 4 g/dL, but
  - Monitor concentration of albumin to ↓ risk of
    - Volume overload
    - Pulmonary edema
    - Heart failure
  - Albumin challenge
    - 1 g/kg per day for two consecutive days
    - If no ↓ Cr_s to < 0.3 mg/kg → diagnosis of HRS-AKI
  - Albumin continuation
    - 20-40 g/d plus splanchnic vasoconstrictors (please see below) (do **not** use albumin by itself without the splanchnic vasoconstrictors)
  - While albumin is the recommended volume-expanding agent; if not available use crystalloids
  - benefit
    - ↑ 180 d survival
  - Caution
    - Do **not** infuse more than amounts recommended above to avoid volume overload

- Splanchnic vasoconstrictors (must be used with albumin)
  - Revise the splanchnic vasodilation with is central to the pathophysiology of HRS-AKI (please see above pathophysiology)
    - Begin as soon as diagnosis of HRS-AKI is made
      - Every ↓ of Cr_s by 1 mg/dL → ↓ 27% in relative risk of mortality
  - Choices of splanchnic
    - norepinephrine
    - Vasoconstrictors acting directly on smooth muscle α1 adrenergic reception agonist
    - Midodrine
    - Vasopressin analog
      - Terlipressin
    - Somatostatin analog which ↓ glucagon
      - Octreotide

- Terlipressin
  - Benefit
    - 30% - 40% response risk
      - ↑ survival by 10 d without need for renal replacement therapy (PPT) [dialysis]
  - Contraindication / adverse effect
    - Ischemia
      - Splanchnic digital
    - Cardiac
      - Arrythmia
      - Angina pectoris
    - Lung
      - Respiratory failure
      - Risk factors
        - ↑ baseline
        - ↑ INR
        - ↑ MAP
        - ↑ O_2 saturates
  - Caution: “terlipressin should not be resumed in patients who experience cardiac or ischemic symptoms, even if the symptoms have subsided following discontinuation of treatment”
  - Dosing
    - Terlipressin, 1-2 ng IV q6h for 14 d, or by continuous infusion
    - Stop if no response in 3-4 d
    - Predictors of response*: baseline
      - Laboratory
        - Bilirubin < 10 mg/dL
        - Creatinine < 5 mg/dL
        - Lower stage of acute-on-chronic liver failure (ACLF)
        - MAP < 5-10 mm Hg

- Patient
  - Systemic inflammatory response syndrome (SIRS)
  - Alcohol-associated hepatitis (AAH)
  - Sepsis

*the patient with certain clinical complications, AAH causation, but lesser/laboratory abnormalities is more likely to respond to terlipressin

- Benefits of TER plus albumin
  - ↑ 30-d pre-LT survival
  - May ↑ post-LT survival

- Norepinephrine
  - Dosing
    - 0.5 mg/h, increasing q4h by 0.5 mg/h to maximum of 3 mg/h, to target MAP ≥ 10 mm Hg / or UO > 50 mL/h for ≥ 4 h
  - Benefit
    - Norepinephrine (NOR)
    - Terlipressin (TER) until
      - INR > 1.5
      - Bilirubin > 5 mg/dL
      - Hepatic encephalopathy (HE) / ascites

    ▪ Benefit of TER > NOR
  - Causing
    - Norepinephrine may cause similar adverse effects as terlipressin (cardiac arrhythmias / angina, splanchnic / digital ischemia, respiratory distress)

- Midodrine plus octreotide
  - Do **not** give octreotide without midodrine (not effective)
    - Inferior to benefit of terlipressin
  - Adverse effects
    - Midodrine
      - CNS: palpitations
      - CVS: headache, blurred vision
      - Skin: rash
    - Octreotide
      - Fatigue
      - Backpain
      - GI: nausea/vomiting, abdominal pain

- Renal replacement therapy (RRT)
  - Indications
    - Lack of response to terlipressin, norepinephrine, or midodrine plus octreotide, activity as
    - All course of AKI, including HRS-AKI, if the patient is or might become a candidate for LT
    - ATN, and not a candidate for LT
  - Use continuous RRT
  - Outcomes
    - If > 7 d RRT required, mortality rate ~60%
    - The longer RRT given before LT, the ↑ risk of renal function not recovering (everyday of RRT before LT ↑ risk of non-recovery of renal function by ~5%)
  - ↓ likelihood of renal recovery
    - HRS-AKI
    - ATN

    } Duration of renal injury

- Do **not** use transjugular intrahepatic portosystemic shunt (TIPS)

- Liver transplantation (LT)
  - MELD score
    - Used to stage/score patient priority for LT
    - ↑ Cr_s → ↑ MELD score, but MELD does not take into account the AI (i.e., ATN, HRS-AKI, hypovolemia)
  - Benefit
    - Recovery of renal function, 75%
    - No benefit, 25%
      - Risk factors for post-LT dependent on RRT
        - Young
        - Chronic renal disease (CRD)
        - RRT required pre-LT

- Liver plus kidney transplantation
  - Indications
    - Patient on RRT, or
    - GFR (measured/calculated) ≤ 25 mL/min for ≥ 6 consecutive wks

LIVER FAILURE

Acute-on-Chronic Liver Failure (ACLF): **ACG Clinical Guidelines** (2022)

Bajaj JS, et al. Am J Gastroenterol 2022; 117: 225-252

- Definition
  - A combination of hepatic and extrahepatic organ failures
  - Since there are major definitions, the accomplishment of a consensus for the development of guidelines is challenging, especially since data has been analysed on studies using varying definitions.
  - The Asian Pacific Association for the Study of the Liver (APASL), European Association for the Study of the Liver – Chronic Liver Failure (EASL-CLIF), and the North American Consortium for the Study of End-Stage Liver Disease (NACSELD) and have varying combinations of definition of organ failure, based upon sex type of organ failure.
  - Prediction of
    - 7 d mortality (early severity) — NACSELD better than EASL-CLIF
    - 90 d mortality — EASL-CLIF better than NACSELD (late severity, prioritize for liver transplantation)

Comparison of the definition for ACLF

	APASL	EASL-CLIF	NACSELD	WGO
Derivative	− Consensus and observational	▪ Prospective, observational study	▪ Prospective study in patients with cirrhosis with and without infection	− Consensus
Patient population inclusion	− Chronic liver disease − Compensated cirrhosis	▪ Compensated /decompensated cirrhosis	▪ Decompensated cirrhosis by implication	− Non-cirrhotic chronic liver disease, compensated and de-compensated cirrhosis
Exclusion	− Infection, previous hepatic decompensation	▪ HCC outside Milan criteria ▪ HIV infection ▪ Significant comorbidity	▪ HIV infection ▪ Previous organ transplantation ▪ Untreated malignancies	− Not stated

	APASL	EASL-CLIF	NACSELD	WGO
○ Severity score	− Liver failure defined as jaundice (serum bilirubin ≥ 5 mg/dL) and coagulopathy (INR of ≥ 1.5 or prothrombin activity of ≤ 40%) − Ascites or encephalopathy develops within 4 wk	▪ Hepatic and extrahepatic organ failure	▪ Extrahepatic organ failure	− Not stated
○ Comments	− Diagnosis can be made early enough for intervention to alter disease course − Diagnosis is sensitive but not specific for early mortality	▪ Diagnosis of ACLF may be made too late to impact disease outcome		− Working definition for data collection to ultimately arrive at a validate definition

Abbreviations: ACLF, acute-on-chronic liver failure; APASL, Asian Pacific Association of the Study of the Liver; EASL-CLIF, European Association for the Study of the Liver Chronic Liver Failure; HCC, hepatocellular carcinoma; INR, international normalized ratio; NACSELD, North America Consortium for the Study of End-Stage Liver Disease; WGO, World Gastroenterology Organization

Printed with permission: Bajaj JS, et al. Am J Gastroenterol 2022; 117: 225-252 (Table 3).

➢ Pathogenesis

- **Brain**
  - Unknown pathogenesis
    - Much data points towards altered intestinal microbiota (dysbiosis)
  - Exclude
    - Other neurological conditions, including
      - Delirium or dementia
      - Drug overdose
    - Psychiatric disorders
    - Infection
    - Hepatic encephalopathy (HE) and its precipitation from
      - Infection (especially spontaneous bacterial peritonitis [SBP])
      - Drugs (opioids, benzodiazepines, NSAIDs, PPIs, ACEI/ARBs)

➢ Recommendations

  - ABCs, IV fluids, antibiotics, ventilation where appropriate, likely ICU admission

- Empiric therapy of HE with lactulose +/- antibiotics
- Hospitalized patients with ACLF
  - Use dexmedetomidine for sedation

  (very low quality, conditional recommendation)

- **Kidney**
  - Acute kidney injury (AKI)
    - ↑ sCr ≥ 0.3 mg/dL in < 48 h, or
    - ↑ 50% above baseline
    - Type 1, HRS = HRS = AKL (functional stage 2 AKI)

    } ▪ Occurring in first 7 d
  - Chronic kidney disease (CKD)
    - eGFR < 60 mL/min for ≥ 3 mon
    - CKD = HRS, type 2
    - If patient has CKD, then a given ↑ sCr indicates a more severe cause of AKI
    - Exclude prerenal azotemia, or bacterial infection
  - Stop vasopressin if terlipressin used for up to 14 d (response rate 44%)
    - < 25% ↓ sCr within 4 d
    - Treatment of HRS (LT transplant)
      - Albumin
      - Vasoconstrictors (such as norepinephrine)
  - Patients with cirrhosis plus AKI (stage 2/3)
    - Give albumin IV plus vasoconstrictors [norepinephrine]
    - Monitor Cr_s (serum creatinine) in hospitalized patients with cirrhosis (↑ baseline Crs associated with poor renal outcomes and low 30-d survival

➢ Recommendations

- In hospitalized patients with HRS-AK and low (not high) grade ACLF
  - Improve renal function with norepinephrine (low quality, conditional recommendation) / terlipressin (moderate quality, conditional recommendation)
- In patients with cirrhosis plus SBP
  - Give antibiotics plus albumin IV to ↓ risk of AKI/organ failure
  - Non-SBP infections
    - Give antibiotics alone rather than antibiotics plus albumin

  (high quality, strong recommendation)
- Vasoconstrictors
  - ↑ renal perfusion/function
  - Adverse effects
    - Ischemia in patients with
      - Coronary artery disease (CAD)
      - Peripheral vascular disease (PVD)

MCQ Diamonds

- Prophylactic antibiotics ↓ risk of SBP, but do **not** completely remove the risk

- Give the risk of SBP in the patient on prophylactic antibiotics for appropriate indications.
  - Prophylaxis
    - Primary, 90%
    - Secondary, 78%

- Give the meaning of the "AKI/CKD viscous cycle".
  - AKI → CRD
    - CRD → CRD + AKI
      - Break this cycle using prophylaxis for SBP, which predisposes ARS / HRS-AKI

- Lung
  - Respiratory failure
    - Respiratory replacement therapy (RRT) may be used as a bridge to LT in persons whose function does not respond to albumin infusion plus vasoconstrictors
    - Perform renal transplantation (RT) at time of liver transplantation if
      - > 60 yr
      - AKI, prolonged
      - Need of RRT for > 90 d before LT
      - Underlying CKD (predisposes patient to other organ failure)
      - Hereditary renal conditions
    - If mechanical ventilation required long-term for brain or respiratory failure
      - Do **not** list for liver transplant to improve mortality
      (very low quality, conditional recommendation)
  - Spontaneous bacterial peritonitis (SBP)
    - Antibiotics plus albumin IV in HRS-AKI with SBP (but not in HRS-AKI with no SBP)
    - Careful adjustment of diuretics/laxatives (to prevent ↑ fluid loss)
    - Large volume therapeutic paracentesis
    - Antibiotics for patients with upper/lower GI bleeding from any cause (including variceal / non-variceal)
    - Guideline-based primary/secondary prophylaxis for SBP
  - There are no data on the use of prophylactic antibiotics to ↓ risk if ventilator-associated pneumonia (VAD) in patients with cirrhosis.

- Patients on ventilators have ↑ risk of upper GI bleeding
  - This ↑ risk is reduced by inhibition of gastric acid
  - The difference between the prophylactic use of proton pump inhibitors (PPIs) versus histamine 2 receptor antagonists is small, but is statistically significant (risk of upper GI bleeding, 1.3% to 1.8%, RR, 0.73; 95%CI: 0.57-0.92)
  - The use of PPIs versus H2RA was associated with ↑ risk of
    - Diarrhea, non-Clostridium difficile infection

Recommendations

- Ventilated patients with cirrhosis
  - Do **not** use prophylactic antibiotics

  (very low quality, conditional recommendation)

- **Cardiovascular System**
  - Vasoconstrictors
    - CLIF organ failure
  - EASL
    - Use of vasoconstrictors: Dopamine, dobutamine, epinephrine, norepinephrine, terlipressin
  - Use vasoconstrictors if systolic blood pressure (SBP) ≤ 40 mm
    - MAP < 60 mm Hg, or
      - ↓ 40 mm Hg in systolic blood pressure (despite adequate fluid resuscitation and cardiac output)

➢ Treatment

- Norepinephrine → ↑ MAP / ↑ SBP → ↑ renal perfusion/function
- An ↑ MAP is protective from ACLF
- Distinguish from
  - Cardiac myopathy
    - Left ventricular ejection fraction (LVEF) ≤ 50%, or
    - Double global longitudinal strain < 18% to 22%
  - Advanced diastolic dysfunction (≥3 of 4 criteria)
    - Septal early diastolic mitral annular velocity < 7 cm/s
    - Mitral inflow early diastolic velocity ratio ≥ 15
    - Left atrial volume index > 34 mL/m^2
    - Tricuspid aggregation velocity > 2.8 m/s (in absence of pulmonary hypertension)
  - A hyperdynamic state is a feature of cirrhosis
    - Associated with ↑ risk of death

❖ **Coagulation abnormalities**

- Because both hyper- and hypocoagulation factors are reduced in patients, the INR does not reflect the patients' coagulation status (↑ INR still reflects ↓ hepatic synthetic function [unless concomitant use of vitamin K])
- The coagulation status in patients with cirrhosis is measured with viscoelastic tests (resistance to stirring of whole blood), named thromboelastography (TEG) or rotational TEG (ROTEM) values
- If TEG/ROTEM values abnormal ("…clear cut offs for type and number of transfusions needed)
  - Give cryo-precipitate or prothrombin complex concentrate (PCC)
    - Do **not** use fresh frozen plasma (FFP)
- A hypocoagulable status in ACLF is usually associated with inflammation
- Hypercoagulability may occur in cirrhosis/ACLF, with venous thrombosis, such as hepatic or portal veins
  - Do **not** give prophylactic low molecular weight heparin (LMWH), but
  - Treat acute thrombosis with full dose anticoagulation LMWH
- For prevention of venothrombotic embolism in hospitalized patients, give LMWH.

MCQ Trick

- Give the exception to withholding VTE prophylaxis in hospitalized patients with cirrhosis/ACLF.
  - Recent upper GI bleeding
    - Bleeding esophageal varices, even if treated with esophageal band ligation (EBL)
      - Wait to start LMWH until ulcerative/erosion of esophagus from EVBL has healed
    - Non-variceal bleeding, such as peptic ulcers
      - Give LMWH once ulceration has healed
  - Thrombocytopenia < 50 x 10^9 /L

➢ Recommendations

- In patients with cirrhosis plus ACLF
  - Do **not** measure coagulation states with INR (very low quality, conditional recommendation) (INR is used to access hepatic synthetic function)
- Patients with cirrhosis have ↑ risk of venous thromboembolism (low quality, conditional recommendation)
- Altered coagulation, do **not** transfuse unless
  - Patient is bleeding
  - Patient to have a [high risk] procedure

  (Low quality, conditional recommendation)

- In patients with cirrhosis who require an invasive procedure
  - Use thromboelastography (TEG) or rotational TEG (ROTEM) methods to assess coagulation status

  (moderate quality, conditional recommendation)

- **Infections**
  - Alternations in the intestinal microbiome provide the "systemic inflammatory marker" for the ↑ risk of bacterial, fungal, and nosocomial infections.
  - The dysbiosis consists of
    - ↑ enterococcaceae, Escherichia, Streptococcus
    - ↓ Lachnospiraceae, Ruminococcaceae

➢ Clinical

- Often infections in ACLF occur with
  - No fever
  - No leucocytosis
- Usual presentation of infection in ACLF
  - CNS
  - Kidney
  - Organ failure
    - Altered mental status
    - AKI

MCQ Laboratory Gem

- Normal WBC in patients with cirrhosis
  - WBC is often normally low in cirrhosis, so
    - WBC in normal range may represent an actual increase from the previously lower but still normal level.
- ↑ CRP, ↑ procalcitonin, ↑ bacterial DNA levels
  - Commonly seen in patients with cirrhosis with no infection

➢ Prognosis

- Infection in patient with ACLF
- ↑ ratio of neutrophils/lymphocytes

→ ↓ 30-day survival (OR, 0.67; 95%CI: 0.48-0.93)

➢ Recommendations

- In hospitalized patients with decompensated cirrhosis
  - Assess thoroughly for possible infection (moderate quality, conditional recommendation)
  - If infection is suspected, treat early (very low quality, conditional recommendation)

- **Bacterial Infection**
  - More common than nosocomial / fungal infections
  - Gram-positive more common than gram-negative organisms
  - Site
    - GI
      - C. difficile, 5%
      - Associated with ↑ risk of death
    - GU
      - Urinary tract infection, 19%
    - Lung, 9%
    - Soft tissue / skin, 10%
  - Fever is uncommon in patients with cirrhosis plus infection
    - Their WBC is often low in cirrhosis, so that a normal WBC may represent on ↑ in WBC
    - Also in cirrhosis without infection, there may be
      - ↑ CRP
      - ↑ procalcitonin
      - ↑ bacterial diet
  - Multidrug resistant or MDR organisms are common in hospitalized patients with cirrhosis (22% - 36% of infections)
    - Treat for MDR infections with
      - Piperacillin, tazobactam, or carbapenem +/- glycopeptide / linezolid / daptomycin
    - Failing to use appropriate early empiric antibiotics against MDR double the mortality rate 26% to 50%
  - Classification

	Time from admission, healthcare exposure	
Community-acquired	< 48 h	> 90 d
Healthcare-associated	< 48 h	< 90 d
Nosocomial	> 48 h	-

    - Likely MD (22-48%) if patient has cirrhosis
    - North America (NA) usually vancomycin-resistant enterococci [VRE]
    - Europe, usually Enterobacteriaceae
    - 28-day mortality rate (MR) 50% unless effectively treated (piperacillin-tazobactam/carbapenem +/- daptomycin/glycopeptide/linezolid (28% MR)
  - Suspect multidrug resistant (MDR) organisms

- **Fungal Infections**
  - 7% risk in hospitalized ACLF patients
    - Usually nosocomial
    - Usually Candida species → fungemia, peritonitis
  - Risk factors for fungal infection
    - ACLF with ↑ number of organ failures
    - Diabetes mellitus (DM)
    - Acute kidney injury (AKI)
    - Previous bacterial infection
    - ↑ length of hospitalization +/- ICU admission

Recommendation

  - In hospitalized patients with ACLF
    - If a suspected bacterial infection does not respond to appropriate antibiotics, suspect multidrug resistant (MDR) organisms, or fungal infection (very low quality, conditional recommendation)

- Prophylaxis for spontaneous bacterial peritonitis (SBP)
  - Secondary
    - In patient with ACLF
      - Norfloxacin, trimethoprim-sulfamethoxazole, or rifaximin
      - Treat each day to ↓ risk of MDR infections
  - Primary
    - Avoid in hospitalized patients (↓ prognosis for primary SBP, but ↑ positive prognosis in secondary prophylaxis in hospitalized patients)

- Upper GI Bleeding Prophylaxis
  - In cirrhosis, PPIs → ↑ risk of infection e.g., SBP (by way of dysbiosis)
  - Use PPIs in patients with cirrhosis only if absolutely indicated and if other acid inhibitory agents (H2RA) fail

➢ Recommendations
  - In patients with cirrhosis plus a
    - History of SBP, use secondary prophylaxis with antibiotics (low quality, conditional recommendation)
    - No history of SBP, use primary prophylaxis with antibiotics (there is no superior antibiotic recommended) (low quality, conditional recommendation)
  - In patients with cirrhosis
    - Do **not** use PPI unless there is a clear induction (very low quality, conditional recommendation)

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- Give the mechanism(s) by which PPIs increase the risk of infection in patients with cirrhosis.
  - ↓ intragastric acid

    → ↑ bacterial overgrowth in small intestine (SIBO)→ dysbiosis

    → ↓ oxidative burst of neutrophils → ↓ immune function

- Non-specific beta-blockers (NSBB)
  - Used for effective
    - Primary/secondary prophylaxis against bleeding esophageal varices
    - ↑ 28-d (but not 90-d) transplant (liver)-free survival
    - "…it is difficult in clinical practice for patients with ACLF to tolerate clinically meaningful doses of NSBB."

- Statins
  - In patient with cirrhosis, statins → ↓ fibrosis, ↓hepatic compensation, ↓ death, especially in patients with CTP-A/-B cirrhosis (some cirrhotics with CTP-B/C may have ↑ ALT on simvastatin 40 mg/d, possibly from high-dose statin hepatotoxicity)

- Rifaximin
  - For treating overt hepatic encephalopathy (HE)
  - Comparable effect to oral quinolone for prophylaxis of SBP.
  - IV fluids used when administering IV antibiotics
    - Total body Na^+ (which is ↑ in cirrhosis) → ↓ Na intake po, as well as IV Na^+, either
      - Concentrating IV medications including antibiotics, or
      - Solubilize drugs in 5% dextrose when being prepared for IV infusion.

❖ Non-infections Precipitating Factors

- Alcohol-Associated Hepatitis (AAH)
  - Commonest precipitating event for ACLF
  - AAH may be diagnosed even if alcohol use was stopped in < 60 d before onset of jaundice

- Assess severity of AAH using Model for End Stage Liver Disease (MELD) score > 20 and Maddrey Discriminant Function Score (MDF) ≥ 32, plus Lille score on day 0 (admission), start prednisone po, and reassess Lille score on day 7 to determine if prednisone should be discontinued in an effort to ↓ mortality at day 28.
- Only alcohol abstinence ↑survival beyond 6 mon.

➢ Recommendation

- In patients with severe alcohol-associated hepatitis (MDF ≥ 32, MELD score > 20), unless other wise contraindicated
  - Give prednisone/prednisolone 40 mg/d (moderate quality, strong recommendation)
  - Do **not** give pentoxifylline (Very low evidence, conditional recommendation)

- Drug-Induced Liver Injury (DILI)
  - DILI-related ACLF is rare, including ACLF related to complementary and alternative medicine (CAM)
    - If there is ≥ grades DILI-ACLF, mortality is 100% in 120 d

- Hepatitis B virus (HBV) Infection
  - HBV-associated ACLF is more common in Asian Pacific countries (~15%) than elsewhere
  - HBV flares are
    - Spontaneous
    - After stopping treatment / development of resistance to nucleot(s)ide analogs
    - Chemotherapy
    - Coinfection with HDV infection
    - Cirrhosis, decompensated

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- Give the mechanism(s) by which HBV may cause ACLF.
  - HBV infection causes necrosis of hepatocytes (sterile inflammation) → submassive necrosis

    → release of damage-associated molecular patterns (DAMPs)

    → background of extracellular matrix

- Surgery

➢ Demography

- In patients with cirrhosis, there is a general risk of developing ACLF within
  - 28-d of surgery, 25%
  - 1 yr, 40%
  - Abdominal non-liver surgery, 35%

➢ Methods (to calculate risk of various surgeries in patients with cirrhosis)

- Mayo Clinical Calculator
- VOCAL PENN
  - Also considers type of surgery

} – Prediction of 30-d mortality

➢ Prognosis of surgery-associated ACLF

- Overall rate of development of ACLF (definition, EASL-CLIF criteria) within 28 d of surgery, 25%; within 1 yr, 40%
  - Non-liver surgery, 35%
- When ACLF develops, usually mild (grade 1), with ↑ Cr_s > 2.0 mg/dL
  - Other organ (renal) failures post-surgery
    - Circulatory, 26%
    - Lung, 26%
    - Brain, 14%
    - Liver, 14%
- Once ACLF develops, subsequent
  - Improvement, 37%
  - Worsens, 14%
  - Predictions of development of ACLD post-surgery
    - ↑ AP > 164 IU/L
    - MELD

- Non-surgical Interventions (TIPS, ERCP)

- ERCP-associated ACLF (usually within grade 1)
  - ACLF in 1 mon after ERCP, 11%, no ERCP, 3%
    - Grade 1, 55%
    - Grade 2/3, 22%
    - Predictor of post-ERCP-ACLF, MELD > 15

} – Usual indications
- Cholangitis, acute
- Choledocholithiasis
- Stricture biliary

- Other non-surgical interventions associated with ACLF
  - GI
    - Other endoscopies
    - TIPS procedure
  - GU
    - Renal replacement therapy
    - Therapeutic paracentesis

➢ Treatment

- ICU management for multi-organ failures
  - Usually due to severe AAH, or infections (including acute viral hepatitis)
- If septic shock develops, mortality rate is ~65%
  - Definition of septic shock
    - Vasopressin needed to maintain MAP ≥ 65 mm Hg
    - Lactate, serum > 18 mg/dL (≥ 2 mmol/L), without associated hypovolemia
- Empirical antibiotics (meropenem plus vancomycin) and volume replacement to maintain MAP ≥ 60 mm Hg in patients with cirrhosis
  - When vancomycin-resistant Enterococcus infection suspected → use linezolid, or daptomycin
- Monitoring
  - Arterial line, including pulmonary arterial catheter to monitor pulmonary arterial pressure (PAP) in patients with pulmonary arterial hypertension (PAH)
  - Central venous pressure (CVP) measurements (note that there is considerable respiratory variation in IVP pressure in presence of tense ascites)
  - Echocardiography
  - Response to volume infusion
  - Lactate, serum
  - Urinary output (Cr_s measurements do **not** reflect renal function in cirrhotic patients with sarcopenia [start antibiotics within 1 h of admission to ICU])
- Norepinephrine
  - Use this vasoconstrictor if MAP ≤ 60 mm Hg, despite volume infusion
  - Norepinephrine causes ↑ preload / ↑ monotropic function of heart to ↑ MAP
  - If volume resuscitation plus norepinephrine fails to correct MAP, add hydrocortisone 50 mg IV q h (↓ shock, but no ↓ mortality)
- Albumin
  - Use to ↓ risk of
    - AKI/HRS in patients with SBP
    - Post-paracentesis circulatory dysfunction (PPCD)
  - Adverse effects: ↑ risk of
    - Pulmonary edema
    - Respiratory infection
  - Best predictor of survival, reaching a serum albumin ≥ 4 g/dL

- Preparations of albumin to use
  - Use 5% albumin, rapidly to ↑ volume expansion
    - Give rapidly over 15 mm to replace volume (benefit is equal to volume of albumin infused)
  - 25% albumin, maintain volume expansion
    - Give slowly to replace volume (benefit is equal to 3.5 to 5x infused volume of albumin)
    - Use this concentration if using albumin to slowly correct the hypervolemia of patients with cirrhosis.

- Nutrition
  - Use guidelines for nutritional support in critically ill patients with cirrhosis
    - Calorie intake, 35 to 40 cal/kg per day
    - Protein intake 1.2 to 2.0 g/kg per day
  - Use parenteral nutrition if
    - GI tract not adequate for intake of patient's needs for nutrition
    - Unprotected airway (risk of aspiration)
    - Hepatic encephalopathy grade ¾

Recommendations

- In hospitalized patients with cirrhosis
  - Do **not** give routine parenteral nutrition (PN), enteral nutrition (EN), or oral supplements to improve mortality
  - Do **not** use albumin IV to ↑/maintain albumin > 3 g/dL, to ↑ survival, to ↓ renal dysfunction, or to ↓ infection (moderate quality, strong recommendation)
  - Do **not** use G-CSF (granulocyte colony-stimulating factor) to ↑ survival (Very low evidence, conditional recommendation).

- Exception: HBV-associated ACLF without sepsis, G-CSF → ↓ short-term mortality (RR, 0.56; 95%CI: 0.39-0.89)
  - Do not use artificial/bioartificial extracorporeal liver support systems (no improvement in survival of patient)

- Liver transplantation (LT)
  - "….controversy exists as to whether ACLF in or of itself demands extra MELD points" for determining the suitability [of the patient] for LT.
    - In hospitalized patients with ACLF
      - Use of the MELD-Na+ score underestimates the 1-/3-mon mortality risk of ACLF
    - Complications but not mortality of LT are more frequent in ACLF-3 than in ACLF-1/2
    - Use of ACLF-3 scire points may be useful to predict

	ACLF-3 Score Points	1 yr Mortality
▪ Mortality rate	> 2 points	92%
▪ Use MELD score and ACLF-3 score to allocate organ for LT	≤ 2 points	16%

    - ↑ risk of LT in ACLF
      - Age ≥ 53 yr
      - Lactate, pretransplant arterial value ≥ 4 mm/L
      - PaO_2/FiO2 of patient on ventilation ≤ 200 mm Hg
      - White blood cell (WBC) concentration, pretransplant

      } − ACLF Model Score

➢ Recommendations

- In hospitalized patients with cirrhosis plus ACLF who are on continued mechanical ventilation for
  - Adult respiratory distress syndrome (ARDS) or
  - For brain-related conditions despite optimal therapy
    - Do **not** list for LT (Very low evidence, conditional recommendation).
- In hospitalized patients with end stage liver disease (ESLD), discuss where appropriate
  - Early goals of care
  - Possible palliative care

  (Very low evidence, conditional recommendation).

TUMOURS

Hepatocyte and Hepatic Tumorigenesis

Donne R, et al. Nat Rec Gastroenterol Hepatol 2020; 17: 391-404

- "The chromosome houses the genetic information specific to all living beings"
  - Humans have 23 chromosomes in the haploid gene
- Ploidy is the number of complete sets of chromosomes in a cell.
  - Somatic individual organisms, tissues and cells can be described according to the number of sets of chromosomes present: haploid (1 set), diploid (2 sets), tetraploid (4 sets).
- Polyploidy is defined on the basis of
  - The DNA content of each nucleus, which is called nuclear ploidy (for example, a cell can be tetraploid mononucleate (4n) or octoploid mononucleate (8n)), and
  - The number of nuclei per cell, which is called cellular ploidy (for example, a cell can be tetraploid binucleate (2×2n) or hexaploid trinucleate (3×2n)). n, chromosome number
- Nomenclature

	Cells	Copy of each Chromosome
-	Haploid (n)	1
-	Diploid (2n)	2
-	Triploid (3n)	3
-	Tetraploid (4n)	4
-	Polypoid	≥ 3 chromosome per cell (whole-genome duplication)
		The additional chromosome sites may have different organs
		Pancreatic acinar cells, 4n
		Hepatocytes, 4n to 8n (in human liver, 30% of hepatocytes are polypoid)
-	Aneuploidy	Increase/decrease copy number of whole chromosomes or chromosome segments

- Importance of polyploidy
  - "Proliferating polyploid cells [are] genetically unstable, thereby potentially facilitating [their] tumour development"

➢ Mechanisms of polyploidy

- Nuclear polyploidy
  - ↑ DNA per nucleus
- Cellular polyploidy
  - ↑ nuclei per cell

- Cell cycle independent (cell fusion)
  - Cell fusion during fertilization without nuclear fusion requires cell adhesion / destabilization of the opposing lipid bilayers → fusogenic protein engagement
  - Some viral infections (e.g., human papilloma virus)
    - Normally, endoplication cyclin-dependent kinases (CDK) serine threonine protein kinases control the four successive phases of the human cell cycle
      - G1, S, G2 and M
    - CDKs associated with cyclin → phosphorylation of substrate → S-CDK-associated mitosis
  - Endoreplication is an alternative cell cycle in which cells successfully replicate their genome in the absence of cell division → mononucleate polypoid progenies
    - Variants
      - Endocycles and endomitosis

↓

- Cells vary between G and S phases, by
  - Inhibiting entry into mitosis by way of ↓ E3 ubiquitin ligase of proteolysis of mitotic cyclins
  - Interactions with cyclin kinase inhibitors
  - Alternating oscillations between
    - Low levels of S-CDK in G phase
    - High levels of S-CDK in S phase

↓

- Cells skip metaphase, anaphase or cytokinesis → altered metaphase-anaphase transition → mitotic slippage

- Failure of cytokines
  - During ANA phase, genomic / cytoplasmic material is evenly distributed through two daughter cells
    - This even distribution depends upon
      - Actinomycin ring contractions
      - Cleavage furrow development
      - Intracellular bridge formation
      - Intracellular bridge degradation
  - Failure of any of these steps (e.g., aurora A, LATS1 [large tumour suppresser 1], MAD2 [mitotic arrest deficient 2])→ failure to cytokinesis → binucleatic polypoid cells
    - Dysfunction of protein controlling cytokines process →

❖ Polyploidy in the liver

- 70% of the liver is made up of hepatocytes
- Source of heterogeneity
  - The function of the hepatocytes varies from the portal axis to the pericentral (e.g., hepatocyte central venous system

Periportal	Pericentral
− Amino acid breakdown	▪ Alcohol detoxification
− Cholesterol synthesis	▪ Glycolysis
− Fatty acid metabolism	▪ lipogenesis
− Glucogenesis	
− Ureagenesis	

- The gene expression profile also changes along the lobule, from periportal to pericentral.
  - The energy needs of the hepatocytes also change along the lobule.
- In human non-alcoholic fatty liver disease (NAFLD)
  - The oxidative stress caused by ↑ reactive oxygen species (ROS) → activation of DNA damage response (ATR–p53–p21).
- This activation → multiple endoreplication cycles →
  - Polyploid mononucleate hepatocytes (for example, a tetraploid mononucleate cell [4n] or an octoploid mononucleate cell [8n]).
- During liver regeneration, there is also a shift from cellular ploidy to nuclear ploidy (for example, a diploid binucleate cell can form two tetraploid mononucleate cells, and a tetraploid binucleate cell can form two octoploid mononucleate cells or a 16n mononucleate cell).
- The hepatic parenchyma is also enriched in polyploid mononucleate hepatocytes (for example, 4n and 8n cells) following an iron or copper overload.

Abbreviation: n, chromosome number; NAFLD, non-alcoholic fatty liver disease

- The capacity of the liver to regenerate depends upon
  - Proliferation, compensating hypertrophy, regeneration →
    - ↓ cellular ploidy (binucleate)
    - ↑ nuclear ploidy (mononuclear)
  - This polyploidy spectrum occurs in
    - HBV, HCV infection
    - Non-alcoholic fatty liver disease (NAFLD)
    - Iron/copper overload (e.g., hereditary hemochromatosis [HH]; Wilson disease [WD])

- Example
  - Non-alcoholic fatty liver disease (NAFLD) → oxidative stress → reactive oxygen species (ROS)

↓

Activation ATP-p53 p21

↓

DNA damage response

↓

↑ endoplication cycles

↓

2n, 4n, 8n

  - Liver regeneration
    - Cellular ploidy → nuclear ploidy
    - Diploid binucleate (2n) cells → two 4 n cells
    - Tetraploid binucleate (2x2n) cells → two 8n cells, or 16n mononucleate cells
- Genetic diversity results from preferably polypoid hepatocytes both increasing their DNA content, as well as reversing it (ploidy reversal)

❖ Tumorigenesis

- The polyploid state
  - Gatekeeper/driver of liver tumorigenesis
    - Depending on the context and especially on the TP53 status (that is, mutated or wild-type)
- Polyploid hepatocytes (for example, 4n and 8n) are more resistant to oncogenic events than diploid hepatocytes, because
  - They possess extra copies of tumour suppressor genes, which
    - Confers protection against loss of heterozygosity by buffering the effects of inactivating mutations.
- The polyploid state hinders hepatocyte proliferation by means of the p53- dependent 'tetraploid checkpoint'
  - Has ↓ proliferation / ↑ commitment to cell death
- Liver tumours stem from diploid hepatocytes.
- TP53 mutation represents a crucial event in the development of polyploid tumours
  - Associated with ↑ aggressiveness and ↓ prognosis.
- Interfering with the p53 pathway allows polyploid cells to resume the cell cycle despite ↓ chromosomal instability → aneuploidy.

- The polyploid state acts as a tumour-promoting mechanism by amplifying genomic aberrations and exacerbating tumour aggressiveness.
- It remains unknown whether polyploid tumours arise from
  - A proliferating polyploid clone or
  - From an initiating diploid tumour that has subsequently undergone polyploidization
- Polypoid hepatocytes have more chromosomes as well as more supernumerary centromeres which form multipolar mitotic spindles, as compared to diploid hepatocytes.
  - The ↑ multipolar mitotic spindles → ↑ chromosome segregation errors
- However, hepatic polyploidization is beneficial for hepatic regeneration, such as acute liver failure.
  - This leads to ↑ hepatic tumorigenesis
    - A "gatekeeper" / driver of hepatocarcinogenesis
    - Diploid cells are less resistant to oncogenic events because they have
      - ↓ tumour suppressor → ↓ protective against loss of heterogeneity / ↓ buffering of inactive mutations
      - ↓ interference of p53 pathway, protecting genomic integrin

Oncology Events

- Gatekeeper
  - Four/eight copies of chromosomes
  - P53 checkpoint
  - Restriction of proliferation
- Diploid Tumour

No Tumour → (Tp53 Driver) → Polyploid Tumour

- Driver to polypoid tumours
  - TP53 mutation
  - ↑ aggressiveness
    - ↑ proliferation rate
  - Poorer prognosis
  - P53 checkpoint
    - ↑ disease relapse

Hepatocellular Cancer (HCC): **Tumour Evolution**

Craig AJ, et al. Nat Rev Gastroenterol & Hepatol 2020; 17; 139-52.

➢ Molecular features

- Interpatient heterogeneity of subclasses
  - Interpatient
    - Proliferation
    - Non-proliferation
  - Inter +/- intratumour
    - Trunk/branch mutations by "…multiregional exome sequencing within single tumour nodules"
    - The major difference is "…the timing of a mutation, rather than clonal selection … as mutation, rather than clonal selection … as mutations are progressively localized into smaller tumour subpopulations"

❖ Tumour initiation

- Cirrhosis / dysplastic nodules
  - Cirrhosis/regeneration nodules → dysplasia → HCC
    - Architectural atypia (low/high grade)
    - Progression:
      - Low grade dysplasia (LGD) → 9%
      - High grade dysplasia (HGD) → 32%
      - Telomere lengthening
      - TERT promotor amplification (44%)
        - Promoter methylation of APC, CDKL2, FOXE3, SEPT9, SOCS1
        - TP53, CTNNB (gatekeeper for tumour progression)
      - Gains/losses of chromosomal area 8p/8q
        - ↑ copy number variations (CNVs)

- Hepatic adenomas
  - Molecular subgroups
    - Inflammatory (40-50%)
      - Gene mutations leading to activation of JAK-STAT pathways (Janas kinase signal and activator of transcription
    - HNF7A-mutated (30-40%)
    - CTNNB1 (10-15%)
    - Sonic hedgehog
    - GL1 family

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- Give the molecular group of hepatic adenomas which are predisposed to malignant transformation.
  - Hepatic adenomas with activating mutations in exon 3 of CTNNB1 have ↑ risk of malignant transformation

  - Cells of origin of HCC
    - Mature hepatocytes
      - Undergoing sequential genomic insults → direct degeneration into HCC
      - Loss of TP53 → differentiating into precursor cells
    - Progenitor hepatocytes

❖ HCC evolution

  - Evolution
    - Neutral evolution
      - Genetic drift → tumour clonal diversification
    - Tumour clonal evolution
      - Subclonal competition: intrinsic genetic factors causing DNA damage → genomic instability

  - In multinodular HCC may represent
    - Synchronous but independent tumours, or
    - True metastatic disease
    - The above two lesions may be differentiated by their single nucleotide variants (SV)

- Intrinsic genetic factors causing DNA damage
  - Checkpoint dysfunction
  - Chromatid cohesion flaws
  - Spindle assembly abnormal

  Chromosome segregation errors →
  - Aneuploidy
  - Genomic instability → mutation mediated by APOBEC cytidine deaminase (cytosine deamination of DNA) → ↑ tumour progression →
    - Double-stranded DNA breaks, and
    - APOBEC 3B-mediated C to U transitions

- Extrinsic factors
  - Neoantigen interact with a T cell receptor (TCR) → binds to major histocompatibility class I complex → triggers immune responses
    - Immunoediting
    - Elimination
    - Equilibrium
    - Escape

    } → Interaction
  - Tumour-stroma interactions → immunosuppressed microenvironment

➢ Diagnostic imaging

- Dynamic contrast-enhanced ultrasound (CEUS)

Fraquelli M, et al. Contrast-enhanced ultrasound for the diagnosis of hepatocellular carcinoma in advanced chronic liver disease. Cochrane Database of Systematic Reviews 2019, Issue 11. Art. No.: CD013483. DOI: 10.1002/14651858.CD013483

  - Microbubble contrast agent
    - No iodine
    - No nephrotoxicity

    } Intravascular → high accuracy for angiogenesis → good details of focal lesions

    But,
    - No demonstration of capsule of liver
    - Demonstrates
      - Arterial enhancement
      - Without phase (portal vein)

      } Real-time
    - Allows assessment of tumour
      - Feeding vessels (including AV communication)
      - Circulatory volume
    - May be used as an add-on test to CT/MRI
    - The speed of the washout phase may have prognostic value
  - The clinical and radiological features of HCC vary according to the etiology of the underlying liver disease, especially with regard to HBV/HCV infection
  - Non-cirrhotic HCC
  - Different
    - Characteristics
    - Treatment
    - Prognosis

- Liver biopsy
  - Concerns
    - Seeding of tumour
    - Bleeding vascular tumour
    - False-negative results
  - Indications (“when us a liver biopsy performed in patients with HCC?)
    - Mass in patient with chronic liver disease but no cirrhosis
    - CT_e/MRI_e non-diagnostic for typical changes of HCC

- Histological heterogeneity

- Cell differentiation
  - Well-differentiated
    - Trabecular pattern of cells
  - Multiple differentiation
    - Pleomorphism of tumour cells
    - Nuclei
      - Hyperchromatic (more nuclei and bigger)
  - Poorly differentiated
    - ↑ nucleus/cytoplasm ratio
    - ↑↑ pleomorphism

- Immune (lymphocytic) infiltration
  - ↑ with grade of differentiation

- Clinical implications

- Predicting prognosis
  - Intratumour heterogeneity correlates positively with poor prognosis
    - The intratumour heterogeneity can be scored from the single nucleotide variants (SNVs), using the Mutant-Allele Tumour Heterogeneity (MATH) score
      - A low MATH score is associated with ↑ overall survival

- Predicting therapeutic response
  - Primary resistance to immune checkpoint inhibitors
    - Somatic mutations in the Wnt-B-catenin pathway
  - Poor response to tyrosine kinase inhibitors (e.g., sorafenib; cabozantinib) associated with
    - ↑ hepatocytic growth factor (HGF)
    - ↑ insulin0like growth factor (IGF-1)
    - ↑ fibroblast growth factor (FGF)

- Biomarkers
  - "Liquid biopsy" (subcutaneous detected in blood which have been released by tumour cells)
    - Cell-free circulating DNA (cfDNA)
    - Circulating tumour cells (CTCs)
    - Exosomes

Perhaps the Future

- "Being able to predict pattern of tumour evolution could revolutionize the clinical management of [patients with] HCC"

➢ Treatment

- Hepatocellular Cancer (HCC): Unrespectable disease treated with Yttrium microsphere radioembolization

Abdel-Rahman O, Elsayed Z. Yttrium-90 microsphere radioembolization for unresectable hepatocellular carcinoma. Cochrane Database of Systematic Reviews 2020, Issue 11. Art. No.: CD011313. DOI: 10.1002/14651858.CD011313.pub4.

- Surgical resection or liver transplantation can be used to benefit only ~20% of patients with HCC.
- Irresectable HCC can be treated with
  - Sorafenib (SOR), or
  - Ablative therapies
  - Transarterial interventions (TACE), including transarterial radioembolization (RE) with selective yttrium-90 microsphere

- Hepatocellular cancer

	RE	SOR	Certainty of Evidence
Advanced HCC			
RE plus SOR			
Serious adverse events	40%	39%	Very low
Hyperbilirubinemia	15%	4%	Very low
Fatigue	35%	24%	Very low
Locally advanced HCC			
All cause mortality, 1 yr	63%	53%	Very low
Serious AEs	21%	35%	
Median time to progression of HCC	6.1 mon	5.4 mon	

  - Hand-foot skin reaction: ↓ with RE vs SOR (RR 0.03; 95%CI: 0.00 to 0.06, p< 0.001; low)

- Intermediate HCC radioembolism (RE) vs chemoembolism (CE)

	RE	CE
− Disease control rate	73%	77%
− Tumour response	52%	63%

- Evidence showing effects if radioembolization with or without sorafenib compared alone in people with unresectable hepatocellular carcinoma is highly insufficient.
- We cannot determine if radioembolization plus sorafenib compared with sorafenib alone affects all cause mortality or the occurrence of adverse events.
- Radioembolization compared with sorafenib achieved equivalent survival and cause fewer adverse effects, but our certainty was very low.
- Evidence showing effects of radioembolization versus chemoembolization in people with unresectable hepatocellular carcinoma is also highly insufficient.
- Radioembolization did not seem to differ from chemoembolization in terms of serios adverse events and quality of life, but the certainty of evidence was very low / further high-quality placebo-controlled randomised clinical trial are needed to assess patient-centred outcomes.

- Contrast-Enhanced Abdominal Ultrasound (CEAU)

Fraquelli M, et al. Contrast-enhanced ultrasound for the diagnosis of hepatocellular carcinoma in advanced chronic liver disease. Cochrane Database of Systematic Reviews 2019, Issue 11. Art. No.: CD013483. DOI: 10.1002/14651858.CD013483

➢ Risk factor for HCC

- Liver
  - Cirrhosis / severe fibrosis
  - HBV, HCV chronic fibrosis
  - Non-alcoholic fatty liver disease (NAFLD)
- Life-style
  - Alcohol (heavy) / tobacco use
  - Obesity
- Comorbidities
  - Diabetes / metabolic syndrome
- Toxins
  - Aspergillus flavus / parasiticus

❖ Metastatic Liver Disease: Percutaneous Infection of Ethanol

Swierz MJ, Storman D, Riemsma RP, Wolff R, Mitus JW, Pedziwiatr M, Kleijnen J, Bala MM. Percutaneous ethanol injection for liver metastases. Cochrane Database Syst Rev. 2020 Feb 4;2(2):CD008717. doi: 10.1002/14651858.CD008717.pub3. PMID: 32017845; PMCID: PMC7000212.

- Evidence for the effectiveness of PEI plus TACE versus TACE in people with liver metastases is of very low certainty and is based on one small randomised clinical trial at high risk of bias.
  - Currently, it cannot be determined whether adding PEI to TACE makes a difference in comparison to using TACE alone.
    - Evidence for benefits or harms of PEI compared with no intervention, other ablation methods, or systemic treatments is lacking.
- Long term prognosis of patients with resected metastases ~50%
- Delivery of therapy to tumours
  - Percutaneous intratumour ethanol injection (PEI)
  - Intraarterial: transcatheter arterial chemoembolization (TACE)

Survival, yrs	PEI plus TACE	TACE
1	92%	78%
3	80%	65%
5	64%	48%

- Comparing PEI plus TACE alone
  - Mortality (RR, 0.69; 95%CI: 0.36 to 1.33; very low certainty of evidence) after 3 yr follow up

	PEI plus TACE	TACE	RR, 95%CI	Certainty of evidence
− Local recurrence	16%	39%	o.41; 95%CI 0.15 to 1.15	Very low
− Tumour shrinkage ≥25%	66%	48%		

➢ HCC Prognosis

- Overall ratio of mortality/incidence, 0.95
- Curative treatment
  - Only 20% of patients qualify
  - 5-yr survival rate for early HCC, 50%
- Using Milan criteria for liver transplantation (LT) for HCC
  - Overall 5-yr survival rate > 70%

Prevention, Diagnosis, and Treatment of Hepatocellular Cancer (HCC): **AASLD Practice Guideline** (2023)

Singal AG, et al. Hepatology 2023; 78(6): 1922-1965.

- Examples of updates
  - Investigate HCC surveillance with both abdominal ultrasound (US) plus blood concentration of alpha-fetoprotein (AFP)
  - Pharmacotherapy
    - Use of immune checkpoint inhibitors (ICH) as first-line systemic therapy
  - Surgery
    - Extended indications
  - Care
    - Multidisciplinary care team (MDT)
    - Advanced care planning (ACP)

- Demography
  - HCC is not common primary cancer of the liver least frequently affected ethnic group non-Hispanic Caucasians (White persons)

- Risk factors
  - Cirrhosis / advanced fibrosis 2% per yr risk of HCC
  - Infection (even without advanced cirrhosis)
    - HBV
    - HCV
    - Post-sustained virological response in HCV infection
  - Intake toxins
    - Non-alcoholic fatty liver disease, diabetes (2x ↑ risk of HCC)
    - Obesity (1.5 – 4.5 x ↑ risk)
    - Smoking (↑ risk of HCC by 20% - 86%)
    - Aflatoxin B1 / aristo cholic acid (cofactors with HBV infection)
    -

- Scoring system
  - Page-B score, comprised of
    - Older age
    - Male gender
    - ↓ platelets

- Primary prevention
  - Treat liver disease early before advanced fibrosis / cirrhosis
  - Vaccination re HBV in newborns, and unvaccinated ↑ risk persons
  - ≥ 1 cup of coffee per day (no cream/sugar)
  - Medications (not recommended yet for chemoprotection of HCC)
    - Lipophilic statins (RR ~ 0.54)
    - ASA use for ≥ 5 yr (↓ risk, 43% - 60%)
    - Metformin (controversial)

Recommendations

- Introduce / follow public health policies / interventions (Level 5, Strong recommendation)
- Vaccinate all newborns at birth for HBV, as well as unvaccinated persons at high risk of HBV (Level 2, Strong recommendation)
- Follow guidelines for treatment of HBV/HCV (Level 2, Strong recommendation)
- Follow a healthy lifestyle for persons with any type of chronic liver disease, including a healthy diet and normal body weight, no alcohol / tobacco, treat comorbidity including all components of the metabolic syndrome (Level 3, Strong recommendation)
  - Coffee intake is encouraged in persons with cirrhosis (Level 5, Weak recommendation)
- Chemoprevention with aspirin, statin, metformin has some evidence for its use in patients with chronic liver disease, but these are not yet recommended to be used in patients with chronic liver disease (Level 5, Weak recommendation), unless the patient has a comorbidity which would require the use of these drugs (Level 3, Weak recommendation)

- Surveillance
  - Objective
    - Offer HCC surveillance to the person "…who would be potentially eligible for curative treatment that can improve survival:
    - This is of benefit to patients with Child-Turcott -Pugh
    - Consider factors related to the
      - Patient
        - Comorbidities
        - Body function
      - Liver
        - Size
        - Number of lesions
        - Location
        - Spread / vessel involvement
      - Physician
        - Training
        - Experience
        - Availability

- Benefits
  - ↑ cure
  - ↑ survival

MCQ Pearl

- Do **not** perform surveillance for HCC in patients with CTP-C cirrhosis
  - Comorbid conditions which limit life-expectancy to < 2 yr

- Special considerations

		Surveillance
- HCV after SVR	Cirrhosis	Yes (HCC risk for 10 yr)
	No cirrhosis	No
- NAFD	No cirrhosis	No
	Advanced fibrosis	Possibly
- HBC	Cirrhosis	Yes
	No cirrhosis	Depends upon age / race

➢ Testing

❖ Biomarkers (in addition to alpha fetoprotein [AFP])

- Lens culinaris lectin (LCA) binding subtraction of AFP, or
- AFP-L3
  - Des gamma carboxy prothrombin (DCP [aka protein induced by vitamin K absence / antagonist II (AVKA-II, a variant of prothrombin), a subtraction of AFP
- FDA approved for
  - Risk stratification
  - Not approach for HCC surveillance
- Gender, age, AFP-L3, AFP, DCP (GALAD)
  - For early detection of HCC, Sn 54%, Sp 90%
- Circulating tumour DNA (ctDNA)
- Useful for CTP class A, B, and C

Recommendations

- Perform HCC surveillance in patients with high-risk for HCC, as long as they are candidates for treatment (Level 3, Strong Recommendations)
- Do **not** perform surveillance in
  - Patients with CTP class C unless they are suitable for liver transplantation (Level 3, Strong recommendation)
  - Patient with life-limiting commodities unless they can be remedied by
    - Liver transplantation
    - Other directed therapies
- Patients who are listed for LT should have surveillance q6mon for HCC (Level 3, Strong recommendation)
- Do **not** do HCC surveillance in patients with HCV infection post-SVR advanced fibrosis but no cirrhosis (Level 3, Weak Recommendation)
  - NAFLD and advanced fibrosis but no cirrhosis (Level 2, recommendation)
- Use best practice alerts or outreach programs to ↑ patient adherence to HCC surveillance (Level 2, Strong recommendation)
- For HCC surveillance
  - Use US plus AFP q6mon (Level 2, Strong recommendation)
  - So not use CT/MRI-based imaging or tumour biomarkers other than AFP (cirrhosis, chronic HBV (Level 5, Weak recommendation), except in patients in which US surveillance is “suboptimal” (Level 3, Weak recommendation)

❖ Diagnostic imaging

- Abdominal Ultrasound (US)

		US	US plus AFP
Performance characteristics	Sensitivity (Sn)	53%	63%
	Specificity (Sp)	91%	-

  - These are lower than CT/MRI
    - Diagnostic adds ration, US plus AFP > US

- CT, 2-phase; MRI, contrast-enhanced and abbreviated MRI (abMRI)
  - MRI has best performance in CTP A

	CT	MRI	AbMRI
Sn	83%	86%	80-90%

  - Interval of surveillance
    - Interval of q6mon is superior to q1yr of survival, 40 mon as 30 mon (P = 0.03)

- Continue q6mon interval for surveillance as long as
  - Good US visualization of liver (Liver Imaging Reporting and Data System (LI-RADS) visualization score A/B (LI-RADS score 0 has ↓ sensitivity for detecting early HCC
    - Poorer visualization
      - Non-viral etiology of cirrhosis
  - No liver lesions (US LI-RADS 1) and
  - AFP normal
- Lesion < 1 cm
  - Repeat US plus AFP q3-6 mon x3 (original plus 2 repeats)
  - If stable on 2 follow ups continue surveillance q6mon
- New / enlarging lesions on US, or ↑ AFP regardless of US → CE MRI
- AFPs 20 ng/mL, abnormal
  - Sn, ~60%
  - Sp, ~90%
- AFPs > 20 ng/mL, no mass
  → MP MRI, CECT, plus
  → CT chest, pelvis
  - PET/CT

Recommendations

- Reports on US surveillance for HCC should comment on visualization (Level 5, Strong recommendation)
  - If US visualization is limited → CE CT or MP MRI (Level 5, weak recommendation)
- Mass < 1 cm on US
  - Repeat US plus AFP in 3-6 mon (Level 3, Strong recommendation)
  - If stable on 2 repeats US, continue US plus AFP q6mon (Level 5, Weak recommendation)
- Mass ≥ 1 cm on US → MP/CE MRI/CT (Level 1, Strong recommendation)
- If AFP ≥ 20 ng/mL, or rising > MP/CE MRI/CT (Level 3, Strong recommendation)

➢ Diagnosis

- Laboratory
  - Alpha fetoprotein (AFP)
    - Not used for diagnosis (previously used to diagnose HCC when AFP > 400 ng/mL but even that concentration had a sensitivity for diagnosis only 60%)
  - Liquid biopsy (measure tumour components in the blood)
    - Circulatory tumour cells ctDNA, also ctDNA methylation
    - Extracellular RNA from exosomes
    - Not yet ready for clinical practice

- Diagnostic Imaging (DI)
  - CT or MRI contrast-enhanced (CE) multiphase (MP) MRI or CT
    - Features
      - Arterial phase, hyperenhancement (APHE), =/-
      - Venous / portal, or delayed phase washout
  - Performance characteristics (PC) → use extracellular or contrast agents hepatobiliary MRI

PC	CE, MP MRI	CT
Sn	82%	66%
Sp	92%	91%

  - Diagnostic algorithm for HCC
    - Tumour size
    - Appearance of capsule
    - APOX
    - Delayed phase washout*
    - Threshold growth (RIM APHE is against diagnosis of HCC)

    → LI-RADS diagnostic algorithm (LI-1 is benign, LI-5 is HCC)

    - Abnormalities required for diagnosis of HCC mass

> 2 cm	APHE plus 1 further major cirrhosis
10-19 mm	APHE plus washout or threshold growth, or APHE plus 2 major criteria

    - Probability of
      - LR-5 HCC lesion to be HCC (validated in non-cirrhotic HBV infection), 95%
      - LR-4, probability of HCC, 75%
      - LI-3, probability of HCC, ~30%

      → Either repeat DI in 3 mon, or → liver biopsy
      - LRM, LR-TIV → liver biopsy

- Liver Biopsy and Histopathology
  - Indications
    - Diagnosis
      - When not LR-5 lesions
      - When DI indeterminant
      - When DI suggests mixture of HCC plus cholangiocarcinoma (CCA)
    - Treatment
      - To determine molecular and immune class of HCC
      - Oncogenic mutations associated with
        - Oncogenic mutations, which exclude criteria phenotypes
        - Gene signatures, which predict response to immunotherapy

- Histopathological changes
  - Report using International Consensus Group of Hepatocellular Neoplasia (ICGHN) major features
    - Stroma invasion
    - Diffuse fatty infiltration
    - ↑ cell density
    - Portal tract tumour cells
    - Arteries unpaired
    - Gland pattern – pseudoglandular

  - Performance characteristics of liver biopsy

Size	Sensitivity (Sn)
< 2 cm	~60%
> 2cm	70-93%

  - Special markers
    - Clathrin heavy chain
    - Glutamine synthase
    - Glypican 3 (GPC3)
    - Heat shock protein (HSP70)

    – ≥ 2 of 4 markers is highly specific or HCC

  - Other markers for
    - Progenitor cells
      - K19
      - Epithelial cellular adhesion molecule
    - Neovascularization
      - CD34

MCQ Diamond

- If HCC suspected from DI and histopathology "does **not** eliminate the possibility of HCC (biopsy is not conclusive such as < LR-5 but features of change in the enhancement pattern or tumour growth are present) – repeat liver biopsy

Recommendations

- Persons with cirrhosis or chronic HBV infection are at ↑ risk of HCC, and diagnosis of HCC should be based upon diagnostic imaging (DI) +/- histopathology from liver biopsy (Level 1, Strong recommendation)
  - DI diagnosis should be based upon LI-RADS criteria (Level 5, Weak recommendation)
  - Histopathological diagnosis of HCC should be based upon the International Consensus Criteria and using both histological and immunohistochemical criteria (level 5, Strong recommendation)
  - Do **not** diagnose HCC based only on the concentration of AFP, biomarkers or liquid biopsy (Level 3, Weak recommendation)
- Do **not** use just DI to biopsy HCC in patients who do **not** have cirrhosis or at risk chronic HSV infection (Level 1, Strong recommendation)
- The DI tests should be dynamic contrast-enhanced MRI or multiphasic CY (Level 1, Strong recommendation)
  - When LR-4 / LR-5 use MDT to
    - Confirm diagnosis of HCC
    - Provide molecular analysis

    (Level 3, Weak recommendation)
  - If the DI is LR-3, repeat CT/MRI in 3-6 mon (Level 2, Weak recommendation)
  - If the DI is LR-4, and after discussion by a Multidisciplinary Team (MDT)
    - Repeat DI in 3-6 mon, or perform liver biopsy immediately (Level 2, Strong recommendation)
  - If an immediate diagnosis of HCC is needed in LR-4, proceed to biopsy rather than waiting to repeat the DI (Level 5, Strong recommendation)
  - If LR-M
    - Perform liver biopsy liver biopsy to male diagnosis of HCC and to exclude mixed HCC or non-HCC tumours (Level 1, Strong recommendation)

➢ Staging

- Use Multidisciplinary Care Team (MDCT) and Staging Systems
  - Barcelona Liver Clinic Cancer (BCLC)
    - 1999
      - Includes Eastern Cooperative Oncology Group Performance Status (ECOG PS) (liver dysfunction and performance status included)
      - Stratification by prognostic stages
        - Stages, very early stage; Stage D terminal
    - 2022
      - Includes
        - Model for End Stage Liver Disease (MELD)
        - ALBI (albumin / bilirubin) score
        - AFP and other biomarkers (down stage and stage migration and personalization possible)

- Italian Liver Cancer (ITC)
- Hong Kong Liver Cancer (HKLC)
- Chinese Liver Cancer systems (CLC)
- TNM do **not** use

Multidisciplinary Care Team (MDCT) (aka Tumour Board)

- Benefits
  - Collaboration, communication, care better
  - Alteration of initial interpretation
    - DI 18%
    - Histopathology, 11%
    - Treatment, 42%
  - ↑ patient
    - Satisfaction
    - Overall survival (OS)

Recommendations

- Evaluate/record tumour stage at time of diagnosis of HCC, and before initiation of treatment
  - Tumour burden
  - Liver dysfunction
  - ECOG PS (Level 5, Strong Recommendation)
- Use a MDCT for staging to optimize DI interpretation and care (Level 3, Strong recommendation)
  - Use the BCLC system for staging (Level 5, Strong recommendation)
- Do DI strategy with contrast-enhanced MRI (ceMRI) or multiphasic CT (mpCT) of the abdomen (Level 2, Strong recommendation)
- For HCC > BCLC stage D
- Do **not** do routine PET CT or radionuclear technetium bone scan (low sensitivity for HCC) (Level 3, Weak recommendation)
  - Please note varying viewpoint presented in data / suggestion provided above

➢ Treatment

❖ Surgery

- Resection
  - Indication
    - Localized HCC, no cirrhosis: curative level for patients with localized HCC in the absence of cirrhosis (this applies in NAFLD and non-NALFD HCC
    - 30% of NAFLD-related HCC occurs without cirrhosis

- Benefits
  - ↓ probability of liver-related morbidity because the non-resected liver is healthy
  - ↓ recurrence
  - ↑ disease-specific survival

- Feasibility of Resection
  - Resection in presence of cirrhosis
    - Rate of surgical resection depends upon multiple factors
    - Tumour
    - Non-resected liver
      - Extent of resection / health of residual liver
      - Size of future liver remnant (FLR)
    - Presence of clinically significant portal hypertension (CSPH)
  - Example of typical hepatic partial resection of HCC
    - "…a single lesion in a patient with compensated cirrhosis without CSPH (hepatic venous pressure gradient [HVPG] > 10 mm Hg) and an adequate FLR
      - No cirrhosis, > 20%
      - Cirrhosis, > 40%

      } − 5-yr survival, 70%
      − Post-operative mortality, < 3%
  - Importance of CSPH (↑ HVPG > 10 mm Hg)
    - ↑ risk of post-resection liver failure

Clinical Tip

- In the absence of the value of the HVPG, give clinical basic laboratory suggests which support or do **not** support the presence of SSPH
  - Against CSPH
    - Ascites
    - Varices
    - Platelet count > 10^5 per µL
  - Supportive of presence of CSPH
    - The opposite of above
    - ↑ MELD / ↑ MELD Na score
    - ↑ ALBI score
    - Abdominal indocyanine clearance score

"Trick on the Tip"

- While transient elastography showing ↑ hepatic stiffness may be used to estimate the presence of CSPH, the above question asked only for "clinical / basic laboratory surrogates"

LIVER TRANSPLANTATION

Liver Transplantation: Immunosuppression to Prevent Graft Rejection

Best LMJ, et al, Cochrane Database of Systematic Reviews 2020, Issue 1. Art. No.: CD013203. DOI: 10.1002/14651858.CD013203.pub2

- Corticosteroids (CS) induction (standard)
  - Graft failure, 12%
  - Death, 7%
- There was no evidence of differences in all-cause mortality and graft failure between other induction immunosuppressants and glucocorticosteroids in either the direct comparison or the network meta-analysis (very low-certainty evidence).
- Basiliximab (BAS) induction vs CS
  - Mortality, HR, 0.53; 95%CI 0.31 to 0.93
  - Graft failure, HR, 0.44; 95%CI 0.28 to 0.70
- Based on low-certainty evidence, basiliximab induction may decrease mortality and graft failure compared to glucocorticosteroids induction in people undergoing liver transplantation.
  - However, there is considerable uncertainty about this finding because this information is based on small trials at high risk of bias.
- Nutrition is an important aspect of management in severe acute pancreatitis. Enteral nutrition has advantages over parenteral nutrition and is the preferred method of feeding.
  - Enteral feeding via nasojejunal tube is often recommended but its benefits over nasogastric feeding are unclear.
  - The placement of nasogastric tube is technically simpler than the placement of nasojejunal tube.
- There is insufficient evidence to conclude that there is superiority, inferiority, or equivalence between nasogastric and nasojejunal mode of enteral tube feeding in people with severe acute pancreatitis.
- There was no evidence of effect of nasogastric (NG) or nasojejunal (NJ) placement of feeding tubes for enteral nutrition on mortality (RR, 0.65; 95%CI: 0.36 to 1.17, very low certainty evidence) due to indirectness and impression.
- Other considerations for which there was no evidence of effect included
  - Organ failure
  - Infection
  - Pain exacerbation
  - Complications
  - Need for surgery / parenteral nutrition

EASL Clinical Practice Guidelines: Liver transplantation

EASL. J Hepatology 2016; 64: 433-485

Recommendations

- Evaluation/MELD Score
  - When a major complication of cirrhosis develops, calculate the MELD score (Grade II-2)
    - Predicts short-term pre-LT mortality (Grade II-1)
    - Objective, and can be used in organ allocation (Grade II-1)
    - Exception points for the MELD score must be considered (such as in persons with HCC) in order to allocate livers fairly (Grade II-3/III)

- Treatment

- **Cirrhosis with no HCC**

- HBV-related liver disease
  - Nucleos(t)ides (NKCs; entecavir, tenofovir)
    - Target undetectable levels of HBV DNA
    - Use for severe reactivation (Grade I)
    - Risk factors for HBV recurrence post-LT recurrence post-LT
      - Immunoglobulin monoprophylaxis
      - Viral replication
      - HCC development (Grade II-2/3)
        - Severe/fulminant HBV hepatitis (Grade II-3)
        - If response to HBV NUCs is poor, assess for possible HDV infection (Grade II-1/2)
    - Continue assessment for possible liver failure, even if patient on HBV therapy (Grade III)

Abbreviations: ABIC score, age, serum Bilirubin, INR, and serum Creatinine score; AIH, autoimmune hepatitis; ALD/AuLD, alcoholic liver disease / alcohol use liver disease; ALG, anti-lymphocyte globulin antibody; ATG, anti-thymocyte globulin antibody; BMD, bone mineral density; BMI, body mass index; CCA, cholangiocarcinoma; CMV, cytomegalovirus; CNI, calcineurin inhibitor; CPR, cardiopulmonary resuscitation; CT, computed tomography; DACD, donation after circulatory death; DSA, donor specific alloantibodies; EGD, esophagogastroduodenoscopy; ERCP, endoscopic retrograde cholangiopancreatography; EVR, early viral response; FAPN, familial amyloid polyneuropathy; HBV, hepatitis B virus; HCC, hepatocellular; HCV, hepatitis C virus; HH, hereditary hemochromatosis; HLA, human leukocyte antigen; HVPG, hepatic venous pressure gradient; Maddrey score, Maddrey discriminant function; MPAP, mean pulmonary arterial pressure; GAHS, Glasgow Alcoholic Hepatitis Score; ICU, intensive care unit; LT, liver transplant; MELD, Model for End Stage Liver Disease; MMF, mycophenolate mofetil; NAFLD, non-alcoholic liver disease; NUC, nucleos(t)ide; PBC, primary biliary cholangitis; PFT, pulmonary function tests; PSC, primary sclerosing cholangitis; PTLD, post-transplantation lymphoproliferative disorder; QoL, quality of life; RCT, randomized clinical trial; TB, tuberculosis; TE, transient elastography; TTE, transthoracic transient elastography; UDCA, ursodeoxycholic acid; WD, Wilson disease

- HCV-related liver disease
  - Ideally treat HCV pre-LT (Grade I)
    - If not possible, treat post-LT (Grade III)
  - Use sofosbuvir, ledipasvir and daclatasvir for compensated/decompensated liver disease (simeprevir in patients with Child Pugh B)

- Alcoholic Liver Disease (ALD)
  - Consider interval of abstinence (e.g., ≥ 6 mon) to provide possible improvement in
    - Liver function
    - Compliance (Grade II-3)
  - Consider LT for highly selected persons with acute alcoholic hepatitis who are not responding to standard of care, including corticosteroids (Grade II-2)

- Non-alcoholic Fatty Liver Disease (NAFLD) and non-alcoholic Steatohepatitis
  - Treat comorbidities pre-/post-LT to ↓ mortality (Grade III)

- Primary Biliary Cholangitis (PBC)
  - Consider LT for
    - Decompensated liver disease / complicated portal hypertension
    - Failing medical therapy
    - Development of hepatocellular cancer (HCC)

    } Grade II-3

- Primary Biliary Sclerosing (PSC)
  - Consider LT for
    - Decompensated liver disease / complicated portal hypertension
    - Recurrence cholangitis
    - Development of HCC

    } Grade II-3
    - Cholangiocarcinoma excludes pre-LT (diagnostic imaging, biological markers (Grade III)
    - Colorectal cancer excluded pre-LT in patients with associated ulcerative colitis [PSC-associated UC] (Grade II-3)

- Autoimmune Hepatitis (AIH)
  - AIH not responding to medical therapy plus decompensated liver function (Grade II-3)

- Genetic Diseases
  - Hereditary hemochromatosis (HH)
    - Decompensated liver disease / complications of portal hypertension (Grade III)
    - Development of HCC
      - Exclude if non-overload associated cardiomyopathy
  - Wilson disease (WD)
    - Decompensated liver disease / complications of portal hypertension
    - Acute liver failure
    - Perform careful neurological examination pre-LT (LT may worsen neurological complications of WD) (Grade III)
  - Familial amyloid polyneuropathy
    - Perform immediately upon diagnosis (Grade III)
  - Primary hyperoxaluria type 1 (Grade III)
    - Liver plus kidney transplant of renal failure
    - Role of LT alone is unclear

- Hepatic Malignancies
  - Hepatocellular cancer (HCC)
    - Use Milan criteria to assess suitability for LT (Grade I)
  - Cholangiocarcinoma (CCA) or HCC plus CCA (mixed)
    - Do **not** perform LT except in centres with clinical research protocols employing adjuvant or neoadjuvant therapy (Grade II-3)
  - Fibrolamellar HCC/epithelial hemangioendothelioma
    - Consider for LT (Grade II-3)
  - Metastatic disease
    - Non liver / non-colon cancers
      - Selected patients
      - Selected centres
      - Research protocols

      } Grade II-3

➢ Assessment of comorbidities

- Cardiovascular function
  - Complete multidisciplinary assessment for patient of any age coming for LT, including EGD / transthoracic echocardiogram (TTE) (Grade II-3/III)
    - ↑ risk patients ≥ 50 yr / multiple cardiovascular risk factors
  - Perform cardiopulmonary exercise test if target HR not achieved on pharmacological stress test

- Pulmonary function
  - Study all persons with pulmonary function tests (PFTs)
    - Especially important to exclude
      - Hepatopulmonary syndrome → LT (Grade II-2/3)
      - Portopulmonary hypertension
        - If mean pulmonary arterial pressure (MPAP) ≤ 30 mmHg and patient responds to pulmonary vasodilators → LT (Grade II-2/3)

- Renal function
  - Hepatorenal syndrome not responding to standard of care → LT
  - Chronic liver disease; severe/irreversible in patient with chronic liver disease → consider LT plus renal transplantation (Grade II-2)

- Immunological assessment
  - Exclude donor specific human leucocyte antigen (HLA) cells antibodies (DSA)
    - ↑ risk of acute/chronic rejection
    - Histopathological damage (Grade III)

- Infection risk
  - It is mandatory to screen for bacterial, viral and fungal infection pre-LT to exclude risk of mortality-reducing active infection (would preclude to LT being performed) (Grade III).
  - CMV infection in the liver donor or recipient determines when CMV prophylaxis is given (Grade II-3)

- Cancer screen
  - Screen for cancer of
    - Ear-nose-throat
    - Lung
    - Esophagus/colon
    - Bladder/prostate
    - Skin
    - All age specific screenings e.g., breast, ovary/uterus-cervix
  - LT possible if patient is cancer-free 5 yr after curative treatment

- Psychosocial
  - Food security, family/friend assistance
  - Adherence risks for non-adherence (drug intake, appointments kept [Grade III])

- Anatomy
    - Perform a contrast scan to determine
        - Anatomy of recipient (Grade II-3)
        - Presence of portal vein thrombosis (PVT) extending to portomesenteric system (this might render LT not sufficiently viable) (Grade II-3)

- Nutritional assessment
    - Difficult to assess in patient with cirrhosis
        - Psoas muscle thickness/area correlate with mortality (Grade II-2)
    - While nutritional improvement is essential, there are no approved protocols (Grade III)
    - Perform assessment of bone mineral density by DEXA scan to diagnosis and indicate lead treatment for osteoporosis (Grade III)

❖ **Organ Donation**

- Extended critical donors (ECD)
    - The ECD graft represents an organ with unfavourable characteristics associated with ↓ post-transplant outcomes that fall into two main risk categories
        - Poor graft function
        - Donation after circulatory deaths (DCDs) and the non-DCDs
    - The Eurotransplant definition of ECD refers to the category of marginal graft dysfunction
        - Patient
            - Donor age > 65 yr
            - ICU stay with ventilation > 7 d
            - BMI > 30 kg/m^2
        - Histopathology
            - Steatosis of the liver > 40%
        - Laboratory
            - Serum sodium > 165 mmol/L
            - Transaminase: ALT > 105 U/L, AST > 90 U/L
            - Serum bilirubin > 3 mg/dL

- Categories

Category	Description
I	○ Dead on arrival − Tissue (corneas, heart valves, skin, bone, etc.) can be recovered from category I donor or any individuals who dies in a hospital in a manner not suitable for solid organ recovery − Since there are no immediate time constraints to minimize tissue injury, there is no requirement for a precisely timed approach to tissue recovery.
II	○ Unsuccessful resuscitation (CPR) − These are patients who suffered a witnessed cardiac arrest outside the hospital and undergo unsuccessful cardiopulmonary resuscitation (CPR) − When CPR fails in a medically suitable organ donor, uncontrolled organ donation is an option.
III	○ Awaiting cardiac arrest following withdrawal of care − With the permission of the donor or donor family, organs may be recovered after death is declared from patients with irreversible brain injury or respiratory failure in whom treatment is withdrawn − Death is declared after predetermined period, usually 5 min, of circulatory arrest
IV	○ Cardiac arrest after brain death − Rarely, a consented brain-dead donor has a cardiac arrest before schedule organ recovery − Such category IV donors should either ▪ Proceed as for a normal multiorgan retrieval, if this has already started or ▪ Should be managed as a category III donor as appropriate to the circumstances of cardiac arrest.
V	○ Cardiac arrest in a hospitalized patient − Category II donor who originates in hospital − This distinction allows for improved tracking of the outcomes

- Infection evaluation

Recommendations

- Screen for bacterial, fungal, and viral infections before LT
  - The presence of an active infection contraindicates LT (Grade III)
- CMV donor/recipient status determines time of prophylaxis (Grade II-3)
- The donor-specific alloantibodies →
  - Acute and chronic antibodies-mediated rejection, and
  - Histological damages (Grade III)

- In selected patients may use donors who are/have
  - Older
  - HCV infection (Grade II-2)
  - Diabetes mellitus, if HCV negative (Grade II-3)
  - Micro-/mild-macrocytosis (Grade II-2)
  - Anti-HBc positive, preferentially directed to HBV-exposed liver transplant candidates
    - Recipients without anti-HBs must be given prophylaxis against HBV, giving lamivudine immediately post-LT (grade II-2)
  - Anti-HCV positive explant given to HCV negative recipient (Grade II-2)
  - Previous malignancy in selected situations, according to tumour site and its stage (Grade II-3)
  - Infections
    - Bacterial
    - Fungal
    - Viral/parasitic
    - Antibiotics given to donor before and to recipient after LT
    - Routinely use
    - "…used according to the type of infection and the severity of recipient's liver disease" (Grade II-3)

- Technical aspects
  - "piggy back" technique recommended (preserved inferior vena cava [IVC], for greater post-op hemodynamic stability (Grade II-3)
  - "Domino" LT for recipient > 55 yr, with familial amyloid polyneuropathy (FAPN) (Grade II-3)
  - "Auxiliary" LT
    - In acute liver failure
    - "functional, congenital or metabolic disorders affecting a normal liver" (possibility of removing grafted liver/stop immunosuppression in recipient if their own [native] liver returns to its normal function (Grade II-3)
  - "Split" LT
    - The left portion of the transplanted liver needs to go to a smaller person who would have had a smaller original liver (Grade II-2)
      - Recipient of the left lobe may have a worse outcome (Grade II-2)
  - Living donor
    - Recommended as long as the weight of the LD's liver portion is 0.8% of the weight of the recipient (Grade III)

- Specific complications post-LT
  - Blood vessels
    - Hepatic artery thrombosis (HAT)
    - May require retransplantation
    - Portal vein thrombosis (PVT) with extensive thrombosis
      - Use a non-anatomical portal revascularization technique, such as renoportal anastomosis (Grade II-3)
  - Biliary tree
    - Leak of biliary anastomosis post-LT →
      - ERCP plus sphincterotomy; if this fails, then
      - Temporary biliary stent (Grade II-3)
    - Ischemic cholangiopathy
      - Retransplantation (Grade II-3)
    - Stenosis of biliary anastomosis
      - ERCP with stenting, if this fails
      - Hepatics jejunostomy (Grade II-3)
    - Biliary duct anastomosis stenosis/heat after partial/split LT
      - ERCP stenosis dilation / stent insertion; if this fails (50%) then hepaticojejunostomy (Grade III)
  - Acute/chronic graft failure
    - Retransplantation (including for HCV recurrence) (Grade II-2, II-3)
    - Repeat the protocols for pre-transplantation (as was done for the first LT) (Grade III)

❖ **Immunosuppression regimens**

- Standard
  - Calcineurin (CNI) plus corticosteroids or azathioprine
    - Patient/graft survival using tacrolimus > cyclosporin (Grade I)
    - CNIs safe with induction agents and can ↓ dose of CNI in persons with renal impairment including pre-LT (Grade I)
    - No advantage of CNI plus MMF (Grade I)
  - Concern expressed for use of IL-2R antagonists
    - High cost, plus
    - Potential negative effect on tolerance (Grade III)

- Liver Donors
  - The complications of liver transplantation are more common if the donors are
    - Older
    - Have fatty liver, or severe HCV infection

    } ▪ ↑ graft loss ▪ ↑ mortality (Grade II-2)

Clinical Tip

- The use of donor livers from persons with diabetes mellitus is acceptable, but only if the donor is HCV-negative.

  - Donors with previous malignancy
    - "…can be used in selected situations according to tumour site and its stage (Grade II-3)
  - Infection
    - Bacterial
      - Treat donor before harvesting, and treat recipients post-LT
    - Viruses/parasites
      - "…use according to the type of infection and the severity of recipients liver disease"
    - Fungal infection in donor
      - Liver donation acceptable (Grade II-3)

- Renal impairment
  - Continuous
    - Monitoring of renal function
    - Treatment of renal dysfunction (Grade II-2)
  - May use
    - Low dose tacrolimus, corticosteroids, mycophenolate (MMF), and IL-2R (Grade 1)
    - CNI-free early viral response (EVR)
      - **Caution**: this may ↑ acute rejection (Grade I)

- Rejection
  - Do **not** use MMF (↑ risk of acute cellular rejection) (Grade I)
  - Conversion to sirolimus (SRL)
    - No ↑ risk of
      - Graft loss / rejection)
      - Infection (Grade I)

- HCV liver transplanted patient

Treatment Alert

- In HCV liver transplanted patients
  - Do **not** use
    - Alemtuzumab
    - OKT3

} Severe HCV recurrence

  - Corticosteroids
    - Unclear whether corticosteroid taper slowly/quickly gives better effect on graft evaluation (Grades I/III)
  - Immunosuppression
    - Unclear whether azathioprine or MMF are superior for maintenance
      - More fibrosis with MMF (Grade II-1)
  - Mammalian target of rapamycin (mTOR), IL-2R antagonists
    - Insufficient data to make recommendation (randomized controlled trials [RCTs] are needed) (Grade I and

- De novo malignancy
  - ↑ risk with use of
    - CNI (↓ calcineurins dose related), but not with MMF (Grade I and III)
      - Tacrolimus = CNI risk (Grade II-2)

- Intended immunosuppression withdrawal
  - Experimental only (Grade III)
  - Post-transplantation lymphoproliferation disease (PLTD)
    - High suspicion for development of PTLD if
      - Fever/night sweats
      - ↓ body weight
      - Lymphadenopathy (Grade III)

❖ **Post-LT Complications**

- HCV Infection

Recommendations

- Assess for possible recurrence (liver enzymes) / function tests, liver biopsy, measurement of HVPG, transient elastography (TG) (Grade II-2)

- Treat HCV recurrence
  - Genotype 1 to 4 +/- cirrhosis
    - Sofosbuvir/ledipasvir plus ribavirin, or sofosbuvir plus simeprevir +/- ribavirin
  - Fibrosis cholestatic hepatitis (Grade II-1)
  - Naïve patients with mild HDV recurrence
    - ABT 450/r, ombitasvir, dasabuvir, and ribavirin, but
    - Drug-drug interaction with CINs
    - Adjust dose of cyclosporine/tacrolimus (Grade II-1)

- HBV infected recipient
  - Treatment
    - Entecavir/tenofovir
      - Controls recurrence (begin immediately), but
      - May not prove HBV raft infection (Grade II-2, I-3)
  - Prophylaxis
    - HBIG, followed by nucleotide addition cycles (NACs)
      - Especially effective if represent HBV DNA not detectable at time of LT.
  - Anti-HBc-positive donors to anti-HBs-negative recipient
    - Lamivudine (Grade II-2)
    - HBIG only if HBsAg negative (Grade II-2)

- Alcohol-related Liver Disease (ArLD)
  - Encourage total abstinence
    - If patient relapses, patient should be seen / followed by
      - Psychiatric counselling
      - LT specialty (Class II-2/3)

- Non-alcoholic Liver Disease (NAFLD)
  - Confirm de novo / recurrent NAFLD
    - Liver biopsy may be necessary (Grade III)
  - Dietary management to achieve normal body weight
  - Treatment of hypertension, hypoglycemia, (Grade III)
  - Cholestatic liver disease
    - AIH
    - PSC
    - PBC

    } Confirm recurrence with
      - Liver biopsy
      - Cholangiography
    - No benefit for post-LT ursodeoxycholic acid (UDCA)

- Hepatocellular cancer (HCC)
  - HCC recurrence
    - Sirolimus (SRL) benefit of HCC within Milan criteria is of benefit in 3 to 5 yr, but not for longer (Grade I)
    - No benefit of “disseminated” recurrence using sorafenib (Grade III)

- Renal dysfunction
  - Use CNI-free immunosuppression (Grade I)
  - May need to perform kidney transplantation

❖ **Prevention and treatment**

- Infections: prophylactic treatment
  - Aspergillus prophylaxis
    - Only in high risk conditions (Grade II-3)
  - Candida, for ~3 mon
  - CMV prophylaxis in first mons (↓ mortality) (Grade II-2)
  - P. jirovecii for 6 to 12 mon in all LT patients
    - Trimethoprim-sulfamethoxazole, plus corticosteroids (adjunctive, to ↓ risk of pulmonary inflammatory / fibrosis)
  - Tuberculosis (TB) monitor for
    - Acute rejection
    - Hepatotoxicity

- Metabolic Syndrome
  - “Healthy diet” and exercise program
  - Monitor and treat
    - Hypertension, hyperglycemia, dyslipidemia, obesity (Grade II-3 / III)
    - Cardiovascular disease
      - Treat modifiable risk factors
      - Optimization of immunosuppression

- Metabolic bone disease (MBD)
  - Pre-LT normal bone mineral density (BMD)
    - DEXA scan q2-3 yr
    - Pre-CT
      - DEXA scan q1yr (Grade II-3)
  - When osteoporosis present
    - Regular weight-bearing exercise
    - Supplementation
      - Calcium / vitamin D
      - Consider use of bisphosphonates (Grade II 2/3)

- De novo malignancies
  - Age-appropriate screening, as per guidelines (Grade II-2)
  - Persons with alcohol-related liver disease (ArLD)
    - More intense surveillance for malignancy
      - Oropharyngeal-laryngeal
      - Lung
      - Upper GI tract (Grade II-3)
  - Persons with LT for PSC who also have
    - Ulcerative/Crohn colitis (PSC-IBD)
    - Annual colonoscopy with multiple biopsies (Grade II-3)

❖ **Long term follow-up**

- Purpose
  - Achieve greatest possible quality of liver (QoL) for the patient (Grade II-2)
- Adherence
  - Improvement/maintenance
    - Multidisciplinary measures (Grade III)
    - Anticipate/address issues of
      - Adverse effects
      - Importance of correct immunosuppression (Grade II-2)
- The job
  - Assistance with obtaining / maintaining employment (apical attention for persons with LT for ArLD)
- Exercise and nutritional program

- Sexual activity / pregnancy
  - Female
    - Avoid pregnancy for 12 to 24 mon post-LT
      - Counseling re use of contraception (Grade III)
      - Safe immunosuppression in pregnancy considered to be corticosteroids, CNIs (Grade II-3)
      - Mycophenolate mofetil (MMF) and azathioprine (AZA) usually not recommended (Grade II-3)
  - Male
    - ↓ spermatogenesis with
      - mTOR inhibitors (Grade II-2)

- Prognostic scoring systems / instruments

	Bilirubin	PT/INR	Creatinine/urea	Leucocytes	Age	Albumin	Change in bilirubin from day 0 to day 7
– Maddrey score	+	+	-	-	-	-	-
– MELD score	+	+	+	-	-	-	-
– GAHS score	+	+	+	+	+	-	-
– ABIC score	+	+	+	-	+	+	+
– Lile score	+	+	+	-	+	+	+

Abbreviations: MDF, Maddrey score / Maddrey discriminant function; GAHS, Glasgow Alcoholic Hepatitis Score; ABIC score, age, serum Bilirubin, INR, and serum Creatinine (ABIC) score; MELD
score, Model-for-End-Stage-Liver-Disease score

- Canadian Guidelines for Drinking Alcohol
  - ≤ 2 per day, ≤ 2 per wk (both males and females

Acute Liver Failure/Liver Transplantation: AASLD Position Paper (2011)

Lee WM, et al. Hepatology 2012;55(3):965-7

- Definition
  - A condition in which rapid deterioration of liver function results in altered mentation (hepatic encephalopathy)
  - Coagulopathy (↑ INR) in patients without pre-existing liver disease

- Diagnostic criteria (AASLD guidelines)
  - INR > 1.5
  - Any degree of Hepatic encephalopathy (HE)
  - No previous diagnosis of liver cirrhosis
  - Illness of < 26 wk duration
  - Still accepted as ALF
    - Vertically acquired HBV
    - AIH with disease of < 26 wk duration and
    - Wilson disease
    - Evidence of cirrhosis

- Causes
  - Inherited
    - Wilson disease
  - Idiopathic
    - 15% has unclear cause
  - Infection
    - Viral hepatitis
      - HBV flare, including use of immunosuppressants
  - Immune
    - Autoimmune hepatitis
  - Infiltration
    - Acute fatty liver of pregnancy and HELLP syndrome
  - Ischemia
    - Ischemic hepatitis
    - Budd-Chiari syndrome
  - Iatrogenic
    - Drug induced (Acetaminophen)
    - Mushroom poisoning (Amanita Phalloides)

- Clinical
  - Asymptomatic
    - Early onset of ALF
    - Later
      - Malaise, nausea, pruritus, jaundice, abdominal pain, bleeding and confusion.
- Laboratory
  - Complete blood count (CBC), Renal, liver panel, INR, lactate, arterial blood gas, plasma ammonia
  - Beta-HCG
  - Ethanol concentration
  - Toxicology screen, especially acetaminophen
  - Viral serology (B/D, C, herpes)
  - Autoimmune Ab
  - Ceruloplasmin level
- Diagnostic imaging
  - Ultrasound with Doppler
  - CT head
    - Cerebral edema
- Evaluation
  - Evaluate every patient with acute hepatitis assessed for
    - HE
    - INR
    - Acetaminophen level
- General management
  - Admit to ICU is preferred
    - Elective intubation if there is advanced HE
  - Contact Transplant center for early transfer
  - Search for underlying etiology
    - Focus on treatable causes of ALF
    - Consider transjugular liver biopsy
    - Consider possible drug-induced liver injury
    - Identify treatable causes
      - AIH
      - HBV, HDV, HSV
      - Wilson disease (WD)
      - Hepatic malignancy (hepatocellular cancer [HCC])

- Treat complications
  - Cerebral edema
    - Consider placement of intracranial pressure (ICP) monitoring device (controversial: not associated with improved survival, and ↑ risk of intracranial hemorrhage [ICH]).
    - If ICP> 25 mm Hg
      - Quiet room
      - Elevate the head of the bed
      - Hyperventilation to pCO_2 25-30 mm Hg
      - Mannitol IV 0.5-1 gm/kg once/twice (as long as osmolality < 320 mOsm/L)
      - Hypertonic saline → target Na^+ (145-155)
      - Consider
        - EEG monitoring
        - Hypothermia
        - Barbiturate coma
      - The goal of treatment will be ICP<25 and cerebral perfusion pressure of > 60 mm Hg
  - Thrombocytopenia and coagulopathy
    - Treatment **not** recommended, except for:
      - Bleeding
      - Prior to invasive procedures
      - In pregnant patients to avoid placental bleeding.
    - Coagulopathy
      - Recombinant factor 7
      - Vitamin K 5-10 mg at least once
  - Acetaminophen / non-acetaminophen
    - N-acetyl cysteine (NAC) →
      - ↓ grade of coma
      - ↑ transplant free survival versus
      - placebo for non-acetaminophen ALF has shown improvement for early coma grade patient in transplant-free survival
  - Early signs of progression to severe HE
    - SIRS
    - Refractory hypotension
  - Refractory hypotension
    - Norepinephrine (target MAP > 75 mm Hg / CCP 60-80)
  - Hypoglycemia
    - Correct with continuous glucose infusion, if needed.
  - Electrolytes (potassium/magnesium/phosphate tend to be low)
    - Monitor and correct on a daily basis.
  - Nutrition is also important.
    - Early use of enteral feedings

- Evaluate for possible liver transplantation
- Continuous renal replacement therapy

- King's college criteria (KCC) for liver transplantation
  - Acetaminophen induced
    - Arterial lactate > 3 mmol/L after fluid resuscitation, or
    - pH < 7.3, or
    - INR >6.5
    - Grade 3 or 4 HE
    - Creatinine > 300
  - Non-Acetaminophen induced)
    - INR >6.5 and any grade of HE, or
    - ≥ 3 the following;
      - Age <10 or >40 yr
      - Jaundice > 7 d before HE
      - INR > 3.5
      - Serum bilirubin > 300 mmol/L
      - Wilson disease or idiosyncratic drug reaction

- Management according to Etiology
  - Acetaminophen toxicity
    - 10 g/d usually causes ALF and
    - 3-4 g/d sometimes causes severe acute hepatitis
    - Activated Charcoal
      - Most effective if given within 1 h of ingestion (can still be used within 3-4 h of ingestion: dose 1 g/kg orally)
    - NAC infusion give as early as possible
      - Should be given even if within 48 hours or more after ingestion
      - Dose: loading 150 mg/kg in 5% dextrose over 15 min
      - Maintenance: 50 mg /kg over 4 h followed by 100 mg/kg over 16 h
      - Stop: either after 72 h or after normalization of liver chemistry
  - Mushroom poisoning:
    - Penicillin G 1 million unit/kg/d, plus silibinin (silymarin or milk thistle) are the accepted antidotes.
  - HBV:
    - Lamivudine used widely in the treatment of chronic hepatitis B, may be considered in patients with acute hepatitis B, although evidence of efficacy is equivocal.
  - Herpes virus infection (immunosuppressed/pregnant patients)
    - Acyclovir (5-10 mg/kg every 8 h for ≥ 7 d)
  - AIH
    - Methylprednisolone, 60 mg IV per day

- Wilson disease:
  - Do **not** use penicillamine (risk of hypersensitivity)
  - Bridge to liver transplantation
    - Albumin dialysis
    - Continuous hemofiltration
    - Plasma-pheresis
    - Plasma exchange
- Acute fatty liver of pregnancy or HELLP
  - Delivery of body

➢ Poor prognosis

- Autoimmune hepatitis (AIH)
- Acute Primary biliary cholangitis (PBC)
- Wilson disease (WD)
- Idiopathic drug reaction
- Mushroom poisoning

• Liver transplantation

- Benefits
  - ↑ survival with end stage liver disease (ESD)
  - Patient survival
    - 1 yr, 90%
    - 5 yr, 80%

➢ Indications

- Decompensated liver cirrhosis (MELD >15)
- HCC (according to Milan criteria)
  - Up to 3 tumours each less than or equal to 3 cm
  - Single mass < 5 cm
  - No extra-hepatic or vascular disease
- PSC/PBC with intractable pruritus or recurrent bacterial cholangitis
- Hepatopulmonary syndrome
- Portopulmonary HTN < 50 mm Hg
- Budd-Chiari syndrome
- Primary hyperoxaluria
- Familial Amyloid Polyneuropathy syndrome
- Biliary Atresia: most common cause in children

- Contraindications
  - Extra-hepatic malignancy
  - Uncontrolled infection
  - Severe portopulmonary hypertension if mean pulmonary pressure > 50 mm Hg, despite treatment
  - Severe non-revascularized coronary artery disease (CAD)
  - Active alcoholism/substance abuse

  * Note:
    - HIV with a negative viral load and CD4> 200 u/L is **not** a contraindication for transplant

- (Graft) Complications

- Primary non-function
  - Rare (1-2%) of transplants
  - Features
    - No bile production
    - Coagulopathy
    - HE
    - Renal failure
  - Treatment
    - Urgent retransplantation

- Surgical complications
  - Post-op hemorrhage in 20%
    - 50% will need reoperation
  - Hepatic artery thrombosis:
    - In 2-12% of the cases
    - If detected
      - Early: urgent surgical repair
      - Late (signs of biliary necrosis and infection), urgent liver transplantation
  - Hepatic venous outflow obstruction:
    - Stenosis of anastomosis at the inferior vena cava (IVC)
    - Ascites in 1-2%
    - Treatment with transvenous dilatation -/+ stenting
  - Biliary leak and strictures
    - Leak usually in first month and stricture later
    - Treatment
      - ERCP / transhepatic cholangiography with stenting or surgical treatment, or
      - Just with antibiotics

- Cardiovascular complications
  - The leading cause of early (<1 year) morbidity and mortality post liver transplantation.
  - Secondary to
    - Fatal arrhythmia
    - Heart failure
- Infections
  - Related to
    - Immunosuppressive therapy
    - Surgical complications, and
    - Length of stay in ICU.
  - Bacterial is most common in the first month from
    - Biliary tree
    - Abdominal cavity
    - Surgical wound
    - Urinary tract, and
    - Lungs
  - CMV/EBV are common after the first month of transplantation.
- Acute rejection
  - 20-30 % of transplant patient cases
  - Usually 1-4 wk post-LT.
  - Rarely causes morbidity/mortality
    - Unless patient is not taking their immunosuppressive therapy
- Chronic Rejection
  - Chronic ductopenic rejection occurs in 5-10%
  - Usually 6 wk to 6 mon after LT
  - Lower incidence if patient maintained on triple therapy (prednisone / Imuran / tacrolimus)

➢ Immunosuppressive agent (pharmacological classes)

- Prednisone
- Calcineurin inhibitors
  - Cyclosporin
  - Tacrolimus (FK506)
- Anti-proliferative agents
  - Mycophenolate mofetil

- Mammalian targets of rapamycin inhibitors (mTOR)
  - Sirolimus, everolimus
- Monoclonal antibodies (anti-CD)
  - Basiliximab

➢ Complications

- Chronic renal failure
- Chronic and failure (CRF)
  - Cyclosporine/Tacrolimus
- CVS
  - Hypertension
- Endocrine
  - Diabetes mellitus
  - ↑ hyperlipidemia
- MSK
  - Osteopenia
- Skin non-melanomatous cancer

➢ Practical consideration Hepatology call

- Home call for Hepatology inpatients and consult service
  - 4-7 calls per block and 1 weekend and have Hepatology staff for review available
- Admission Criteria:
  - Cirrhotic patients listed for liver transplant
  - For transplant assessment/optimization
  - TIPS or TACE (transarterial chemoembolization)
- Practical “on-call” tips
  - Before starting call, ensure you get handover from the inpatient team so that you know about the sick patients and
  - Can plan your night accordingly
- Call admitting at start of call regarding
  - Planned elective transfers / community transfers, and their estimated time of arrival
- Obtain consent from **EVERY** patient you admit (day or night) for
  - Blood transfusion/products
    - Even if the indication on admission is not bleeding or procedural (you never know what can happen)

- For TIPS admissions
  - Do therapeutic paracentesis
  - Ensure the patient has an updated CT (within 2 mon), and
  - Correct INR <1.5 and plt > 50
- For TACE admission
  - Ensure there is an updated CT (within 2 mon) or
  - Per tumour board note.
  - Order alpha fetoprotein (AFP)
  - Correct INR <1.5 and plt > 50.

- Determination of Future Liver Remnant (FLR) Size
  - CT/MRI contrast-enhanced
    - The FLR size may be enhanced, if necessary
      - Pre-resection portal vein embolization (increases size of the collateral lobe)
      - Transarterial radioembolization (TARE) with yttrium-90
      - Liver partition and portal vein ligation

➢ Recurrence of HCC after resection and surveillance

- 5-yr recurrence rate after resection of HCC, 50% - 70%
  - The risk of recurrence is highest in post-operative yr
- Risk factors for HCC recurrence
  - Patient
    - Older man
  - Tumour
    - Size, number
    - Grade/differentiation
    - Macrovascular invasion
    - Satellite lesions
- Laboratory
  - ↑ AFP
- Surveillance for HCC recurrence
  - CT/MRI, contrast enhancement, q3-6 mon, indefinitely

- Adjuvant Therapy to ↓ Recurrence after Resection (Post-Surgical)
  - HCC
    - ↑ survival with direct-acting antiviral (DAAs)
  - TACE
    - Do **not** use preoperative neoadjuvant (↑ risk of progression of HCC)
  - Adjuvant sorafenib
    - No improvement in recurrence-free survival

- Atezolizumab plus bevacizumab
  - Use if high risk of recurrence after resection
    - Tumour > 5 cm, ≥ 3 tumours
    - Vessels, macro-/microinvasion
  - Start adjacent therapy within 12 wk of resection (or recurrence after local ablation)
    - Continue atezolizumab / bevacizumab for 12 mon
    - Treatment related severe (grade 3-4) adverse events, 35%
- Recurrence after resection plus atezolizumab plus bevacizumab (A+B)
  - Repeat A+B
  - Downstage, then liver transplant
  - Systemic therapy, if
    - Vascular invasion
    - Extrahepatic spread
    - Patient not suitable for TACE
- Neoadjuvant: cabozantinib plus nivolumab
  - Clinical trial data
    - Margin-negative resection, 80%
    - Major pathological response, 42%
  - Nivolumab +/- ipilimumab, major pathological response, 30%

Recommendations

- Surgical resection
  - The treatment of choice for localized HCC in the absence of underlying cirrhosis (Level 2, Strong recommendation)
  - Consider in patients with well-compensated cirrhosis but
    - Limited tumour burden
    - No clinically significant portal hypertension (CSPH)
    - Adequate future liver remnant size
- Perform minimally invasive surgery (MIS) may be performed in selected patients in order to
  - ↑ recovery
  - ↓ morbidity post-operatively

  (Level 3, Weak recommendation)
- Following resection of HCC, perform contrast-enhanced multiphasic CT/MRI q3-6 mon (Level 3, Strong recommendation), for an indefinite surveillance (Level 5, Weak recommendation)
- Post-resection adjuvant therapy
  - Treatment to be chosen upon pattern of HCC recurrence (Level 4, Weak recommendation)
  - Do **not** use adjuvant immune checkpoint inhibitor-based systemic therapy for post-resection recurrent HCC (Level 2, Strong recommendation)
  - Neoadjuvant therapy
    - Only use as part of a clinical trial (Level 2, Weak recommendation)

❖ Liver transplantation (LT)

➢ Indication
- Early-stage HCC in patients who is not eligible for surgical hepatic resection because of
  - Tumour
    - Multifocality
    - Malfunction

    } Aims both HCC and underlying liver disease
  - Patient must meet certain criteria (please see below)

➢ Outcomes
- LT
- Median survival, 10 yr
- Risk of recurrence of HCC, 10% (resection, HCC recurrence is 50% -60%)

- Selection Criteria (based in sickest patient has greatest ranking on the LT list: patient on LT waitlist with decompensated cirrhosis and highest risk of death)
  - Milan
    - One lesion, between 1-5 cm, or
    - 2-3 lesions, between 1-3 cm
  - UCSF
    - ↑ size acceptance, total tumour volume ≤ 115 cm
      - 4 yr survival, 81%
    - Up to 7 criteria
      - 5 yr survival, 71%
  - Extended Toronto
    - 5 yr survival, 68%
  - Kyoto
    - 5 yr survival, 68%
  - MELD, MELD-Na, MELD with exception points

- Eligibility for MELD Exception Points
  - Milan criteria (“downstaging” to with in Milan criteria

- Downstaging
  - Definition
    - “Tumour downstaging is a reduction in the size of viable tumour using locoregional therapy (LRT) to meet acceptable LT criteria”
    - Downstaging → ↑ survival (5 yr survival, 77%)

- Criteria for downstaging (United Network of Organ Sharing [UNOS] downstaging [UNOS-DS])
  - One lesion, between 5.1-8 cm
  - 2-3 lesions < 5 cm
  - 4-5 lesions < 3 cm

    } ▪ Total tumour diameter < 8 cm

    plus
  - If baseline AFP > 1000 ng/mL, must fall to < 500 ng/mL for downstaging
- Patient who are otherwise transplant eligible except with initial tumour burden exceeding the Milan criteria, particularly those within UNOS downstaging (UNOS-DS) criteria
  - Wait 3 mon to award MELD exception points
    - Then considered for LT following successful downstaging to within Milan Criteria after successful downstaging to Milan
- Consider downstaging only in patients with CTP class A/B bilirubin < 3 mg/dL
- Patients receive an exception score of 3 points lower than the median MELD (score) at transplant (MMaT-3) for the area of distribution" (a concentric circle around the donor hospital)
- Arterial phase hypoenhancing lesions, Organ Procurement and Transplant Network (OPTN) class 5 (consistent with HCC); presence of
  - Venous, or
  - Delayed phase washout, or
  - Peripheral rim enhancement on delayed phase
  - Arterial phase enhancing lesions, between 1-2 cm plus both washout and peripheral rim enhancement or threshold growth
- In the future. "…patients will be required to have UNOS T2 NC…to be eligible for MELD exception points"

➢ Salvage Liver Transplantation

- Definition
  - "…s strategy with HCC who have undergone resection and develop either
    - Liver decompensation, or
    - Tumour recurrence

    } − Within acceptable LT criteria
- Outcomes of salvage LT strategy
  - 5-yr overall survival, 69%
  - Cured by resection or undergoing successful LT for HCC, 55%
- Prediction of non-transplantable HCC recurrence after resection
  - Microvascular invasion
  - Satellite lesions

➢ Living Donor Liver Transplantation (LDLT)

- May be used for patients with HCC who are "…beyond typical LT criteria"
  - Post-LT survival recurrence rates after LDLT for HCC, when considered on an (intention-to-treat) basis, show "excellent" results

- Bridging Therapy
  - There is common interval before awarding exception points, and locoregional therapy (LRT), ablation and external radiation therapy (EBRT) as a "bridge" to
    - Possible future growth of HCC, and
    - ↓ dropout
    - From LT waitlist
    - No particular LRT is better
  - The use of checkpoint inhibitors (ICIs) may be safe to use in some patients before LT, but generally speaking, it is best to stop ICIs ≥ 3 mon before LT, ↓ risk of rejection / loss of graft
  - T1 HCC treatment (unresectable, HCC tumour < 2 cm)
    - Cross-sectional CT/MRI q3mon
    - When tumour become T2, then perform local regional therapy (LRT), immediately or when T2 needed

- Biomarkers in LT
  - Alpha-fetoprotein (AFP) is a biomarker of HCC tumour biology (high-risk explant pathology) post-LT outcome is best predicted with both tumours burden (size, number) but also by AFP
    - An example of action taken by level of AFP: MELD exception points for LT for HCC cannot be given until an initial AFP > 1000 ng/mL falls to < 500 ng/mL as the result of LRT
    - Alternate to AFP under study to identify high-risk explant pathology
      - AFP-14
      - Deoxy carboxyprothrombin (DCP)
      - Neutrophil to lymphocyte ratio (NLR)

- Post-LT Recurrence / Surveillance
  - Post-LT HCC recurrence in patient liver meeting the Milan criteria, 10%-15% (most common cause of death)
    - ~20% of these post-LT recurrence are treatable wit resection, and they cannot generally be treated with ICIs
    - Median survival if HCC recurs, ~ 1yr
  - Estimate post-LT recurrence of LT using the Risk Estimation of Tumour Recurrence After Transplant (RETREAT) stratification score, based upon
    - Tumour
      - Diameter of largest tumour
      - Number of viable tumour on explant
      - Vascular invasion
      - Biology
        - AFP concentration

    - Sum the number

- 5-yr recurrence rate
  - Low risk (retreat 0), < 3%
    - No viable tumour, on explant
    - No microvascular invasion
    - AFP < 20 ng/mL
  - High risk, RETREAT > 5, up to 7.5%

- Recurrence stratification score
  - Other
    - Post-MORAL
    - UCLA prognostic nomogram

➢ Surveillance

- Post-LT recurrence
  - Lung metastasis, 40%, liver recurrence, 33%
  - Contrast-enhanced CT/MRI of chest, abdomen
  - Suggestion to alternate between testing is not yet defined
  - Suggestion to alternate between surveillance scan
    - ↑ benefit
    - ↑ survival
    - ↑ chance of cure

- Pharmacotherapy (to ↑ recurrence-free survival)
  - Immunosuppression
    - Use mTOR inhibitors for post-LT immunosuppression
    - Do **not** use calcineurin inhibitors (↑ HCC recurrence)
    - Sirolimus does not ↑ recurrence-free beyond 5 yr

Recommendations

- Early stage HCC
  - Decompensated cirrhosis +/- clinically significant portal hypertension (CSPH) treated with LT (if LT-eligible) (Level 2, Strong recommendation)

- Recurrent HCC within Milan criteria after resection → LT (Level 3, Strong recommendation)

- Patients being evaluated for/on the LT list and adequate hepatic reserve
  - Use locoregional therapy (LRT) (↓ waitlist dropout) (Level 3, Strong recommendation)
  - Any approved LRT is acceptable, using the criteria of
    - Tumour size / location
    - Expertise of the LT care

    (Level 3, Weak recommendation)

- Decompensated cirrhosis with T1 HCO, monitor with cross-sectional CT/MRI ≥ 3 mon until patient develops criteria for MELD exception points for LRT (Level 3, Weak recommendation), but
  - If patient is not eligible for LT or if ↑ AFP may do immediate LRT (Level 3, Strong recommendation)
- Do **not** use systemic therapy for bridging therapy, but
  - If systemic therapy has already been given, the patient may still have a LT (Level 5, Weak recommendation)
- In the patient with HCO > Milan criteria but is otherwise eligible for LT, and who meets the UNOS downstaging criteria, and downstaging is successful on the HCO now reaches Milan criteria, consider LT (Level 2, Strong recommendation)
- If the AFP is > 1000 mg/mL, successful downstaging includes being within Milan criteria plus AFP < 500 ng/mL (Level 2, Strong recommendation)
- Post -LT for HCC, perform abdominal control-enhanced CT-MRI plus CT of chest to detect early recurrence of HCC (Level 2, Strong recommendation)

❖ Local Ablative Therapy (LAT)

➢ Indications

- Very-early-stage HCC
- Centrally located tumours which require major hepatectomy
- Solitary HCC but
  - Patient
    - Not eligible for resection / LT
    - Decline surgery
- Consider radiation segmentectomy / EBRT id
  - HCC > 3 cm
  - HCC close to
    - Heart
    - Diaphragm large vessels
    - Central bile ducts

- Thermal Ablation
  - Options
    - Cryoablation
    - Microwaves
      - May cause ↓ sink effects near large blood vessels
    - Radiofrequency

- Outcomes
  - Overall survival (OS), 76^
  - Recurrence-free survival, 46%

  } Unifocal HCC < 3 cm, at 3 yr

  - > 3 cm
    - Lower OS, lower objective response rate
    - ↑ recurrence

    } Compared to > 3 cm

    (consider ablation plus TACE)
- Adverse effects
  - Pain/fever
  - Bleeding/abscess
  - Pleural effusion
- Surveillance
  - Contrast enhanced abdominal ultrasound after ablation (to detect any remaining HCC)
- Post-resection / LAT
  - ↑ risk of HCC recurrence 2-5 cm
    - Multifocal HCC
  - Use adjuvant therapy in this highest setting, using atezolizumab plus bevacizumab

- Radiation Segmentectomy / Selective TARE

➢ Definition

- Administration of Y90 microspheres into
  - 1 segment of liver, or
  - 2 adjacent segments
- Subcapsular tumours
  - In sites which are different to reach by ablation
    - Subdiaphragmatic
    - Peri-cardiac
  - Microsatellites
- Benefits
  - Time to progression (TTP)
  - Bridge to LT

- External Beam Radiation Treatment (EBRT)
  - If thermal ablation is not possible, give multiple (4-5) session of EBRT
    - Proton beam therapy (RBT), or
    - Stereotactic body radiation therapy (SBRT)

- Use EBRT when not possible to do with thermal ablation (radiofrequency or microwave)
  - Central tumour
  - Tumour adjacent to blood vessels
  - Bridge of LT

  ▪ No age or limit of tumour size
- Contraindications
  - Risk of change to liver, stomach, small bowel
  - Uncontrolled ascites / HE
  - CTP score ≥ 8
- Outcome
  - Add sorafenib to SBRT to improve survival, 16 mon vs. 12 mon (P=0.55)
  - 2 yr progression free survival
    - PBT, 93%
    - Radiofrequency, 83%
  - ↑ CTP score from therapy
    - PBT, 8%
    - Radiofrequency, 20%

Recommendations

- In patients with solitary HCC < 5 cm
- Inpatients with early-stage HCC < 3 cm

– Who are not eligible / refuse surgery

▪ Use local ablation therapy with intention to care (Level 1, Strong Recommendation)

▪ Use radiotherapy or microwave (thermal) ablation

(Level 1, Strong Recommendation)

- In patients with BCLC Stage A HCC > 3 cm and not eligible for resection
  - Use BBRT or radiation segmentectomy as alternatives to thermal ablation

(Level 3, Strong recommendation)

❖ Transarterial Therapies

• Transarterial Chemoembolization (TACE)

➢ Indication

- TACE is the primary treatment option for patients with BCLC Stage B HCC

➢ Pharmacology

- The arterial blood supply of HCC is greater than that of the portal vein, so the chemoembolization goes more to the tumour than to the non-tumour liver, targeting drug delivery.
- The drug can be in Lipiodal® solution (concentrated), or in drug-eluting beads (DEB-TACE)
  - The outcomes with both forms of TACE is equivalent
    - Use selective catheterization of segmental / distal branches, with c-arm CT

- Outcomes
  - Objective response rate (ORR), 53%
  - Median survival, 19 mon
- Adverse events
  - ↑ liver enzymes (LE) / fever, ~18%
  - Bone marrow toxicity, 14%
  - Pain, 11%
  - Vomiting, 6%
  - Mortality rate, 0.6%
- Risk Factors for Poor Response to TACE
  - Hepatic dysfunction
  - Large intrahepatic tumour burden
  - Portal vein tumour thrombosis (PVTT)

  } − No established scoring systems

  - TACE has poor prognosis because of above risk factors, consider treatment with systemic therapy
    - Intra-arterial immunotherapy not yet established
    - Segmentectomy

- Transarterial Radioembolization (TARE); Y90 Glass Microspheres, Radiation

- Indication
  - Intermediate-stage HCC
    - ≤ 8 cm, single, CTP-A cirrhosis
- Outcomes
  - Objective response rate, 88%
  - Duration of response (DoR) ≥ 6 mon, 76%
  - DEB-TACE, BOL-C A/B
    - Time to progression (TTP), 17.1 vs. 9.5 mon
    - Hazard ratio (HR), 0.36
    - Overall survival (OS), 30 vs. 16 mon
    - Personalized dosimetry, gives superior outcomes compared with standard dosimetry
      - Objective response, 77% vs. 22%
      - Downstaging to surgical treatments, 35% vs. 4%
      - Median survival, 27 vs. 11 mon

- Downstaging to Milan Criteria with Embolic Therapies

➢ Indications

- Intermediate HCC, LT eligible, goal to render patient suitable for LT (to Milan criteria)

➢ Diagnostic imaging (DI) and measurement of response to TACE/TARE

- TACE DI following
- Multiphase (MP) T / Contrast-enhanced MRI (CE MRI)
  - 6 wk post-TACE
  - Duration
    - Viable disease, as needed
    - Non-viable disease, q3-6 mon
- TARE / EBRT (external beam radiotherapy)
  - 12 wk post TARE/EBRT
  - Response to TACE for ≥ 6 mon, then local progression → require additional locoregional therapy
  - No response to TACE/TARE or progression after 1-2 TACE/TARE treatments → consider TACE/TARE refractory → systemic therapy
- Criteria for evaluation of DI response
  - Early/intermediate stage HCC
    - Locoregional therapy
    - Modified Response Evaluation Criteria in Solid Tumours (mRECIST)
  - Advanced stage HCC, systemic therapy
    - mRECIST or RECIST v1.1

Recommendations

- Treat patients with BCLC Stage ACC with transarterial chemoembolization (TACE) (Level 1, Strong recommendation)
  - An acceptable alternate is radioembolization (Level 3, Strong recommendation)
- Use selective / segmental TACE / TARE rather than lobar treatment to ↓ risk of hepatic dysfunction (Level 5, Strong recommendation)
- In routine treatment of BCLC Stage B HCC, do **not** add systemic therapy with TACE/TARE (Level 2, Strong recommendation)
- Use systemic therapy for intermediate HCC patients who cannot have, or are refractory to locoregional therapies because of
  - Contraindications
  - Worsening hepatic dysfunction
  - Progression of HCC
  - Lack of objective response

  (Level 3, Strong recommendation)

❖ Systemic Therapy

➢ Indications

- Patients with unresectable HCC, not suitable for locoregional therapy because of
  - BCLC Stage B
  - HCC progression despite locoregional therapy (failed LR therapy)

➢ Types

- Anti-angiogenic
  - Multikinase inhibitors (mTKIs)
    - Cabozantinib
    - Lenvatinib
    - Regorafenib
    - Sorafenib
  - Monoclonal anti-angiogenic antibodies (bevacizumab, ramucirumab)

- Mechanism of Action

- Anti-angiogenic, mTKI which targets the vascular endothelial growth factor (VEGF) receptor intracellular kinase pathway / other kinases

- Immune checkpoint inhibitors (ICIs)
  - Inhibitors of programmed death (PDI)
    - Nivolumab
    - Pembrolizumab
  - PD-L1
    - Atezolizumab
    - Durvalumab
  - CTLA4 (cytotoxic T lymphocyte-associated protein)
    - Ipilimumab
    - Tremelimumab

➢ Adverse Effects

- mTKIs
  - Fatigue / weight loss
  - Skin
    - Hand foot skin reaction
  - GI
    - Diarrhea

- MTRs / anti-angiogenic antibodies (AAA)
  - CVS
    - Hypertension
  - Blood
    - Thromboembolism
  - GI
    - Perforation
    - ↑ risk of graft (LT) loss / mortality
  - GU
    - Proteinuria

Do Nots

- Do **not** combine 2 ICIs
  - Use in patients with mild/moderate autoimmune disease
  - Use in post-LT (any transplant) patients

- First-Second-Beyond Second Line Therapies

➢ First-line

- Sorafenib
  - Anti-angiogenic, mTKI which targets the vascular endothelial growth factor (VEGF) receptor intracellular kinase pathway / other kinases
  - Absolute survival benefits vs. placebo
    - 11 vs. 8 mon

- Lenvatinib
  - Overall survival equivalent to sorafenib
  - Superior to sorafenib
    - Objective response rate (ORR)
    - Progression-free survival (PFS)
    - Quality of life (QoL)
    - Time to progression (TTP)

- Nivolumab (PDI [programmed death inhibitor])
  - Adverse effects (vs. Sorafenib)

Less	More
▪ Alopecia	▪ Dysphonia
▪ Hand-foot skin reaction	▪ Hypothyroidism
▪ Diarrhea	▪ Hypertension
	▪ Proteinuria

  - No ↑ overall survival vs. sorafenib better tolerability

- Programmed Death Inhibitor ligand, immunotherapy, atezolizumab, plus monoclonal antiangiogenic antibody, bevacizumab
  - First-line therapy for advanced HCC
    - Overall survival, 19 mon
    - Superior to sorafenib
    - ↑ ORR, time to deterioration, PFS
    - Also ↑ risk of GI bleeding

MCQ Gem

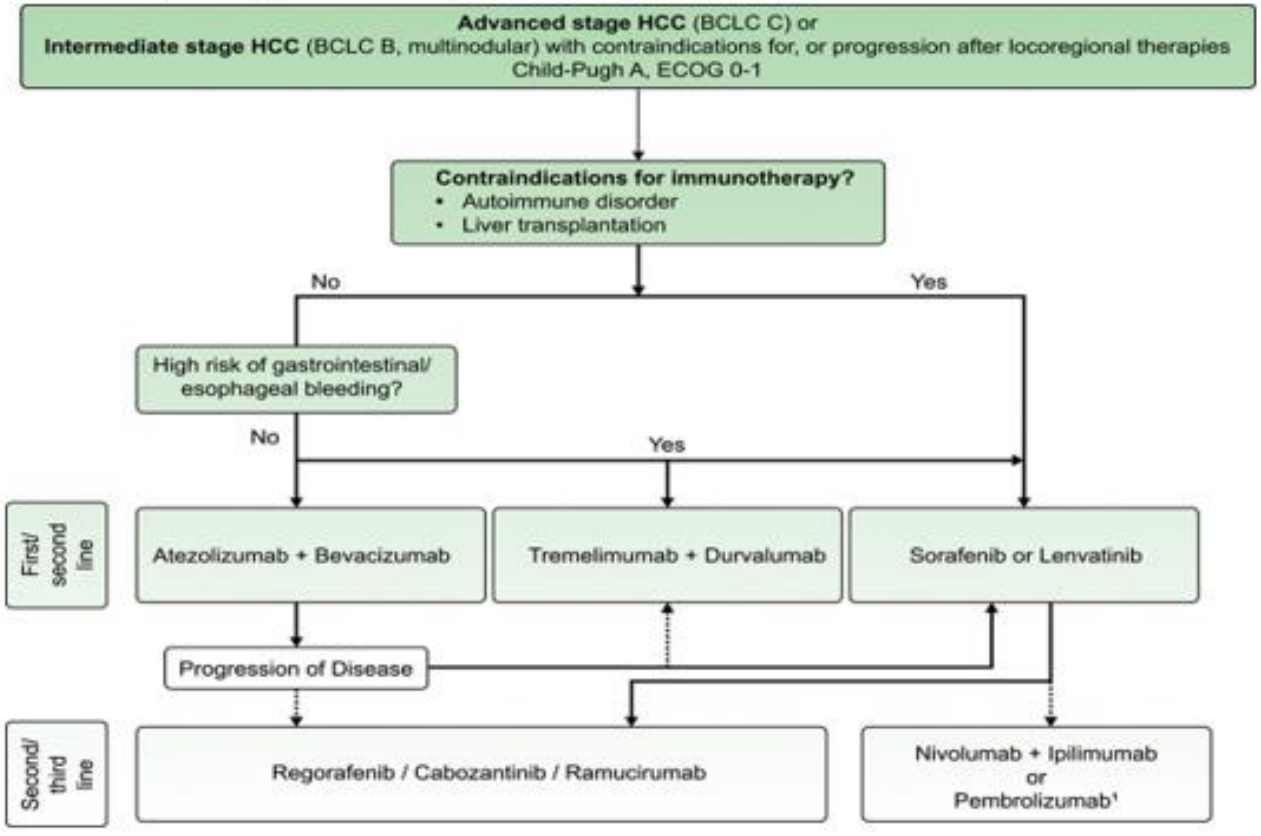
- The best systemic therapy for advanced HCC is the combination of atezolizumab plus bevacizumab but because patients with HCC often have cirrhosis with esophageal varices, and because this combination is associated with ↑ risk of GI bleeding
  - Before initiating therapy, esophagogastroduodenoscopy (EGD) must be preferred
    - If varices are present, begin primary prophylaxis with either esophageal variceal band ligation (EVBL) or starting a non-specific beta blocker such as carvedilol.

- PD-L1 inhibitor durvalumab (CTLA4 inhibitor [cytotoxic T lymphocyte-associated protein 4)
  - Suitable for persons not suitable for anti-VEGF therapy
  - Median overall survival (MOS) vs. sorafenib, 16 vs 14 mon
  - Serious immune-related adverse events (IR AE) combination vs. durvalumab, 13% vs. 6%
  - Lenvatinib plus pembrolizumab, or
  - Cabozantinib plus atezolizumab

➢ Second-Line Therapy and Beyond

- Possibly
  - Ramucirumab
  - Pembrolizumab
  - Ipilimumab plus nivolumab

- Treatment Sequencing Systemic Therapies



Abbreviations: BCLC, Barcelona Clinic Liver Cancer; ECOG, Eastern Cooperative Oncology Group; HCC, hepatocellular carcinoma. Solid arrows indicate treatments for which there is clear evidence; gray dotted arrows indicate treatments in the second/third line for which further studies are required. Treatments that got FDA accelerated approval based on phase II studies.

Printed with permission: Singal AG, et al. Hepatology 2023; 78(6): 1922-1965 (Figure 16).

Recommendations

- First-Line
  - Atezolizumab plus bevacizumab
    - EGD, EV →
      - Primary prophylaxis (NSBB, EVBL)
      - Use durvalumab plus tremelimumab
  - Use first-line systemic therapy
    - CTP A
    - Well-selected CTP B stage cirrhosis
    - European Cooperative Oncology Group (ECOG) Performance Status
    - BCLC Stage B HCC, not curable to or progressing after locoregional therapy

    (Level 1, Strong recommendation)
  - Advance HCC, CTP stage A cirrhosis
    - Atezolizumab plus bevacizumab
      - Perform EGD to detect varices or other bleeding

    (Level 5, Strong recommendation)
    - If varices present
      - Use EVBL (≥ 1 session of esophageal band ligation) or
      - Non-specific beta blocker (NSBB), carvedilol

    (Level 5, Weak recommendation)
  - If recent GI bleeding within 6 mon, or ↑ risk stigmata for bleeding
    - Either treat varices or
    - Use durvalumab plus tremelimumab

    (Level 5, Strong recommendation)
  - If CTP stage A cirrhosis but above medications (atezolizumab plus bevacizumab, or durvalumab plus tremelimumab are contraindicated
  - In well-selected patients with CTP cirrhosis B, use one of
    - Sorafenib
    - Lenvatinib
    - ICI
      - Anti-PD1
      - Anti-PDLA

    (Level 3, Weak recommendation)

- Second-Line and Beyond
  - Patients with CTP Stage A cirrhosis or well-selected CTP stage B cirrhosis or ECOG PS 0–1, in whom their HCC progression or there is intolerance to first-line therapy
    - Use second line therapy

    (Level 1, Strong recommendation)

- After first-line therapy with atezolizumab plus bevacizumab
  - Enroll patient in a clinical trial

  (Level 5, Weak recommendation)
  - Use sorafenib or Lenvatinib, or
  - Use cabozantinib, regorafenib, or
  - Ipilimumab plus nivolumab

  (Level 5, Weak recommendation)
- After first-line therapy with durvalumab plus tremelimumab
  - Enroll in a clinical trial, or
  - Sorafenib or Lenvatinib

  (Level 5, Weak recommendation)
- After failed sorafenib or Lenvatinib, use
  - Clinical trial, or
  - Cabozantinib or ramucirumab (Level 1, Strong recommendation), or
  - Ipilimumab plus nivolumab or
  - If no prior immunotherapy, use pembrolizumab
  - If AFP ≥ 400 ng/mL use regorafenib

- Second Line
  - mTKI (sorafenib or lenvatinib), or
  - If AFR ≥ 400 ng/mL
    - Sorafenib or lenvatinib, or
    - If AFP ≥ 400 ng/mL, ramucirumab

  If not eligible, use
  - Ipilimumab plus nivolumab

- CTP B cirrhosis
  - mTKI drugs
  - Sorafenib
    - Lenvatinib
  - Anti-PDI
    - Nivolumab
    - Pembrolizumab
  - Anti-PD-L1
    - Durvalumab

- All lines of Therapy
  - Recurrent HCC after LT, use
    - Sorafenib or lenvatinib
      - Do **not** use ICIs

    (Level 4, Strong recommendation)
  - All patients who receive
    - Palliative intent therapy, or
    - Best supportive care

    (Level 5, Weak recommendation)

    - Provide care planning (ACPI defining goals, set expectations)

At-Risk Population for Surveillance

Population Group	Incidence of HCC
• Sufficient risk to warrant surveillance	
○ Cirrhosis	≥1.0% per year
− Child-Pugh A–B cirrhosis, any etiology	
▪ Hepatitis B	
▪ Hepatitis C (viremic or post-SVR)	
▪ Alcohol associated cirrhosis	
▪ Non-alcoholic steatohepatitis	
▪ Other etiologies	
− Child-Pugh C, transplant candidate	
Population Group	**Incidence of HCC**
○ Non-cirrhotic chronic hepatitis B	≥0.2% per year
− Man from endemic country[a] age >40 yr	
− Woman from endemic country[a] age > 50 yr	
− Person from Africa at earlier age[b]	
− Family history of HCC	
− PAGE-B score ≥ 10[c]	
• Insufficient risk and in need of risk stratification models/biomarkers	
○ Hepatitis C and stage 3 fibrosis	< 0.2% per year
○ Noncirrhotic NAFLD	

Abbreviation: HCC, hepatocellular carcinoma.

[a]Endemic country as defined by AASLD hepatitis B virus guidance.

[b]Surveillance initiated as early as third decade of life given median age 46 yr at HCC diagnosis.

[c]Other risk calculators can be considered, although PAGE-B has been validated in Western populations on antiviral therapy.

Performance Characteristics of Surveillance Tests for the Early Detection of HCC

Test	Performance characteristics	
	Sn	Sp
○ AFP-L3%	62%	90%
○ DCP	40%	81%
○ Doylestown plus	90%	95%
○ GALAD	54–72%	90%
○ Multitarget algorithm	82%	87%
○ US plus AFP	61%	92%

Abbreviations: AFP, alpha fetoprotein; AFP-L3%, *Lens culinaris* lectin binding subfraction of AFP; DCP, des-gamma carboxyprothrombin; GALAD, gender, age, AFP-L3%, AFP, and DCP model; Sn, sensitivity; Sp, specificity; US, ultrasound

➢ Factors Suggesting TACE or TARE-Refractory HCC

- TACE or TARE refractoriness
  - Lack of objective response
    - >50% definite viable disease after 2 TACE treatments or 1 TARE treatment
  - Development of new HCC within treatment zone after 2 consecutive TACE
  - Lack of improvement for tumour markers (e.g., AFP) after 2 consecutive TACE or 1 TARE
  - Stage migration to advanced HCC, including new vascular invasion or extrahepatic metastases

Abbreviations: AFP, alpha fetoprotein; HCC, hepatocellular carcinoma; TACE, transarterial chemoembolization; TARE, transarterial radioembolization

INHERITED LIVER DISEASES

α1-Anti-trypsin Deficiency

➢ Physiology

- Lung (loss of function)
  - α1-AT is a protease inhibitor which degrades serine proteases in tissue/serum
  - In the lung, the important serine protease is neutrophil elastase (NE)
  - α1-AT binds to this elastase to inhibit NE, and thereby prevents NE from degrading the extracellular matrix.
    - In α1-AT deficiency, there is ↓ binding to NE, and thus ↑ degradation of extracellular matrix → emphysema

- Liver (gain in function)
  - The α1-AT protein is misfolded, becomes polymerized and the "target substrates" are retained in the ER for ER-associated degradation (ERAD) and ER overload response pathway)
    - The target substrates are recognized by chaperones and retrolocated to the cytoplasm
      - The cytoplasmic target substrates are degraded by the ubiquitin-proteosomes
    - The ER quality control mechanism is autophagy, which ↓ ER stress from abnormal aggregation of protein.
    - When α1-AT deficiency affects the liver the ↓ ERAD is defective → ER portions plus protein aggregates become enclosed in autophagosomes
    - The common mutant PiZ produces a mutant α1-AT protein.
      - Accumulation of PiZ in the cell activate autophagia → autophagy-mediated distinction
    - The autophagosomes deliver the ER portion protein aggregates to lysosomes.
      - The lysosomes destroy/degraded to ER proteins plus protein aggregates.
  - The ER overload response pathway
    - Release of proinflammatory release of IL-6 / IL-8

- **Wilson Disease** (WD)

➢ Physiology

- Intestinal absorption
  - Copper (Cu) transported by jejunal enterocytes into portal blood
  - In portal blood, Cu bound to
    - Albumin
    - A2-microglobulin
    - Histidine
- Hepatic sinusoidal membrane (SM)
  - Cu crosses SM by way of CTR1
  - In cytoplasm Cu is bound to apoceruloplasmin to become ceruloplasmin
  - Intracellular Cu bound to
    - Metallochaperones (low-molecular weight proteins that deliver Cu to target molecules)
    - Metallothionein
    - Glutathione
  - Metallochaperones
    - Copper chaperones for superoxide dismutase (CCS) → Cu/Zn superoxide in hepatocyte cytosol
    - Cytochrome C oxidase 17 (COX17) → synthesis of cytochrome C oxidase 1 (SC)1) → transports Cu into mitochondria
    - Antioxidant 1 copper chaperone (ATOx1) → ATP7B (cytochrome oxidase) "Wilson ATPase"
- Hepatic canalicular membrane
  - ATP7B traffics to trans-golgi network (TGN) → cytoplasmic vesicles → Cu pass across canalicular membrane into bile in bile canalicular.

➢ Pathophysiology

- Mutations in ATP7B prevents transport of intracellular Cu across CM into bile canalicular
  - There are multiple mutations in the "Wilson ATPase", including
    - Metal binding domains (MBDs) 1 to 5
    - Nucleotide binding domain
    - Activator domain

- Laboratory
  - ↓ serum ceruloplasmin (often 50% ↓)
    - Supports diagnosis of WD
      - False negative (FN) may be normal with
        - Hepatic inflammation
        - Pregnancy, estrogen therapy
      - False positive (FP) may be reduced with
        - Malabsorption
        - Aceruloplasminemia
        - WD heterozygotes (Grade II-1, A-1; AASLD Class 1, level B)
  - Serum copper
    - Bound N/↓
    - Free > 1.6 µmol/L
      - FN, if ↑ ceruloplasmin as a result of the immunological assay
  - 24-h urine collection > 1.6 µmol/ 24 h
    - FN
      - Incorrect urine collection
    - FP
      - Hepatic necrosis
      - Cholestasis
      - Contamination of urine with Cu (Grade II-2, B-1; AASLD Class 1, Level C)
  - Hepatic copper > 4 µmol/g dry weight (in 50% on WD)
    - FN
      - Active liver disease
      - Regenerative nodules
    - FP
      - Cholestasis (Grade III, B-2; Class 1, Level B)
  - Mutation analysis
    - Numerous genetic abnormalities
    - Not useful for diagnosis of index patient, but
      - Is useful for screening first-degree relatives of persons with WD in whom the mutation is known (Grade II-2, B-1; AASLD, Class I, level B)
  - Hepatic parenchymal copper content

µmol copper per g dry weight of liver	
0.64 to 0.8	> 4
↓	↓
Very unlikely to be WD	Suggestive of WD

- Scoring System (Leipzig) for WD
  - Typical Clinical Symptoms and Signs

KF rings	Present	2
	Absent	0
Neurologic symptoms / abnormal brain MRI	Severe	2
	Mild	1
	Absent	0
Coombs-negative hemolytic anemia	Present	1
	Absent	0
Liver copper (in the absence of cholestasis)	> 5x ULN (> 4 µmol/g)	2
	0.8-4 µmol/g)	1
	Rhodanine-positive granules	-1
Urinary copper (in the absence of acute hepatitis)	Normal	0
	1-2x ULN	1
	> 2x ULN	2
	Normal, but > 5x ULN after D-penicillamine	2
Mutation analysis	On both chromosomes detected	4
	On 1 chromosome detected	1
	No mutations detected	0

TOTAL SCORE	Evaluations / Diagnosis
≥ 4	Established WD
3	Possible, more tests needed
≤ 2	Very unlikely to be WD

- Clinical
  - Suspect WD in a person of any age with
    - Abnormal liver enzymes
    - Extrapyramidal neurological movement disorder / neuropsychiatric disorders (Grade II-2, A-1; AASLD Class 1, level B)
  - In a person with suspected WD
    - Perform slit-lamp examination for Kayser-Fleischer rings (RFRs) (present in 50%) (Grade II-2, A-1; AASLD Class 1, level B)
      - FN
        - Asymptomatic siblings
        - May be absent in WD 50%
      - FP
        - PBC
  - Also suspect WD if
    - Kayser-Fleischer rings (not always present in WD)
    - Coombs-negative hemolytic anemia
    - Fanconi syndrome

- Treatment
  - Perform MRI of brain before Cu chelation therapy for
    - Neurological WD
    - Evaluation of any patient presenting with neurological symptoms consistent with Wilson disease.
  - Asymptomatic/symptomatic patients in these with neurological diseases.
    - Chelation therapy
      - D-penicillamine
      - Trientine
      - Zinc po
    - If couple planning pregnancy, switch from D-penicillamine (teratogenic) to oral zinc during pregnancy, or use Zn long term if 24-h urinary Cu normalized.
  - Acute liver failure (ALF) in WD / decompensated cirrhosis not responding to chelation therapy → liver transplantation
  - Consider intake of low copper diet
  - D-penicillamine/trientine
    - Symptomatic (Grade II-1, B-1; AASLD Class, level B)
    - Asymptomatic (Grade II-1, B-1; AASLD Class I, level B)
    - Neurological disease, maintenance (Grade II-1, B-1; AASLD, Class 1, Level B)
  - Zinc (Zn)
    - Symptomatic (Grade II-1, C-1; AASLD, Class II, Level C)
    - Monitor ALT/AST
    - Stop Zn and switch to chelators if ↑ALT/↑AST
  - Cirrhosis
    - Decompensated as above (Grade II-2, B-1; AASLD, Class 1, Level B)
    - If no response to chelation therapy → LT
  - Acute liver failure
    - The only successful therapy is liver transplantation (LT) (Grade II-1; B-1; AASLD Class 1, Level B)
  - Treatment is lifelong (or until LT) (Grade II-1, B-1; AASLD Class 1, Level B)
  - Pregnancy
    - Plan pregnancy for 24-h urine after penicillamine challenge is normal, and patient is maintained on zinc.
    - If patient becomes pregnant but is on penicillamine (teratogenic)
      - Cut dose by 50% (Grade II-3, B-1; AASLD Class 1, Level C)
      - Switch to trientine
    - If patient becomes pregnant and on trientine, some experts recommend ↓ dose by 50%, and others suggest the drug may be safe in pregnancy.
  - Monitoring
    - q6mon ALT/AST, AP; INR, bilirubin, albumin; CBC non-ceruloplasmin; bowel serum copper (Cu; “free copper”); urine analysis
    - q6-12 mon 24 h urine, 2 d after stopping chelation therapy (Grade II-3, B-1; AASLD class 1, Level C)

Diagnosis and Management of Wilson Disease (WD): **Practice Guidelines** (AASLD 2022)

Schilsky ML, et al. Hepatology 2023 Apr 1;77(4):1428-1455.

- Demography
  - Prevalence
    - Prevalence
    - More common with marriage of first cousins
      - There us a “disciplinary of allele prevalence and clinical WD

- Physiology (copper [Cu])
  - Intake 2-5 mg/d
  - Cofactor for numerous metalloproteins
  - Absorbed in jejunum, bound in blood to albumin and histidine
    - In liver, Cu taken up and bound to ceruloplasmin
  - In liver, Cu taken up and bound to ceruloplasmin
  - An ATPase copper transporting (a metal transporting P-type adenosine triphosphatase) in the cytosol of the hepatocytes
    - Membranes
      - Functions
      - Transmembrane transport of Cu from hepatocytes into bile
  - In WD, the autosomal recessive mutation in the ATPase lead to loss of function, and thus
    - ↓ incorporation of Cu into ceruloplasmin in hepatocytes
      - Depression, psychosis, neurosis
      - Bipolar disorder
    - ↓ export of copper from hepatocytes → cholestasis / ↑Cu storage in other organs

- Clinical
  - Presentation (3-55 yr)
    - Children/teens
      - Liver
    - Adults
      - Psychological, neurological
        - Decline in coagulation
        - Dysarthria
        - Dysautonomia
        - Dysphagia
        - Dystonia
        - Insomnia
        - Seizure
        - Tremor

- Other body systems
  - Heart
    - Dysrhythmias
    - Cardiomyopathy
  - Eye
    - Kayser-Fleisher rings
    - Sunflower cataracts
  - Kidney
    - Aminoaciduria (Fanconi syndrome)
    - Nephrolithiasis
  - Blood
    - Coombs-negative non-immune intravascular hemolysis
    - Splenomegaly
    - ↑ non-specific autoantibodies
  - MSK
    - Arthritis
    - Osteoporosis
  - Endocrine
    - Hypoparathyroidism
  - GU
    - Infertility
    - miscarriage

- GI/liver
  - Asymptomatic +/- transaminitis
  - Acute hepatitis, liver failure (ALF)
  - Like autoimmune hepatitis (AIH)
  - Non-fatty alcoholic fatty liver (NALFD)
  - Portal hypertension / cirrhosis
  - Pancreatitis
  - The non-hepatic conditions will not be discussed further; please refer to the above publication

Clinical Guidelines

- Consider diagnosis of WD in patients of any age with "…liver abnormalities of uncertain cause"
- Exclude WD in any patient with "…unexplained liver disease associated with neurological or psychiatric disorder"
  - Consider consultation with neurologic and/or psychiatrist [does not include hepatic encephalopathy]

- Exclude WD in patients with ALF, especially if there is acute intravascular hemolysis / non-immune hemolytic anemia
  - These patients should have urgent referral to a hepatologist / liver transplantation evaluation
- Urgently exclude WD in patients with recurrent self-limited non-immune hemolysis
- When patient presents with hepatic/neurological sign features, determine of there is involvement of other body systems

➢ Laboratory

- Standard laboratory tests
  - ↑ALT/ ↑AST, AST > ALT, ↓ alkaline phosphatase
  - Unconjugated hyperbilirubinemia
    - Acute liver injury
    - Intravascular hemolysis
    - Rule out Gilbert disease
  - Ceruloplasmin
    - Synthesize in liver as halo ceruloplasmin
    - Most halo ceruloplasmin binds Cu to become ceruloplasmin (non-exchangeable Cu)
    - A small amount of ceruloplasmin does not bind Cu the liver, is excreted into portal blood, and is called apoceruloplasmin
    - Functions
      - Ferroxidase
      - Nitric acid oxidase
      - Acute phase reactant
      - Estrogen responsive
        - ↑ ceruloplasmin
          - Pregnancy
          - Estrogen supplementation
          - Some oral contraceptive agents (OCAs)
    - Hypoceruloplasmin (< 220 mg/dL)
      - WD and some other inherited disorder
      - ↓ intake, ↓ absorption of Cu (bariatric surgery), ↑↑ intake of Zn
      - Protein loss syndrome
        - Proteinuria
        - Protein enteropathy (PLE)
        - Chronic liver disease (CLD) → ↓ synthesis of metalloprotein

MCQ Clinical Alert

- "Serum ceruloplasmin within the normal range does not exclude the diagnosis of WD".

Serum Ceruloplasmin (mg/dL)	Predictive Value for Diagnosis of WD	
	Positive PPV	Negative NPV
20	48	99
14	100	97
10	100	92

- Genetic testing for
  - Multiple mutations in ATP7B on whole-exome/genome sequencing
    - "…particularly effective in identifying siblings of probands with two identified ATP7B mutations

Curiosity

- Uric acid
  - May be ↓ serum uric acid in symptomatic hepatic/neurological WD (due to ↓ renal reabsorption of urate

- Serum copper
  - Non-exchangeable, 70% (bound to ceruloplasmin)
  - Exchangeable, 10% (non-ceruloplasmin-bound copper, which is bioavailable)
  - Total serum copper ↑ in proportion to ↓ ceruloplasmin
  - Methods to measure non-ceruloplasmin copper (direct free [unbound] Cu) which are not yet used for standard clinical practice
    - Exchangeable copper (Cu exc) in serum
    - Relative exchangeable copper (REC): Cu exc / total serum copper
    - The advantage of REC > 18.5% suggests homozygous rather than heterozygous WD, normal persons, or persons with chronic liver disease
- 24-h urine copper
  - The serum non-ceruloplasmin copper (NCC) is excreted in the urine
  - The amount of basal Cu in the urine is proportional to the serum NCC
  - Measuring basal and then post-D-penicillamine may be useful to suggest that ↑ 24 h urine Cu reflects diagnosis of WD rather than other causes of (↑ urine Cu, e.g., other cholestatic / acute and chronic liver disease, proteinuria)
    - This D-penicillamine challenge test should not be used for screening asymptomatic persons for WD because of its poor sensitivity in the group
- Radiocopper incorporation of Cu into ceruloplasmin
  - ↓ Cu into ceruloplasmin may prove to be useful in
    - Symptomatic persons with WD
    - Not in asymptomatic persons

- Pathogenic gene variants in ATP7B
  - Most common gene changes/mutations
    - Missense
    - Deletions
    - Insertions
  - Most patients are "…compound heterozygotes harboring different mutations on each allele"
  - Testing
    - Patient with known genotype, two disease-specific transmutations, on each allele of chromosome 13
    - Do **not** direct mutational analysis in the first-degree relatives (WD with known gene mutation)
    - When genotype unknown, screen with analysis of the entire ATP7B (including its promoter region, with attention to
      - Intron/exon boundaries, and possible occurrence of
      - Large deletion
      - Sensitivity, > 99%
      - Other high throughput methods
        - Denaturing high performance liquid chromatography
        - Automated single-stranded conformation polymorphism analysis
      - Sometimes analysis has to be performed on both DNA plus RNA (to detect any large deletions)
    - Genetic analysis of ATP7B to predict progression/clinical cause of WD
      - Early onset of liver disease – ATPase loop
      - Acute liver failure (ALF) – copper binding areas

- Hepatic histopathology

- Light microscopy
  - Wide range of changes similar to
    - NAFLD, but starting periportal
    - May contain Mallory hyaline (aka Mallory-Dent bodies)
    - Multi-lobular confluent necrosis (ALF)
    - Other findings suggestive of WD
      - ↑ apoptotic hepatocytes
      - ↑ nuclei with glucagon
      - ↑ size of hepatocytes with granular eosinophilic cytoplasm (↑ mitochondrial oncocytic cells)
      - ↑ simple steatosis (mild)
      - ↑↑ hepatic Cu in hepatic / lysosome, variable distribution, staining positive with aldehyde fuchsin, orcein (Shikata type stains for Cu-binding proteins [rhodamine, rubeanic acid, modified Timm's stain]; these stains have poor performance characteristics)
  - Hepatic complications of WD include
    - Hepatic cellular cancer (HCC)
    - Cholangiocarcinoma (CCA)

- Electron microscopy
  - Mitochondria of hepatocytes
    - Size/shape variable
    - Cristae
      - ↑ intracrystal shape
      - ↑ dilation of tips
  - Matrix
    - Dense
    - Inclusions
  - Lysosomes
    - Deposits, dense

- Hepatic Copper Concentration (HCuC)
  - Perform two passes to obtain more parenchymal tissue for histopathology and for measurement of HCuC
  - Values of hepatic Cu content

Condition	mg/g dry weight of liver
Normal	< 50
WD	> 207 (sensitivity, 99%; specificity, 96%)

  - Mutations to measure HCuC
    - Autonomic absorption spectroscopy (AAS)
    - Qualitative inductively coupled plasma mass spectroscopy (ICP-MS)
    - Laser ablation ICP-MS
      - Shows highly variable hepatic distribution of Cu

Guidance Statements

- When WD is suspected
  - Perform complete history/physical examination, especially considering liver and neurological/psychological disease
  - Screening laboratory
    - CBC
    - Liver enzymes and function tests, including ALT/AST, AP, INR, bilirubin, serum ceruloplasmin, and possibly 24-h urine copper
  - Basal 24 h urinary copper, abnormal value

Asymptomatic	> 0.6 µmol / 24 h	> 40 ng / 24 h
Symptomatic	> 1.6 µmol / 24 h	> 100 µg / 24 h

- Liver biopsy
  - To help make diagnosis of WD, including hepatic parenchymal copper content (HCuC)
    - Exclude other diagnosis
    - Stage/grade liver disease
    - HCuC
      - < 50 µg/g dry weight of liver biopsy high suggestion that WD is excluded
      - > 250 µg/g dry weight suggests WD
  - Electron microscope of liver biopsy may have findings suggestive of WD, especially in children/teens
- Appropriate testing of other organ testing for involvement of WD
- When diagnosis of WD more likely, refer to clinical genetical for molecular genetic study for possible mutations of ATP7B

Clinical Tip

- Cautiously consider significance of results of measuring serum ceruloplasmin
  - Normal
    - Does not exclude WD
  - Low
    - Does not by itself diagnose WD
    - If serum ceruloplasmin < 5 mg/dl more strongly suggests WD than does modestly ↓ limits

SO YOU WANT TO BE A GASTROENTEROLOGIST!

- Give the genetic/metabolic disorder which are similar phenotype to WD (meets diagnostic thresholds for WD using the Leipzig diagnosis score" and ↑ urine 24 h Cu there is ↑ HCuC.
  - Variations in a specific ATP7B variant may not necessarily pathogenic in a given patient
  - The ATP-binding gene ABCB4 (ATP-binding cassette subfamily B membrane 4) will be abnormal. Not ATP7B as in WD, is faulty, causing MDR3 deficiency, resulting in
    - Progressive familial intrahepatic cholestasis type 3 (PFIC3)
      - PFIC3 presents with cholestasis due to defective bile canalicular transport ↑ urine Cu, ↑ HCuC, ↑ Leipzig score

MCQ Challenge

- Give why there are sometimes disassociation between WD genotype and phenotype (lack of good correlation between WD genotypes and phenotype)
  - Epigenic factors
    - Epigenic/methylation
    - Cu intake
  - Modifier gene

Guidance Statements

- Consider doing genetic testing for ATP7B mutations as part of a "routine evaluation"
  - For diagnostic confirmation when the other laboratory tests
  - To screen first-degree relatives of a proband

➢ Differential

❖ Hepatic

- Autoimmune Hepatitis (AIH)
  - If patient with AIH
    - Fails to respond quality to standard treatment
    - Might have both AIH plus WD

- NAFLD

Test	NAFLD	WD
Serum ceruloplasmin	N/↓	↓
Urine 24 h Cu	↓	↑
Hepatic Cu content (HCuC)	↓	↑
Genetic ATP7B – NAFLD plus WD may consist	-	+

- Acute Liver Failure (ALF)
  - In the patient with ALF, screen for WD
    - Especially important to have ↑ suspicion for WD in patients with ALF plus
      - Female (WD with ALF, F>M 2-4:1)
      - Viral infection / drug toxicity triggering ALF in WD

- Laboratory suspicion
  - Blood
    - Acute intravascular hemolysis (hemolytic anemia, Coombs test (negative)
    - ↑ AL / ↑ AST, but ≥ 2000 IU/L; AST > ALT
    - ↓ alkaline phosphatase (AP)
    - Coagulopathy [↑ INR] unresponsive to parenteral vitamin K
    - ↑ serum creatinine (Cr_s) rapid progressive to renal failure

– Ratios	Sensitivity	Specificity
▪ AP / total bilirubin (B) < 4	94%	96%
▪ AST / ALT > 2.2	94%	86%
▪ AP/B plus AST/ALT tests	100%	100%

- Rapid diagnosis of WD as cause of ALF
  - Mortality of 80% - 90% without early liver transplantation (LT)
    - If hepatic encephalopathy develops; mortality rate is high
  - Laboratory tests as expected for WD
    - ↓ serum ceruloplasmin; ↑ urine 24 h Cu, ↑ HCuC

❖ Non-hepatic

- Aceruloplasmin (ACP)
  - Serum ceruloplasmin ↓↓↓, but other Cu other Cu tests are normal, including liver HCuC
    - In ACP, but not in WD
      - ↑ AIC (↑ hepatic iron concentration)

- MDR3 deficiency
  - MDR3 is a transporter in the liver and bile canaliculi which is associated with cholestatic disease
    - Progressive familial intrahepatic cholestasis type 3 (PFIC3)

Test	MDR3 Deficiency
○ Serum ceruloplasmin	N
○ Urine 24 h Cu	
○ HCuC	↑
○ Gene mutation	ABCB4
○ Meets diagnostic criteria by the Leipzig score	+

- Congenital disorders of Glycosylation (CGDs)

CDG phosphoglucomutase 1 deficiency (PGM1-CDG)

Test	PGM-1 CDG
○ Serum ceruloplasmin	↓
○ Urine 24 h Cu	N
○ HCuC	↑

➢ Scoring System for Diagnosis

- Leipzig score components
  - ○ Components
    - − Kayser-Flesher rings
    - − Neuroproliferative symptoms
  - ○ Laboratory
    - − ↑ serum Cu plus hemolytic anemia, Coombs test negative
    - − ↓ urine 24 h Cu
      - ▪ No acute hepatitis
      - ▪ Before/after d-penicillamine 500 mg b.i.d., “after” 1 day later
    - − ↑ liver Cu
      - ▪ Quantitative
      - ▪ Qualitative (Rhodamine-positive hepatocytes present)
    - − Disease causing mutations in ATP7B

- New Wilson Index (NWI)
  - ○ Components
  - ○ NWI ≥ 11 predicts mortality from WD if LT not performed
    - − MELD score used to prioritize patients requiring patients requiring LT such as with ALF from WD

Guidance Statements

- ○ Validated diagnostic scores
  - − Helps to rule in / rule out a diagnosis of WD
- ○ Prognostic scores
  - − Helps to estimate severity / likely mortality, and the urgency / appropriateness of liver transplantation

Guidance Statements (Indications for screening)

- ○ All first-degree relatives of patient with newly diagnosed WD (with or without symptoms)
- ○ Any person in the family (pedigree) with a person with WD
- ○ If there is a proband with WD has a known disease-specific mutation, do molecular testing for mutations of ATP7B

➢ Treatment

- Trientine
  - MoA
    - Chelation of Cu → ↑ renal excretion of Cu → ↑ renal excretion of Cu
    - ↓ dose
      - Pregnancy
      - Perioperatively
  - Complications
    - GI
      - Loss of taste
      - Esophageal discomfort
      - Gastritis, hemorrhagic
      - Colitis
      - Toxic product results when Fe taken with trientine
    - Blood
      - Aplastic/sideroblastic

- Zinc salt
  - MoA
    - Induces metallothionein
    - ↓ Cu absorption
    - Low risk of neuropsychiatric worsening on initiation of Zn therapy
    - No med to ↓ dose with pregnancy/perioperatively
  - Complications
    - GI
      - Gastritis
      - Pancreatitis
    - Possible immune changes
  - Key principles to treatment
    - Diagnose WD early and treat asymptomatic persons
    - Use Zinc as
      - Maintenance therapy after excess Cu has been deleted
      - Primary therapy
      - Combination of chelation plus Zn
      - Safe use in pregnancy
    - Use restriction of dietary Cu plus pharmacotherapy
    - If pharmacotherapy plus dietary Cu restriction is ineffective, or
    - For acute liver failure
    - Asymptomatic WD patients
      - May have or have no organ damage
    - Symptomatic patients
      - May have organ involvement, especially liver and neuropsychiatric systems
      - Treat these symptoms as well as the Cu accumulation which causes the WD symptoms

    ▪ Refer patient for evaluation for LT

- All WD patients should have age-specific vaccinations including AAV, HBV, COVID-19, varicella, pneumococcus, adult booster for MMD
- Time to resolution of jaundice, 2-6 mon
- Time to liver failure after stopping therapy, 1-12 mon
- Time of response to initial reduction of excess body Cu
  - Chelators, 6-18 mon
- A major challenge to successful therapy is patient adherence to uninterrupted therapy
- If maintenance drugs are stopped, or be suboptimal doses are taken, may lead to
  - Recurrent symptoms
  - Acute liver failure / ↑ mortality unless urged liver transplantation (LT)

❖ Individual Drugs

- D-penicillamine
  - MoA
    - The free sulfhydryl group in the drug binds to Cu and provides for renal excretion of Cu in the urine
      - The excretion T1/2 is 1.7 – 7 h
  - Renal excretion
    - Early after starting D-penicillamine
      - The 24 h urine copper excretion is > 1000 μg/d
      - There is ↑ metallothionein
      - The 24 h urine Cu declines as the body Cu stores also decline
      - Most D-penicillamine-induced urinary Cu excretion is in the first 48 h but for months after the D-penicillamine is stopped, small amounts remain in the urine
  - Absorption
    - The disulfide in the penicillamine Cu complex binds to the brush border membrane (BBM) of the enterocytes
    - Uptake across the BBM is by pinocytosis
    - The efficacy of absorption of D-penicillamine is only 40% - 80%
    - The absorption of D-penicillamine is ↓ by food
    - Once absorbed, D-penicillamine is mostly bound to plasma proteins, with most Cu bond to the D-penicillamine-protein complex
  - Clinical effects
    - D-penicillamine mobilizes the excess Cu in the affected organs, and the symptoms arising from these damaged organs decline
    - However, all the Cu-chelating drugs as well as Zn may ↑ neurological symptoms early after treatment and despite the ↑ loss of C from the body
      - The paradoxical worsening of the neurological symptoms is most common with D-penicillamine (~15%)
      - This initial worsening of neurological symptoms is more common in WD patients who already have neurological symptoms, and lessens with time despite continuation of pharmacotherapy

- Complications
  - ↑ neuropsychiatric symptoms (10-20%) when starting treatment
  - ↓ dose
    - Pregnancy
    - Perioperative
- System
  - General fatigue
  - CNS
    - Retinitis
  - Skin
    - Rash
    - Degenerative changes
    - Elastosis perforans serpiginosa (EPS)
    - Pemphigus / pemphigoid lesion
  - Blood
    - Bone marrow toxicity
      - Aplasia
      - Thrombocytopenia
      - May be irreversible even when drug is stopped
    - IgA
  - GU
    - Proteinuria
    - Nephrotic syndrome
  - GI
    - Hepatotoxicity
  - MSK
    - Lupus-like syndrome
    - Myasthenia gravis
- Adverse effects (AEs)
  - Frequency of AEs severe enough to require the D-penicillamine to be stopped, ~30%
  - Frequency of AEs may be reduced by starting does of 250-500 mg/day, then q4-7 d, to a maximum dose of 500 mg q.i.d.
  - Once the 24 h urine Cu is normal, continue membrane D-penicillamine as 10-15 mg/kg per day taken in 2 daily doses (b.i.d.)
  - Because food reduced absorption/bioavailability of D-penicillamine, give the drug 1 h before or 2 h after meal

Treatment Alert

- All patients given D-penicillamine should take pyridoxine 25-50 mg po per day

- Trientine
  - Triethylenetetramine dihydrochloride chelate
    - Polyamine structure
    - No sulfhydryl group
    - Chelates Cu for urinary excretion
  - Do **not** administer with food
    - Poorly absorbed, median T1/2 for absorption in WD, 1.5 h
    - When treatment initiated, urinary excretion of Cu is > 1000 µg per day
      - As the amount of body Cu falls, the amount of Cu in the urine also falls
      - The T1/2 for urinary excretion of 1% of the administered trientine and 8% of the metabolized / biotransformed metabolite are ~3h
  - Trientine binds Cu, as well as zinc (Zn) and iron (Fe) and excretes these metals in the urine
  - Indications, rather than using D-penicillamine
    - Can be used in
      - Patients with decompensated liver disease
      - If the patient already has thrombocytopenia, neutropenia (from splenomegaly)
      - Less paradoxical neurological worsening upon starting drug
  - Initial dosing t.i.d., slowly ↑ dose to 15-20 mg/kg per day in divided doses (maximum 2000 mg daily individual doses, 2-3 taken 1 h before or 2 h after meals)
  - Adverse effects
    - Normal 24 h urinary Cu, 150-500 µg/d
    - If patient's maintenance 24 h urinary Cu is higher than the target dose, consider
      - Patients not adherent to dosing recommendation (↑ serum Cu)
      - Dosing taken with food (↓ absorption)
      - Intercurrent acute liver injury (ALF)
    - If patients 24 h urine Cu < 100 µg/ 24 h
      - Patient's dose of drug may be excessive, with development of Cu deficiency

MCQ Diamond

- Give the complications of overdosing the patient.
  - ↑ iron in liver (hemosiderosis)
  - Cu deficiency
    - Neutropenia
    - Sideroblastic anemia

- Zinc Salts (Zn)
  - MoA
    - Zn → ↑ metallothionein a natural [in diagnosis] chelator)
  - Enterocytes affinity for metallothionein is greater for Zn than for Cu
    - When Zn given po, there is less uptake of Cu than of Zn
    - The Cu which does bind to metallothionein remains in sloughed enterocytes, and passes into the cytosol
    - Zn also ↓ absorption of Cu in saliva / gastric juice → ↓ tissue Cu
  - Hepatocytes
    - The ↑ hepatocyte metallothionein (stimulated by Zn) binds to some hepatocyte metallothionein → ↑ resistance to Cu toxicity
    - Zn partially reverses Cu-mediated interference with hepatocyte nuclear receptors → impaired hepatic metabolism
  - Adverse effects
    - Dyspepsia/gastritis (change the Zn salt)
    - Early paradoxical worsening of neurological symptoms is uncommon
    - Incidental hyperamylasemia (no signs/symptoms of pancreatitis)
  - Indications
    - Patients with WD and ↓ renal function used first-line for
      - Asymptomatic WD patients
      - Patients with WD and neurological symptoms
      - Maintenance therapy after successful initial chelation therapy
  - Monitoring intake
    - Serum ALT/AST when ↑ AST / ↑ ALT, suspect
      - ↓ adherence (check of urinary Zn > 1.2 mg (24 h)
      - ↑ intake of Cu

- Tetrathiomolybdate (TTM)
  - Chelating agent
    - TTM, serum albumin and Cu from a non-reactive tripartite complex
    - Removes Cu bound to metallothionein
    - ↓ absorption of Cu in food (give TTM with meals)
    - Not yet ready for clinical use

- Antioxidants (e.g., vitamin C/E)
  - Under study

Clinical Gems

- Use chelating agents or Zn in asymptomatic WD to
  - ↓ development of symptoms
  - ↓ progression of disease
- Monitor patients first 2-6 mon on full dose initial intake to estimate when
  - Place on lower dose chelator or Zn or
  - Switch from chelator to Zn

- Adherence to therapy
  - Almost normal survival
  - Early hepatic disease treated, neuropsychiatric disease (including ↓ executive function)
  - Treating asymptomatic disease ↓ risk of future symptoms

Guidance Statements

- All newly diagnosed patients with WD should be started on pharmacotherapy and lifestyle changes, continued for life
  - Children < 3 yr require individualized decision as to when to start therapy
- Symptomatic
  - Start initial therapy with a chelating agent, D-penicillamine or trientine (few side effects)
- Asymptomatic
  - Start with a chelating agent at a low dose, or with a zinc salt
- The time to switch from starting drug therapy to maintenance therapy depends upon patient's
  - Symptoms
  - Biochemical improvements
  - Duration of initial therapy (usually 1 yr)

➢ Nutrition

	mg/d
Timely intake of Cu	
Recommended	0.9
US	1 – 1.6

- The benefit of low Cu diet is modest because
  - The difference between the actual and recommended intake is relatively small
  - The foods containing large amounts of Cu are not foods eaten everyday, e.g.,
    - Chocolate
    - Mushrooms
    - Nuts
    - Organ meat (e.g., brain, pancreas, kidney, liver)
    - Shellfish (except scallop)
    - Soy
    - Vegetable-derived meat products
- Beneficial to obtain nutritional guidance from registered dietitian
  - Have drinking water checked to be sure Cu < 100 µg/L (let tap water run for > 30 sec, even if the pipes are copper, to flush the copper in the stagnant water)
    - Consider using a home water filtration system
    - Do **not** use
- Persons with WD who have swallowing difficulty
  - Liquid thickness
  - Positioning during/after meals
  - Speech therapist
  - Enteral feeding
- Nutrition supplement, as necessary

Guidance Statements

- Especially in the first year of pharmacotherapy, do **not** ingest large amounts of Cu in food or in beverages.
  - Consider consultation with registered dietitian
  - If nutritional intake inadequate, arrange for nutritional support using low Cu supplements

➢ Monitoring

- During initial year evaluate twice a year at least of pharmacotherapy
  - Adherence
  - Adverse effects
  - MELD score
  - Benefits
  - Clinical biochemical (24 h urine Cu, INR, bilirubin, CBC)
- Reasons for failure of therapy
  - Progression of associated hepatic neuropsychiatric (HP) disease (↑ Fib-4, ↑ AST / platelets)
  - Development of second hepatic / HP disease
  - Non-adherence to drug

- If failure diagnosed and cannot be corrected
  - Liver biopsy
  - Refer to a liver transplantation centre of MMELD score > 15 after ≥ 18 mon of treatment

Guidance Statements

- Monitor at least 2x per year using history/physical examination, biochemistry
  - Patients who are on chelation therapy long term require long term CBC, routine urinalysis
    - The 24 h urine measurement monitoring be performed while the patient is on or off chelation therapy, and should be done 1/yr (or 2x per yr or more depending upon circumstances, e.g.,
      - Suspicion of non-adherence
        - ↑ serum Cu
        - Serum Cu disproportional high for serum ceruloplasmin
      - Consideration of need to change dose of drugs
- Support overtreatment of
  - Chelation, if
    - Development of cytopenia
    - ↑ serum ferritin
    - ↓ serum Cu
    - ↓↓ 24 h urine Cu (< 100 µg / 24 h; < 1.6 µmol / 24 h
  - Zn therapy
    - 24 h urine Cu = 20 µg / 24 h; < 0.3 µmol / 24 h
  - If overtreatment confirmed, reduce dose and follow closely
- Treatment failure
  - May occur with any WD drug and at any time
    - Exclude concurrent disease and non-adherence
  - Modify dose or ensure adherence
    - Consider need for liver transplantation

➢ Methods to ↑ adherence

- Education, coping strategies, “partnership” with WD non-judgmental interaction, dedicated pharmacy, weekly pillbox, patient support groups, reminders (smartphone, social media)
- Awareness of result of ↓ adherence
  - May “…precipitate a clinical catastrophic”
    - New or ↑ neuropsychiatric symptoms
    - Progression of liver disease, and acute liver failure
    - Restarting pharmacotherapy may not lead to a response, and these patients may require liver transplantation

Clinical Alert

- Advise female patients with WD to
  - Take anti-pregnancy measures
  - If a non-expected pregnancy occurs
    - Patient
      - Do **not** suddenly stop your (chelator) medication
    - Physician
      - Reduce the dose of chelator, but do **not** stop (please see section on Pregnancy, which follows)

Guidance Statements

- Use all possible methods to ensure patient with WD adheres to their medical regimen

➢ Complications

- Decompensated cirrhosis
  - In patients with acute liver injury (ALI) consider using intensive regimen of chelator plus Zn (dispersed times of intake 4-5 h between chelator and Zn)
    - Once stabilized in 3-6 mon, may switch to monotherapy

Guidance Statements

- Give patients with WD plus severe liver disease (regardless of any neuropsychiatric disease) and intensive medical regimen, such as chelator plus Zn
  - Continue longitudinal assessment and be prepared to refer for a possible liver transplantation (LT)
- Failure to respond to or to tolerate pharmacotherapy is also an indication for LT

- Acute Liver Failure (ALF)
  - Oral chelators may be effective until there is renal failure or less of renal support
    - In 10% of ALF patients with ALF there may be a response to
      - Albumin dialysis
      - Exchange transfusion
      - Molecular absorbance recirculating system (MARS)
      - Plasma exchange
      - Plasmapheresis
      - Renal replacement therapy
  - Liver transplantation, not medical therapy, is useful required for the WD patient from ALF

- Liver transplantation in WD
  - Indications
    - Acute liver failure
    - Chronic liver failure
      - Failed therapy
      - Progression / portal hypertension
      - HCC
  - Cautions towards LT in patients with WD plus neuropsychiatric disease (NPD)
    - Sometime, NPD improves, sometimes worsens (possibly ↑ non-adherence)
    - Sometimes, NPD with dystonia, Parkinsonism impair
  - A patient with WD may receive
    - A living donor LT
    - A donor who is a family member who is a heterozygote carrier for WD
  - Long term outcome of LT in WD
    - Normalizes
      - Hepatic modulation
      - Extrahepatic organ Cu
      - Excellent outcome

Guidance Statements

- Immediately refer patients with acute liver failure (ALF) from WD to a liver transplant centre
- Patients with acute liver injury (ALI) may respond to dual medical therapy with chelator plus Zn
  - After LT, medical therapy for WD is **not** necessary
- While ALF/HCC are accepted indications for LT in WD
  - "Neurologic WD remains a controversial indication"

- Hepatocellular Cancer (HCC) and Cholangiocarcinoma (CCA)
  - Follow guidelines for screening/surveillance for HCC/CCA

Guidance Statements

- Perform screening/surveillance for HCC and CCA in patients with WD and cirrhosis or regressed outcomes
  - CCA should also be suspected in patients with WD cirrhosis or regressed cirrhosis
- Adverse effects of WD in pregnancy are usually due to patients with previously underdiagnosed WD

- Pregnancy
  - Ideally, plan timing of pregnancy with appropriate methods of contraception until the initial reduction of body Cu has been achieved
    - The ↓ conception rates in women with WD are corrected by pharmacotherapy
    - Trientine is FDA category C
    - D-penicillamine is FDA category D
  - If patient on chelator when pregnancy begins, ↓ dose by 25% to 50% at the pre-pregnancy dose
  - Continue this lower dose of chelator until 2-3 wk after delivery
  - Genetic consultation to family of risks of WD in the offspring
  - Once 24 h urinary Cu normalized, maintain Zn therapy, which is safe to use in pregnancy
  - Use a multidisciplinary team (MDT)
  - Monitor 24 h Cu 3x during pregnancy
  - If upper endoscopy done within past 12 mon in patient with portal hypertension
    - Perform endoscopy if esophageal varices found perform esophageal variceal bowel ligation, or give non-specific beta blockers
  - Cu, Zn, and D-penicillamine
    - The amount if Cu in milk of mothers with WD treated with D-penicillamine may be low risk and cause harm to infant
    - The ↑ D-penicillamine in mother's milk may be harmful for the infant

Guidance Statements

  - Perform preconception counseling
    - Genetic testing
    - Medication issues related to mother and infant
  - The chelating agents are potentially harmful to the fetus
  - If mother is switched to organ Zn before pregnancy, ensure there is clinical and laboratory "stabilizing" before proceeding with pregnancy and continuation of the Zn
  - The pros and cons of breastfeeding must be discussed on an individual basis

- **Drug-Induced Liver Injury** (DILI)

Idiosyncratic Drug-induced Liver Injury: ACG Guideline *(2021)*

Chalasani NP, et al. Am J Gastroenterol 2021; 116; 878-98.

Please also see Sandhu N and Navarro V. Hepatology Communications 2020; 4: 631-645 and Hoofnagle JH and Björnsson ES. N Engl J Med 2019; 381(3): 264-273.

➢ Background

- DILI is a diagnosis of exclusion, so a thorough medication history is essential, including history of
  - Use of over-the counter medications (OTCs), herbs and diet supplements (HDS)
  - Chronic liver disease (Strong recommendation, low level of evidence)
  - Hepatotoxic drugs (Strong recommendation, low level of evidence)
- Call the patient's pharmacist to confirm past/present prescriptions
- Use the "R-value" (described below) to determine whether the abnormal liver enzymes (ALT, AP) represent hepatocellular, cholestatic or mixed types of DILI.
- If patient taking a potentially hepatotoxic drug, measure ALT/AP q4-6wk for 26 wk (Conditional recommendation, very low level of evidence)

$$R = \frac{ALT/ULN}{AP/ULN}$$

R ≥ 5, hepatocellular disease
R < 2, cholestatic disease
2 > R < 5, mixed

} Use the baseline value (The R value may change with DILI)

➢ Terminology and Definitions

- Chronic DILI – Failure of return of liver enzymes or bilirubin to pre-DILI baseline, and/or other signs or symptoms of ongoing liver disease (e.g., ascites, encephalopathy, portal hypertension, and coagulopathy) 6-9 mon after DILI onset.
- Hy's law – Observation made by late Hyman Zimmerman suggesting a 1 in 10 mortality risk of DILI of the following three criteria are met:
  - Serum ALT or AST > 3xULN
  - Serum total bilirubin elevated to > 2xULN without initial findings of cholestasis (elevated serum alkaline phosphatase)
  - No other reason can be found to explain the combination of increased aminotransferases and bilirubin, such as viral hepatitis A, B, C, or other pre-existing or acute liver disease.
- Idiosyncratic DILI – Hepatotoxicity affecting only rare susceptible individuals
  – Reaction less dose dependent and more varied in latency, presentation, and course.

- Intrinsic DILI
  - Hepatotoxicity with potential to affect all individuals to varying degrees.
  - Reaction typically stereotypic and dose dependent (e.g., acetaminophen)
- Latency
  - Time from DILI onset to return of enzymes and/or bilirubin or pre DILI baseline levels.
- RUCAM
  - Diagnostic algorithm that uses a scoring system based on clinical data, pre-existing hepatotoxicity literature on the suspected agent, and rechallenge.
- R-value
  - ALT/ULN ÷ AP/ULN. Used t0 defined hepatotoxicity injury patterns: hepatocellular (R > 5), mixed (R = 2-5), and cholestatic (R < 2).
- Temple corollary
  - An imbalance in the frequency at ALT > 3xULN between active treatment and control arms in a randomized controlled trial.
  - This is used to assess for hepatotoxic potential of a drug from premarketing clinical trials.
- Washout, resolution, dechallenge
  - Readministration of medication or HDS to a patient who already had a DILI to the same agent.

Abbreviations: Alk, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DILI, drug-induced liver injury; HDS, herbal and dietary supplements; RUCAM, Roussel Uclaf Causality Assessment Method; ULN, upper limit of normal

- Natural history
  - Hepatomegaly and ↑ INR ("coagulopathy")
    - AF in 10% → bad prognosis (cancer, ↑ MELD score)
      - Mortality ~40%
      - Require LT 40%
    - Prognostic scores for DILI are not valuable.

- Scoring system
  - Several causality assessment methods developed "the validity of the method vary as a result of differences in prioritizing the parameters…causality scales are confounded by the absence of a true "gold standard".
  - The DILIN score has been used to attach a probability of the diagnosis of DILI to an adjective
    - Definite, > 95%
    - Highly likely, 75-95%
    - Probable, 50-75%
    - Possible, 25-49%
    - Unlikely, < 25%
  - This DILIN method has not been verified externally with Sandla V and Navarro V. Hepatology Communications 2020; 4: 631-645.

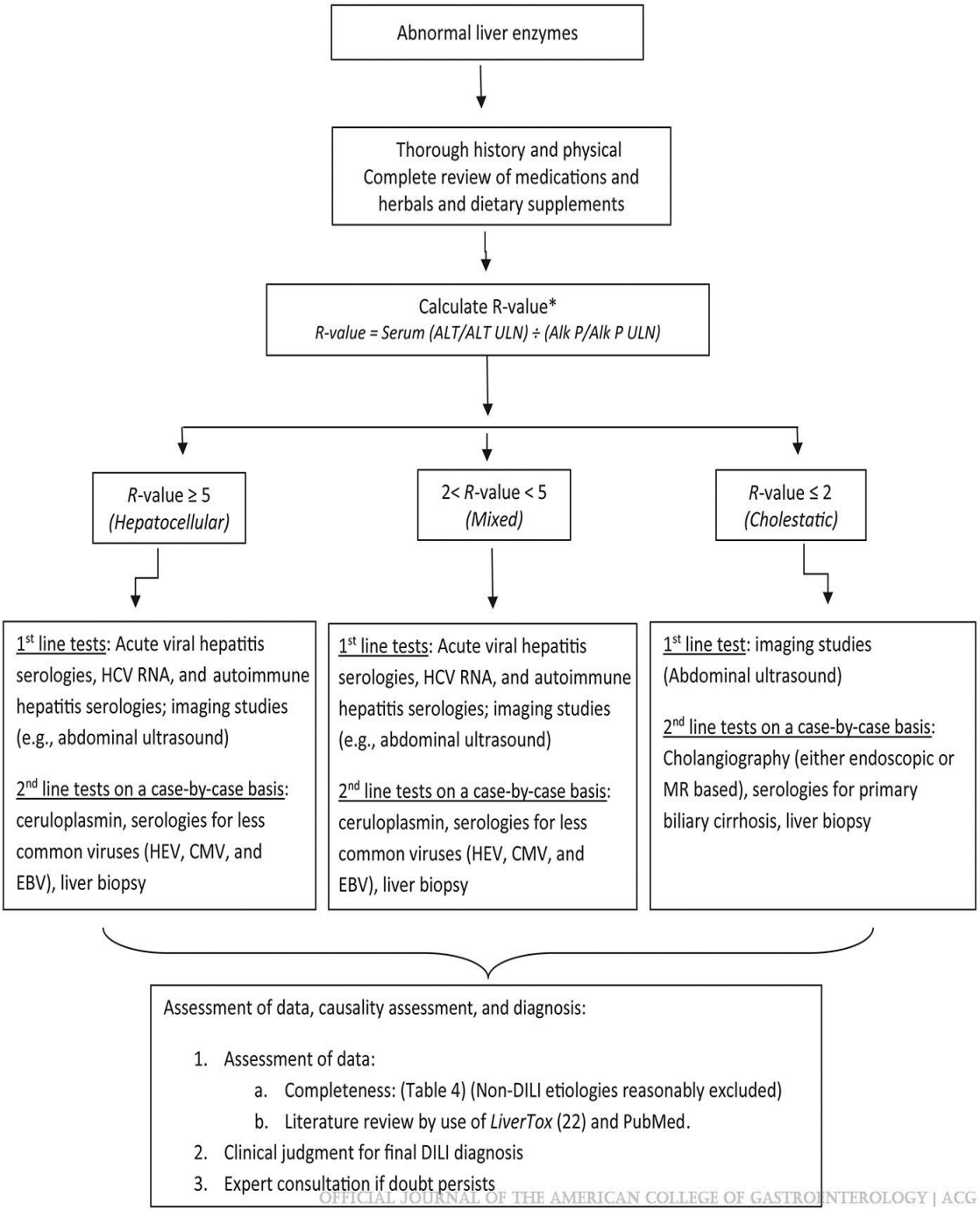
➢ Laboratory

- Recommendations
  - Suspected hepatocellular/mixed DILI
    - Exclude HAV, HBV, HCV and autoimmune hepatitis (AIH), anti-smooth muscle (ASM), and anti-DNA antibodies (Strong recommendation, very low level evidence)
      - In some Celtic-settled areas where celiac disease prominent (↑ risk of AH), measure tissue transglutaminase (tTG) serology
    - Only if clinical setting
      - HEV (anti-HEV IgM antibodies)
      - CMV, EBV, HSV, Wilson, Budd Chiari syndrome (Strong recommendation, very low level of evidence)
    - Serum immunoglobin concentrations may be useful to diagnosis
      - Alcoholic liver disease (ALD); IgD
      - Primary biliary cholangitis (PBC); IgM
      - Autoimmune hepatitis (AIH); IgG
  - Suspected cholestatic disease
    - Serology
      - Anti-mitochondrial antibody (AMA positive, suggesting PBC)
    - Diagnostic imaging
      - Abdominal ultrasound (sometimes with Doppler), CT scan, MRCP
        - Biliary duct stones
        - Pancreatitis-biliary cancer
        - Primary sclerosing cholangitis (Strong recommendation, low level of evidence)
  - Liver biopsy
    - In only some patients
      - Diagnosis needs to be confirmed or if diagnosis still unknown
    - If patient is being considered for
      - Immunosuppression
      - Worsening of clinical/laboratory status (Strong recommendation, low level of evidence), despite suspected drug(s) causing DILI have been stopped, e.g., suspected
        - Hepatocellular DILI, and no peak ALT ↓ by 50% within 1 to 2 mon
        - Cholestatic DILI, and no peak ↓AP by 50% within 6 mon (Conditional recommendation, very low level of evidence)
        - If ↑ALT or ↑AP persist beyond 6 mon (Conditional recommendation, very low level of evidence)
      - Suspected DILI but drug in question cannot be stopped / needs to be restarted (Strong recommendation, very low level of evidence)
  - Algorithm for evaluation (Strong recommendation, low level of evidence)

Abbreviations: AIH, autoimmune hepatitis; ALF, acute liver failure; ASM, anti-smooth muscle; CMV, cytomegalovirus; CT, computed tomography; DILI, drug-induced liver injury; EBV, Epstein Barr virus; HBV, hepatitis B virus; HCV, hepatitis C virus; HEV, hepatitis E virus; HSV, herpes simplex virus; INR, International Normalized Ratio; LT, liver transplant; mon, month; NAC, N-acetyl cysteine

➢ Algorithm

An algorithm to evaluate suspected idiosyncratic drug-induced liver injury (DILI).



- The R-value cutoff numbers of 2 and 5 serve only as a guideline.
- Which tests and their order must be based on the overall clinical picture including risk factors for competing diagnosis (e.g., recent travel to HEV endemic area), associated symptoms (e.g., abdominal pain and fever), and timing of laboratory tests.
  - The R-value may change as the DILI evolves).

Abbreviations: Alk P, alkaline phosphatase; ALT, alanine aminotransferase; CMV, cytomegalovirus; EBV, Epstein-Barr virus; HCV, hepatitis C virus; HEV, hepatitis E virus; HSV, herpes simplex virus; ULN, upper limit of normal

Printed with permission: Chalasani NP, et al. Am J Gastroenterol 2021; 116; 878-98 (Figure 1).

➢ Treatment

- Treat herbal and dietary supplements (HDS) like DILI (Strong recommendation, low level of evidence)
- ↑ ALT / ↑ AP plus ↑ INR, ↑ bilirubin → immediately stop suspected culprit drug(s)/herbs (Strong recommendation, low level of evidence)
- Rechallenge
  - No response to suspected DRI outpatient especially in
    - ALT > 5x ULN
    - Hg law present
    - Jaundice

    } Life threatening situations where there is no suitable alternative (Strong recommendation, low level of evidence)
- Early acute liver failure (ALF) (adults only)
  - N-acetyl cysteine (NAC)
- Late AF
  - Use guidelines for ALF, including possible liver failure (LT)

- **Drug-Induced AIH-Like Disease** (DI-AIH)

➢ Definition

- The patient with suspected AIH must be considered to possibly have drug-induced AIH.
- The patient with suspected DI-AIH must be considered to possibly have AIH.

➢ Demography

- ~10% of patients diagnosed with AIH have drug-induced liver injury (DILI), i.e., drug-associated AIH
  - F > M (as in non-drug associated AIH)

- Causes/associations
  - The drugs associated as being associated with DI-AIH which are classified as having an association which is definite, probably or possible
    - The two drugs used in a gastroenterological practice which are definitely associated with DI-AIH include the anti-TNFα drugs used in persons with IBD, namely adalimumab and infliximab.
  - There is no association of DILI with
    - Other autoimmune conditions
      - HLA DRB1* 03:01, or
      - DRB1*04:01

- Drugs associated with AIH

Association		
Definite	Probable	Possible
○ Minocycline	− Atorvastatin	▪ Atezolizumab (anti-PD-L1)
○ Nitrofurantoin	− Clometacin	▪ Black cohosh (herbal medicine)
○ Infliximab	− Diclofenac	▪ Dai-saiko-to (herbal medicine)
○ Alpha-methyldopa	− Etanercept	▪ Germander (herbal medicine)
○ Adalimumab	− Isoniazid	▪ Ipilimumab (anti-CTLA-4)
○ Halothane	− Propylthiouracil	▪ Nivolumab (anti-PD-1)
○ Oxyphenisatin	− Rosuvastatin	▪ Pembrolizumab (anti-PD-1)
○ Dihydralazine		▪ Tremelimumab (anti-CTLA-4)

  - Latency between drug exposure to acute onset and hypersensitivity
    - 1 wk to 1 yr
      - The exception: minocycline and nitrofurantoin may be > 1 yr

- Laboratory
  - "Hy's law" (scoring system) for DI-AIH
    - ALT or AST > 3x ULN
    - Bilirubin > 2x ULN
    - ▪ ↑ mortality → ↑ need for liver transplantation → indication for corticosteroids (CS)
  - Scoring for DI-AIH plus ALF
    - ALT > 17.3x ULN
    - Bilirubin > 6.6x ULN

    } Performance characteristics for DI-AIH plus ALF diagnosis
      - ▪ Sensitivity 80%
      - ▪ Specificity ~80%
  - US-DILI network (6.6x ULN)

➢ Differential

- Comparison of drug-associated and non-associated AIH.

Characteristic	AIH	DI-AIH
F > M	+	+
Associated autoimmune disorders	+	-
HLA association*	+	-
Acute onset	> 20%	10%
Associated fever, rash	30%	-
Eosinophilia (hypersensitivity)	30%	-
At presentation		
− Cirrhosis	~30%	-
− Centrilobular zone 3 necrosis	+	+
− Bridging fibrosis, Ishak score ≥ 4	+	-

➢ Treatment

- Stop offending drug
- Corticosteroids
  - If Hy's law is satisfied
  - ALT or bilirubin fail to improve when offending drug stopped
  - ↑ ALT/bilirubin or ↑ symptoms at any time
  - Corticosteroid withdrawal and sustained biochemical resolution →
    - Supports likelihood of drug-associated with development of AIH
  - Corticosteroid withdrawal and biochemical recurrence → suggests non DI-AIH → treat longer with corticosteroids +/- azathioprine (as per protocol for AIH)

- Recommendations
  - When the diagnosis of AIH is considered, always think about the possibility of drug-induced autoimmune hepatitis (DILI-AIH).
  - If the clinical/laboratory parameters of the patient with suspected DILI-AIH do **not** improve with the drug withdrawal, or if the patient's condition meets the criteria to diagnose Hy law → use corticosteroids (CS).
    - If the biochemistry improves with use of CS, and then worsen when CS are tapered/withdrawn → suspect AIH.

Abbreviations: 6-MP, 6-mercaptopurine; AIH, autoimmune hepatitis; APRI; AST/platelet ratio index; AZA, azathioprine; BMD, bone mineral density; BMI, body mass index; CS, corticosteroid; d, days; DI-AIH, drug-induced autoimmune hepatitis; ELFT, enhanced liver fibrosis test; ENT, entecavir; F, female; FIB-4, fibrosis 4 index; HBV, hepatitis B virus; HLA, human leukocyte antigen; LDL, low-density protein; M, males; mon, month; MRE, magnetic resonance elastography; po, by mouth; RBC, red blood cell; TAC, tacrolimus; TE, transient elastography; TEN, tenofovir; TG, triglyceride; TNF, tumour necrosis factor; TPMT, thiopurine transferase; ULN, upper limit of normal; VCTE, vibration-controlled transient elastography; WBC, white blood cell; yr, year

Diagnosis and Treatment of Acute Hepatic Porphyrias (AHPs): **AGA Expert Reviews and Clinical Practice Update** (2023)

Wang B, et al. Gastroenterology 2023; 164: 484-491

- Definition
  - "… inherited disorders in the heme biosynthesis due to mutations that lead to partially defective activity in heme synthesis enzymes"
    - Three of ACPs are autosomal dominant
      - Only ALAN (5-aminolevuline acid dehydrate, ALAD) is autosomal recessive

- Demography
  - Sympathetic
    - Acute hepatic porphyria $1/10^5$
    - W > M (except ALAD, M < F) age 15-50 yr
    - Commonest acute hepatic porphyria acute intermittent porphyria (AIP)

- Types

- Acute Hepatic porphyria (AHP)
  - Acute intermittent porphyria (AIP)
    - Gene abnormality, HMBs
  - Variegate porphyria (VP)
    - Gene abnormality, PPOX
  - Hereditary coproporphyria (HCP)
    - Gene abnormality, CPOX
  - 5-aminolevulinic acid dehydrase (ALD)
    - Gene abnormality, ALAD (≥ 4 /yr)

- Pathophysiology
  - As a result of the genetic mutations which occur in AHPs, and the ~50% reduction in the corresponding heme synthesis enzymes, there is accumulation of the "…specific intermediates that accumulate before the defective enzymatic step"
  - The abnormalities in the enzymes
    - Hydroxymethylbilane synthase (HMBs)
    - Coproporphyrinogen oxidase (CPOX)
    - Protoporphyrinogen oxidase (PPOX)

- Clinical
  - Neuromuscular
    - Muscle weakness
    - Neuropathy
  - Cardiovascular
    - Tachycardia
    - hypertension
  - GI
    - Severe, recurrent abdominal pain
    - Nausea/vomiting
    - Constipation
    - Hepatocellular cancer (HCC)
  - GU
    - Chronic renal failure
  - Skin manifestations
  - The four non-AHPs have autonomous manifestations

Clinical Gem

- Consider diagnosis of AHP in young women with "…unexplained recurrent severe abdominal pain" especially if there is a positive family history.
- Precipitating factors
  - Menstrual cycle, lacteal period
  - Drug* (porphyrinogenic medications)
  - Alcohol
  - Acute illness
  - Fasting
  - Smoking
  - Age 15-50 yr with unexplained, recurrent severe abdominal pain "…without a clear etiology" Best Practice Advice screen for an AHD in women

  - Phenotypic penetrance in
    - Asymptomatic AIP (AA) carries ~1%
    - Families with a symptomatic AHP members, 20%

➢ Laboratory

- ALA/PBC
  - In the AHPs, AIP, HCP and VP
  - ↑ blood/spot urine samples (concentration of creatinine to normalize to urine)
    - ↑ ALA (alpha-aminolevulinic acid)
    - ↑ PBG (porphobilinogen)

    ▪ Urine ALA/PBG > 10 mg/g creatinine
  - ↑ ALA / ↑PBG may be seen in asymptomatic patients
  - Ideally measure the ALA, PBG during an attack, but measurements may remain abnormal for > 1 yr afterwards

MCQ Gem

- Usually in AHP there is ↑ urine ALA and PBG
  - If AHP is suspected and there is ↑ urine ALA, but normal PBG → measure urine organic acids to exclude
    - Lead poisoning
    - Hereditary tyrosinemia

Best Practice Advise

- In the suspected with AIP, measure ALA< PBG and creatinine in a random urine sample
  - If the ALA plus PBG are both increased, perform sequencing for

AVP	Gene
AIP	HMBS
ACP	CPOX
VP	PROX
ALAD	ALAD

➢ Treatment

- Hemin, Carbohydrate, Givosiran
  - Give hospitalized patients with AAP hemin 3-4 mg/kg body weight (a heme bound to human serum albumin) daily for 4 d into a high-flow central vein (peripheral inserted central catheter / central part)
    - Hemin
      - Give early to ↓ risk of long-term neurological complications
      - Symptoms of AHP attack decrease in 2-3 d
    - Complications to manage
      - Abdominal pain
      - Nausea/vomiting in hypertension
        - Tachycardia
        - ↓ Na^{+}_{s}, ↓ Mg^{2+}_{s}
      - Depression, anxiety
    - Carbohydrate loading, 300 g early attack of AHP

SO YOU WANT TO BE A GASTROENTEROLOGIST!

- Fasting may induce an attack of AHP, and carbohydrate loading may ↓ symptoms; give the mechanism
  - Fasting → ↑ PPAR α coactivator 1α → ↑ ALAS1 → ↑ ALA / ↑ PBG
  - Carbohydrate load → ↓ PPAR → ↑ ALAS1 → ↓ ALA / ↓ PBG

- Avoid identifiable triggers of AHP
- ↓ frequency of acute attacks with
  - Hemin IV given prophylactically (may screen for secondary iron overload)
  - Givosiran
    - Interfering RNA linked to N-acetyl galactosamine and given subcutaneously (SQ)
    - Taken up by hepatocytes → single strands → bind to ALAS1 messenger RNA → ↓ translation of ALAS1 / ↓ ALA production

- Liver Transplantation
  - Related
    - Living donor screen for AHP
  - Non-related donor transplantation
    - Curative in 90%
    - Survival rates
      - 1 yr, 92%
      - 5 yr, 82%
    - Poorer outcomes in patients with AHP plus baseline neuropathy +/- renal dysfunction

➢ Follow-up
  - Liver
    - Iron overload: serum ferritin
    - HCC / CCA (cholangiosarcoma)
      - May occur in the absence of severe fibrosis / cirrhosis
      - Perform abdominal ultrasound q6mon at ≥ 50 yr
  - Kidney
    - Hypertension, 43%
    - Chronic kidney disease, 29%
      - May require kidney transplantation
    - Porphyria-associated kidney disease

Hereditary Hemochromatosis (HH): **ACG Clinical Guidelines** (2019)

Kowdley KV, et al. Am J Gastroenterol 2019; 114: 1202-1218

Please also see: Brissot P, et al. Nat Rev Dis Primers. 2018; 4:18016
Fitzsimons EJ, et al. Br J Haematol 2018;181(3):293-303

➢ Definition
  - "An inherited iron overload disorder characterised by excessive [intestinal] absorption of iron, sue to the deficiency of [normally effective] hepcidin"

➢ Pathophysiology

- Iron absorption
  - Body iron stores (BIS) are regulated by modifications in the proximal intestinal absorption of iron
    - Through/by means of inverse regulation by functionally normal hepcidin
  - Stomach
    - Breakdown in dietary non-heme iron (Fe^{2+}) in the presence of gastric HCl and pepsin activated from pepsinogen
    - Fe^{3+} is further reduced to Fe^{2+} by brush border membrane (BBM) ferric reductase
    - Solubilization of the Fe^{2+} is enhanced by some dietary components, such as ascorbic acid, and is decreased by phytates for example
  - Duodenocytes
    - BBM dimethyl transferase 1 (DMT1) actively transporters Fe^{2+} into the cytosol of the duodenocytes
    - Some Fe^{2+} binds to apoferritin to form ferritin in the cytosol
    - Fe^{2+} which is not bound to ferritin traffics to the basolateral membrane (BLM)
    - Fe^{2+} binds to BLM ferroprotein 1 (FPN 1) which transports the Fe^{2+} across the BLM, and the BLM, and is delivered to BLM ferric oxidase, hephaestin, from Fe^{2+} to Fe^{3+}
    - Fe^{3+} released from hephaestin and binds to transferrin 1 (TFN1) in the plasma
    - Fe^{3+} TFN-1 delivers Fe^{3+} to
      - Bone marrow for erythropoiesis, or
      - The hepatocytes to feedback on the production of hepcidin

- Hepcidin
  - The concentration of hepcidin produced is dictated by the amount of Fe^{3+} on
    - TSN1 and TFN2
    - Body iron stores

    } ▪ Hepcidin concentration
  - With ↓ BIS, there is ↓ hepcidin (Hep) and ↑ ferroportin (FPN) in the BLM there is also ↑ DMI 1 so there is ↑ uptake of iron into the cell (BBM) as well as ↑ exit by FPN1 (BLM)
  - Thus with ↑ BIS, Fe absorption is by there being ↑ hepcidin and thus more FPN1 in the BLM (↑ exit) rather than ↑ Fe storage in duodenocytes
  - With ↓ BIS, Fe absorption increases because there is ↓ hepcidin, ↑ FPN in BLM, ↑ exit across BLM

- Inverse
  - ↓ BIS (iron deficiency)
  - Bleeding/anemia
  - Inflammation
  - Hypoxia

    ▪ ↓ hepcidin → ↑ Fe absorption
  - HH (inappropriately ↓ hepcidin related to ↑ transferrin saturation (TS), ↑ body iron stores (BIS)
  - Hepcidin also stores Fe in cytosol of microphages
  - With ↓ hepcidin, there is
    - ▪ ↑ FPN in BBM / ↑ iron exit (absorption), plus
    - ▪ ↑ exit of iron stored in macrophages
- Fe^{3+} in plasma binds to transferrin 1 (TFN1), then some to TFN2 bone morphogenic protein (BMP) and SMAD proteins, plus the ratio of TFN1-Fe to TFN2-Fe serve as the sensors of body iron stores
- Normal, with ↑TS / ↑BIS → hephaestin → ↓ iron absorption
  - In HH, there is ↑BIS but ↑ iron absorption, despite hepcidin, but because of the incorrect sensing of BIS from the defective instruction of the genetically altered hephaestin with the sensing system for body iron stores, the ↑ stores are incorrectly associated with ↑ absorption

➢ Classification of hereditary hemochromatosis

Type	Gene	TS	SF	↑BIS	Hepcidin
• Autosomal dominant					
○ Hereditary hemochromatosis (HH)					
− 1A	C282Y homozygote	↑	↑	+	↓
− 1B	C282Y, plus compound heterozygote	↑	↑	-	↓
	H63D	↑	↑	+	↓
− Type 1C	S65C	↑	↑	+	↓
○ Juvenile (HH)					
− 2A	Hemojuvelin (HJV)				↓
− 2B	Hepatic antimicrobial problem (HAMP) (iron reflux from RBC)			+++	↓
○ TFR2 disease					
− 3	Transferrin receptor 2 (TFR2)				↓
• Autosomal recessive					
○ FPN disease					
− 4A	↓ function of ferroportin (FPN)	N/↓	↑	+	N
− B	↓ internalization of FPN (resistance to hepcidin)			+	

Abbreviations: SF, serum ferritin; TS, transferrin saturation

➢ Demography

- HH type 1A
  - HH type 1A ↑TS +/- SF Men, 75% Women, 50% } US

➢ Screening of HH type 1A

- Do **not** screen for HH in general population
  - Autosomal positive, but
    - Wide range of prevalence of C282Y gene
    - Low penetrance of genotype to phenotype
    - Clinical manifestation of HH rarely present before age 18
      - Can delay screening until then
- Screen first-degree relatives of patients with HH (HFE gene testing or TS)

Recommendation

- Screen for HH in family of patients with HH, especially first-degree relatives (Strong recommendation, moderate degree evidence)

➢ Secondary iron overload

- Chronic liver diseases
  - Alcohol use disorder (AKD)
  - Dysmetabolic iron overload syndrome
  - HBV, HCV infection
  - Hepatocellular cancer (HCC)
  - Non-alcoholic liver disease (NAFLD)
  - Prophyria cutanea tarda (PCT)
- Hematology
  - Chronic anemias
  - RBC transfusions
  - Iron infusions/injections
- Renal
  - Chronic renal disease
  - Hemodialysis
- Malignancy
  - Breast
- Chronic inflammation
  - Muscular skeletal / rheumatological disease

- Examples
  - Alcohol (PUD)
    - ↑ TS, ↑ SF, ↓ hepcidin (alcohol-induced down regulation of the transcription factor regulating the expression of hepcidin

- Non-alcoholic fatty liver disease
  - ↑ TS, ↑ SF, ↑ TS, plus ↑ SF,
  - ↑ SF, NS1
    - T2DM → insulin resistance → ↓ hepcidin (dysmetabolic overload syndrome [DOS] aka insulin-resistance hepatic iron overload syndrome [IR-HIO])
  - HCV infected patients who are heterozygous for HFE mutations
- HCV infection
  - ↑ TS, ↑ SF, ↑ SI in 30%
  - ↑ Fe in Kupffer cells of reticuloendothelial system (RES)

➢ Clinical

- CNS
  - Fatigue
  - Parkinsonism
    - Chorea
    - tremor
- Skin
  - Bronze color in HH
  - Iron in skin → ↑ melanin production/deposition hyperpigmentation (grey/bronze) on
    - Face, neck
    - Lower forearms, extensor surfaces
    - Dorsa of hands
    - Lower legs
    - Genital region
- GI tract
  - Iron overload → dysregulation of CD8+ T cell → ↑ growth of some enteric bacteria
    - Escherichia coli
    - Listeria monocytogenes
    - Yersinia enterocolitica
    - Vibrio vulnificus
- Joints
  - Arthralgia/arthritis
    - Symmetrical, mono-/polyarticular
  - Hands
    - Proximal interphalangeal joints
    - Metacarpal head, hook-shaped osteophytes
  - Arms
    - Wrist, elbow, shoulder
    - Osteoarthritis
    - Calcium pyrophosphate deposition disease (CPPD)
  - Hips
  - Differential
    - Osteoarthritis
    - Calcium pyrophosphate deposition disease (CPPD)

Joints	CPPD	HH
− MCP joints involved	-	+
− Metacarpal head hook-shaped osteophytes	-	+

- Heart
  - Arrhythmias
  - Cardiomyopathies (restrictive, dysfunction)
  - Heart failure
  - Suden cardiac death (SCD)
  - Risk of cardiomyopathy in HH, 3%
  - Death from HH cardiomyopathy ~1%, usually in those with SF > 1000 mg/mL
- Liver
  - Often family-related genetic screening, or
  - Symptomatic ↑ALT/ ↑AST
  - Non-specific
    - RUQ pain
    - Fatigue
  - Consumption of alcohol
    - >60 g/d → ↑ development of symptoms/cirrhosis
    - > 80 g/d → ↑ mortality
  - ↑ iron overload with alcohol plus smoking
  - Untreated HH in men ~10% develop cirrhosis
    - HCC in cirrhosis HCC develops in 6% - 10%
  - Complications of cirrhosis, including HCC
    - HCC deaths occur in 45% of persons with HH-associated cirrhosis

Management Tips

- In the patient with HH
  - If SF > 2000 ng/ml
    - ↑ risk of HCC
- Patients who have HH
  - Cirrhosis which is treated by phlebotomy
  - ↓ risk of HCC< but
    - Continue ultrasound surveillance q6-12 mon after excess iron is removed: HCC can develop “years after successful iron depletion”
- Patients with advanced fibrosis may have ↑ risk of HCC even before development of cirrhosis
  - HBV, HOV, NAFLD, ALD, PBC, but
  - It is unknown whether patients with HH with stage 3 fibrosis are at increased risk of HCC.

Recommendations

- Do **not** do routine HCC surveillance for patients with HCC with stage 3 fibrosis cirrhosis (Conditional recommendation, very low quality of evidence)

- Endocrine
  - Diabetes
    - Prevalence
      - Overall, 13% - 25%
      - Type 4, 25%

    − Iron in pancreas drainage islet cells
    − Liver injury → hepatic resistance to insulin
  - Hypogonadism
    - Iron deposition in pituitary gland
  - Hypothyroidism, M > F
    - Men impotence / ↓ libido
    - Women amenorrhea promotes menopause
  - Osteoporosis in HH, 25%

➢ Laboratory

- Standard iron tests
  - Serum iron (SI)
  - Transferrin (TS)
    - > 45% identifies 98% - 100% of C282Y homozygotes
  - Serum ferritin (SF)
    - May be ↑ despite normal TS, especially in non-HFS related iron overload
    - Predicts advanced fibrosis, but poor performance characteristics fir HH screening
    - In C282Y homozygotes
    - Better test than HIC to predict fibrosis
  - Unsaturated iron binding capacity (WIBC)
    - I/TS equivalent value as TS to screen for HH
  - WIBC < 26 µmol/L, detection of HH
    - SF > 1,000 mg/mL, ↑ALT, ↓ platelets correctly predict HH in 80%
    - SF when normal (men < 360 ng/mL, < 200 mg/mL in women [postmenopausal]), TS < 45% excludes HH, NPV 97%

- Genetic testing
  - Othe MHC-class I -like HFE genes
    - C282Y (83% of HH)
    - H63D (20% have ≥ 1 copy)
    - S65C

    ▪ Neither the homo- or heterozygotes cause pathologically import iron overload (without C282Y allele)

Recommendations

- Tell screened persons with H63D or S56D or S65C alleles (in the absence of C282Y) that they are not at risk of iron overload (Conditional recommendation, very low quality of evidence)
- In atypical patients with iron overload, such as younger patent presenting with endocrine or cardiac involvement, consider testing for non-HFE genes, such as those encoding
  - Hemojuvelin
  - Hepcidin
  - Transferrin receptor 2 (TFR2)
  - Ferroportin (FPN)

- Magnetic resonance imaging (MRI)
  - T2-weighted imaging
    - ↑ liver Fe → ↓ signal in proportion to the signal in the liver, as compared to signal in the liver, as compared to signal in the infected spleen (as in HH)
    - The actual result reflects the hepatic iron content (HIC)
    - MRI HIC (T2 spin echo, T2* gradient-recalled echo) is best to exclude rather than to include the diagnosis of HH, or
      - Positive predictive value (PPV), 0.74-0.81
      - Negative predictive value (NPV), 0.83-0.88

MCQ Pearl

- Give the use of MRI to distinguish iron overload from HFE-, and ferroportin (FPN) disease or secondary iron overload.
  - Spleen iron (reticuloendothelial system, RES)
    - ↑ FPN disease, iron overload

- Liver biopsy
  - Stage fibrosis, especially in C282Y homozygotes with SF > 1000 ng/mL
    - If C282Y homozygotes with SF < 1000 ng/mL, do **not** do liver biopsy (risk of fibrosis/cirrhosis < 2%)
      - Unless there is a second risk factor for fibrosis/cirrhosis such as HBV, HCV, AUD, NAFLD
  - Stain liver biopsy
    - Hematoxylin and eosin (H&E)
    - Masson's trichome to stage fibrosis
    - Perl's Prussian blue stain to stage iron overload, and to determine if iron is mainly in the hepatocytes (HH) or in the RES (Kupffer cells)

- Measurements of hepatic iron
  - Hepatic iron content (HIC)
  - Hepatic iron index (HII); HIC (patient's age, yrs) homo- from compound heterozygotes helps distinguish HH C282Y
  - HIC also useful to predict long-term risk of developing, cirrhosis in persons with iron-loading anemias (HIC is a surrogate measure of total body iron stores [BIS])
  - Predict whether patient with HH is homozygous or those with secondary iron overload heterozygous, or homozygous
    - HIC > 71 µmol/g dry weight
    - HII ≥ 19

    } > values in homozygotes than in heterozygotes / secondary iron overload

- Distribution of iron in hepatocytes is Kupffer cells
  - In HFE-related HH
    - Initially in HFE-related HH is in periportal hepatocytes
    - Progresses from
      - Periportal to midzone → centrilobular
      - Into biliary epithelium
  - In secondary iron overload
    - Irons in Kupffer cells / RES cells
    - Little iron in periportal hepatocytes
    - Lack of gradient from periportal hepatocytes
    - Lack of gradient from periportal to centrilobular hepatocytes
- Transient elastography (TE)
  - Not yet validated to assess fibrosis stage in HH
  - Initial data suggests that in HH, TE does not correlate with value of SF

Recommendations

- Measure HIC with MRI
  - Fibrosis with liver biopsy

  (Conditional recommendation, low quality evidence)

➢ Screening (from Fitzsimons EJ, et al. Br J Haematol 2018;181(3):293-303)

Recommendation

- For patients with confirmed [HH] cirrhosis with α-fetoprotein (AFP)…and hepatic ultrasound every 6 mon

➢ Treatment

- C282Y homozygotes
  - When TS ≥ 45%, plus SF
    - Men, > 300 ng/mL
    - Women, > 200 ng/mL

- When SF normal
  - Surveillance with ALT/ASF and SF
- When SF > 1000 ng/mL, there is likely already organ damage, but
  - Phlebectomy is recommended at lower levels of SF (men, > 300 ng/mL; women SF > 200 ng/mL) because in time, the SF will increase and be associated with multiple organs, with ↑ risk of progression (man, 13% to 35%; women, 16% to 22%) to SF > 1000 ng and cirrhosis/HCC, cardiovascular complications, extrahepatic cancer
- Early phlebectomy at these lower levels of SF has multiple benefits
  - ↑ quality of life (QoL)
  - ↓ fatigue
  - ↓ mortality from
    - CV events
    - Extrahepatic cancers

- C282Y/H63D compared heterozygote, H63D homozygotes
  - Iron overload is rare unless associated
    - Alcoholic use disorder (AUD)
    - Non-alcoholic liver disease (NAFLD)
    - Type 2 diabetes mellitus (T2DM)

- H63D homozygote
  - In these patients, especially if SF > 1000 ng/mL
    - Perform liver biopsy to determine
      - Stage of fibrosis
      - Hepatic iron content (HIC)
      - HIC, consider phlebotomy

- Types of treatment
  - Phlebotomy
    - 250 mL packed red blood cells (PRBC) remove 250 µg of iron
    - Repeat phlebotomy as tolerated by patient (suggested q1-2 wk)
    - Stop phlebotomy when SF at upper limit is normal (~50 ng/mL)
    - Phlebotomy to maintain SF at this level (usually repeat maintenance phlebotomy q3-4 mon
    - Some patients with advanced liver disease from HH cirrhosis do **not** tolerate phlebotomy
  - Diet
    - Some nutritionists suggest reducing/avoiding vitamin C (vitamin C increases iron absorption)

- Benefits
  - ↓ fibrosis in persons with initial mild/moderate fibrosis
  - ↓ risk of HCC
  - ↓ skin bronzing
  - ↓ arthralgia, but not arthropathy
- No benefit
  - Cirrhosis
  - Arthropathy
  - Diabetes
  - Cardiomyopathy
  - Hypogonadism

Recommendations

- Phlebotomy is first-line therapy in patients with HH and
  - C282Y
  - C282Y/H63D

  (Strong recommendation, moderate quality of evidence)
  - Key concept
    - Goal of phlebotomy is to maintain SF between 50-100 µg/L

- Chelation therapy for secondary iron overload
  - These are not used in patients with HH because of the only modest amounts of iron removed and removal is slow and in HH the objective is to remove excess iron before it causes AEs

Name	Route	Dose	Indications	Adverse Effects (AEs)
– Deferoxamine	SC/IV	20-60 mg/kg per day (IV, over 8-24 h, 5-7 d per wk)	Thalassemia	Retinopathy Auditory toxicity
– Deferiprone	PO	75-100 mg/kg per day, t.i.d.	▪ Thalassemia transfusion-dependent to supplement incomplete response to deferoxamine	Agranulocytosis Neutropenia
– Deferasirox	PO	5-15 mg/kg per day	▪ HH, patients who are intolerant/ refractory to phlebotomy or ▪ Phlebotomy harmful (patient with severe anemia or heart failure	Skin, rash GI, upset Liver, ↑ALT/↑AST Kidney, ↑Crs (serum creatinine) (10%)

Recommendations

- Do **not** use chelation therapy in HH as first choice (Strong recommendation, low quality evidence)
  - Do use chelation therapy in the patient with
    - HH, intolerant/refractory to phlebotomy
    - Severe anemia
    - Heart failure

    } Potential for phlebotomy to be harmful (Strong recommendation, low quality evidence)

- Erythropheresis
  - Selective removal of 350-800 mL RBC every 2-3 wk, maintaining post-procedure hemoglobin > 10 mg/dL
    - If > 500 mL removed at one setting, replace give 0.9% saline in a volume which represent 30% of the volume of RBC removal (i.e., 30% x 500 mL = 150 mL 0.9% NaCl)
  - Adverse effects (rare)
    - Citrate present in the exchange fluid
      - Nausea
      - Muscle cramps
      - Paresthesia
  - May be used in place of membrane removal of iron by phlebotomy
  - Pantoprazole 40 mg/d given to C282Y homozygote patients with HH reduced the number of maintenance phlebotomy required
    - Use only in selected patients with HH
  - Do **not** use PPIs as primary therapy for HH (Strong recommendation, low quality of evidence)

- Secondary Iron Overload
  - Use chelation therapy or phlebotomy
    - Begin treatment due to
      - Excess transfusion, SF> 1000 ng/mL
      - Non-transfusion-dependent iron-loading anemia, when SF > 800 ng/mL (SF underestimates HIC in BTDILA ng/mL

- Other hepatic cause of secondary iron overload
  - AUD
    - Control the ALD
    - Not just the iron overload
  - HDV
    - Phlebotomy improves unlogical response to interferon-based therapy
    - When using directly acting (non-interferon) therapy, viral response is so effective that phlebotomy is not necessary
  - NAFLD
    - Phlebotomy reduces the elevated SF, but controversial whether the NAFLD is improved

- Liver transplantation (LT)
  - Useful for ↑ MELD score
    - Associated cirrhosis or HCC
    - Survival
      - No cirrhosis
        - Similar to other types of liver disease
      - Cirrhosis
        - Reduced survival due to
          - ↑ CV disease
          - ↑ infections
  - Because transplanted liver would not be producing defective hepcidin (as in HH), the reduced hepcidin level pre-LT would be restored to normal, and iron balance would become normal post-LT.
  - Continue phlebotomy up to the time of LT, but
    - Do **not** defer LT until after all excess Fe is removed by phlebotomy/chelation

Recommendation

- In patients with HH-associated decompensated cirrhosis/HCC plus an appropriate MELD score consider liver transplantation (Strong recommendation, low quality of evidence)

NONINFECTIOUS PRECIPITATING FACTORS

- Alcohol-associated hepatitis (AAH)

Recommendations:

- In patients with severe alcohol-associated hepatitis (AAH; Maddrey discriminant function [MDF] ≥ 32; MELD score > 20)
  - In the absence of contraindications, use of prednisolone or prednisone (40 mg/d) orally to (improve 28-d mortality) (moderate quality, strong recommendation).
  - Do **not** use of pentoxifylline to improve 28-day mortality (very low quality, conditional recommendation).

Key Concept Statements:

- AAH leads to ACLF because of
  - Severe SIRS and
  - Sepsis.

➢ Clinical

- Acute alcohol-associated hepatitis (AAH)
  - Duration of alcohol use is required to get AAH not well defined
  - Usually heavy alcohol use for years but can be heavy
- ACLF
  - Active alcohol use
  - Alcohol-associated hepatitis (AAH)
  - Bacterial infections
- Jaundice
- Malaise
- Tender hepatomegaly
- Decompensation
  - Ascites
  - Hepatic encephalopathy (HE)

➢ Laboratory

- Bilirubin > 50 µmol/L
- AST > 50, AST:ALT: 1.5
- Maddrey score > 32 (severe)

➢ Scoring system

- MELD, AIBC, Glasgow alcoholic hepatitis score (GAHS) → superior to Maddrey score

➢ Treatment

- MGMT
  - Prednisolone
  - Do **not** use pentoxifylline (no improved survival when combined with corticosteroids)
- STOPAH trial
  - Multicentre, randomized double blind trial (pentoxifylline and prednisolone for AAH)
  - MELD < 25
    - Prednisolone associated with ↓ 28-d mortality, but not significant, no improved outcomes at 90 d or 1 yr
    - Pentoxifylline did not improve survival in patients with AAH
  - MELD > 25
    - No improvement at day 28 with prednisolone
  - Multiple other large meta-analyses and studies
    - Demonstrated improvement in short term (28 d) mortality with corticosteroids
  - Best predictor of mortality at 2 and 6 mon
    - A combination of MALD at baseline and Lille score at 7 d
  - Survival beyond 6 months only associated with abstinence from alcohol
  - LT may be considered in highly selected patients
- Drug-induced Liver Injury (DILI)

Key Concept Statements:

- DILI
  - Causes by both prescribed and nonprescribed medications can cause drug-induced liver injury (DILI).
    - The most common prescribed medications that cause DILI, the antimicrobials.
    - Self-medication with complementary and alternative medicine (CAM) is common, spreading often through social media.
- DILI is often underreported, and most patients have an uneventful recovery.
- Most common type of DILI acute liver failure (ACLF)
  - Formal studies in patients with pre-existing liver cirrhosis are lacking.
  - Estimated incidence in
    - Asia, ~10%
    - United States, ~7%.
- DILI in the setting of advanced liver disease ↑ risk of poor outcome.
- When DILI causes ACLF usually occurs on average 1 mon after taking the offending medication, but
  - Can be delayed for up to 3 months.

- Mortality in DILI-related ACLF is >50%
  - Predictor of mortality is the ACLF grade
- ACLF ≥ grade 2 → ↑ mortality
- Key to the prevention of DILI-associated ACLF
  - Limiting use of pharmacological agents
  - Avoiding use of complementary and alternative medicine (CAM)
- Monitor liver enzymes when new medications with hepatotoxic potential are given to patients with liver disease.

- Viral Hepatitis

Key concepts statements:

- In patients with underlying liver disease (A, B, C, D+B, E) may lead to
  - This may occur from acute disease flares, suddenly stopping antiviral drugs, superinfection, or disease progression.
    - Also, in patients with a viral hepatitis, a bacterial infection may trigger the onset of ACLD.
- All patients with chronic liver disease need to be vaccinated against HAV and HBV, unless they are not already immune.
- Vaccinate patients with chronic liver disease against hepatitis A and hepatitis B.

- Surgical Procedure

Key concepts statements:

- Surgery of any type in patients with cirrhosis is associated with significant risks of organ failure and ACLF development when compared with patients without cirrhosis.
- In patients with cirrhosis contemplating surgery, both the Mayo Clinic score and the VOCAL PENN score are available on-line for calculating the risks of mortality with surgery.

- Non-surgical Interventions

Key Concept Statements:

- Incidence of ACLF after non-surgical intervention is unknown, but
  - ERCP associated with ↑ risk of CLD in the patient with sever liver disease
  - Always consider the risks and benefits of any procedure
  - Follow standard of care close monitoring of patients in the post-procedure period
- ERCP-associated complications ~11%, especially if MELD > 15
  - Renal replacement therapy (RRT) also a common post-procedure risk of ACLF

- Critical Care Management

Key concept statements

- Use a multidisciplinary team (for example, including ICU, transplant hepatology) for patients with ACLF
  - Goals of therapy
    - Reverse causes of ACLF
    - Treat ACLF, e.g.
      - SIRS
      - Sepsis
      - HE
      - AKI
    - Liver transplantation, where appropriate
    - Quality of life if ACLF survived

Suggested Algorithm for the critical care management of acute-on-chronic failure in cirrhosis

- Goal-directed therapy
- Broad-spectrum antibiotic administration within 1 h of presentation
  - Empiric vancomycin plus meropenem recommended for septic shock
- Monitoring of tissue oxygenation
- Support of failing organs

- Hepatic encephalopathy grade III, IV → Airway protection
- Hypoxemia $PaO_2 \leq 80$ mm Hg → Chest X-ray CT: Evaluation for HPS, therapeutic para/thoracentesis as needed; FIO_2, and consider ventilation
- Hypovolemia → Volume challenge, using echocardiogram monitoring
- Hemoglobin < 7 g/dL → Transfuse PRBC to Hgb > 7 g/dL or > 9 g/dL with cardiovascular risk factors
- MAP < 60 mm Hg (see septic shock) → Assess volume; Evaluation for GI bleeding; Sepsis evaluation

- Sepsis Evaluation
  - Investigations →
    - Paracentesis, culture blood, ascites, urine
    - Chest x-ray
    - ↑ serum lactate
      - ↓ hepatic clearance
      - ↑ tissue hypoxia

      (more likely cause of lactate continues to ↑
  - Treat infection →
    - Vancomycin 15 mg/kg q6h, plus meropenem 1 g q8h
    - Antifungal therapy if inadequate response in 48 h
  - General measures →
    - Fluid resuscitation within 3 h
    - Therapeutic paracentesis
    - Aspiration precautions
    - DVT prophylaxis
    - Stress ulcer prophylaxis
  - MAP < 60 mm Hg
    - Septic shock →
      - Norepinephrine infusion
    - Persistent shock →
      - Hydrocortisone 50 mg q6h

Adapted from: Bajaj, JS, et al. Am J Gastroenterol 2022; 117(2): 225-252 (Figure 5)

- Nutrition

Recommendations

- Use parenteral nutrition, enteral nutrition, or oral supplements in hospitalized patients with cirrhosis to improve mortality.

Key concept statement

- Use enteral nutritional with caution in all patients with ↑ risk of aspiration e.g., cirrhosis patients with hepatic encephalopathy

Evidence:

- There are no clinical trials evaluating use of nutrition in ACLF.
  - Use published guidelines for critically ill patients
    - 30-40 cal/kg body weight/day
    - Protein 1.2-2.0 g/kg body weight/day

❖ Specific Treatments

- Albumin

Recommendation

- In hospitalized patients with cirrhosis
  - Do **not** use daily albumin to maintain the serum albumin >3 g/dL to, including do **not** use to ↓ mortality, prevent renal dysfunction/infection (moderate quality, strong recommendation).

Key concept statements

- Use IV albumin in patients with SBP to
  - ↑ risk of AKI and subsequent organ failures in patients diagnosed with SBP.
- Do **not** use IV albumin to prevent organ failures in patients with cirrhosis who have infections other than SBP.
- Preparations
  - Rapid volume expansion, 5% albumin
  - Maintenance of normal volume expansion, 25%
  - Because of osmotic effect, IV albumin expands to volume by ~4x the actual volume infused, but will be slower correction for 25% than for 5%
  - Carefully monitor patients for
    - Pulmonary edema
    - Respiratory infections

INTERVENTIONS OTHER THAN TRANSPLANT OR SPECIFIC ORGAN SUPPORT

- Liver-assist Devices

Key concept statements

- Plasma exchange ↑ survival in patients with ALF
  - Roles of plasma exchange in ACLF is unknown
- It is not clear if artificial liver support systems +/- biological component provide any clinical benefit.

Evidence:

- Artificial extracorporeal systems remove water-soluble and albumin-bound toxins through “albumin dialysis”
  - Not approved for clinical use (no strong evidence they are useful)
- Improvement in short-term survival demonstrated with PLEX in patients with HBV infection and ACLF.

- Granulocyte Colony-stimulating Factor (G-CSF)

Recommendation

- Do **not** use G-CSF in patients with cirrhosis and ACLF (very low evidence, conditional recommendation).

Key concept statement

- The impact of G-CSF may vary according to precipitating ACLF factors or other unmeasured confounders.

Evidence:

- Two non-randomized clinical trials from India and China showed that G-CSF ↓ short-term mortality in patients with ACLF.
  - Predominantly patients with HBV reactivation or alcohol-associated hepatitis without sepsis
- An interim European RCT did not demonstrate benefit from G-CSF
- Cannot be routinely recommended

- Stem Cell Therapy (SCT)

Key concept statement

  - Stem cell therapy represents a novel and promising therapeutic strategy to bridge patients with ACLF to more definitive therapy (e.g., control of acute infection, LT), but evidence to support its use in routine clinical practice is currently insufficient.

Evidence:

  - Meta-analysis of 4 RCTs and 6 non-randomized clinical trials:
    - SCT ↓ bilirubin, ALT, albumin, and MELD score at 12 mon of therapy evaluate outcome of mortality
    - Did not but not in INR

- Transplant vs. Futility for ACLF

Recommendations

  - In patients with cirrhosis and ACLF who continue to require mechanical ventilation due to adult respiratory distress syndrome (ARDS) or to brain-related conditions despite optimal therapy
    - Do **not** for LT to improve mortality (very low evidence, conditional recommendation).
  - In patients with end-stage liver disease admitted to the hospital
    - Consider early goals of care discussion and
    - Referral to palliative care (if appropriate) to improve resource utilization (very low evidence, conditional recommendation).

Evidence:

  - Controversy as to whether ACLF by itself should provide extra MELD points towards consideration for liver transplantation (LT)
    - Some patients retroactively labelled as ACLF have had acceptable post-LT outcomes
    - UNOS data showed that patients with ACLF, EASL-CLIF3, did well after transplant, but
      - Not those on mechanical ventilation
    - NACSELF prospective analysis showed that patients who had ACLF before LT had acceptable outcomes after LT
    - There may be selection bias towards transplantation only “the best” of ACLF-3 patient
  - UNOS analysis has shown that MELD-Na underestimates 1 and 3 mon mortality risk in ALCF patients
    - ACLF patients at disadvantage with respect to receiving timely LT in a traditional MELD-based allocation

CHOLECYSTITIS

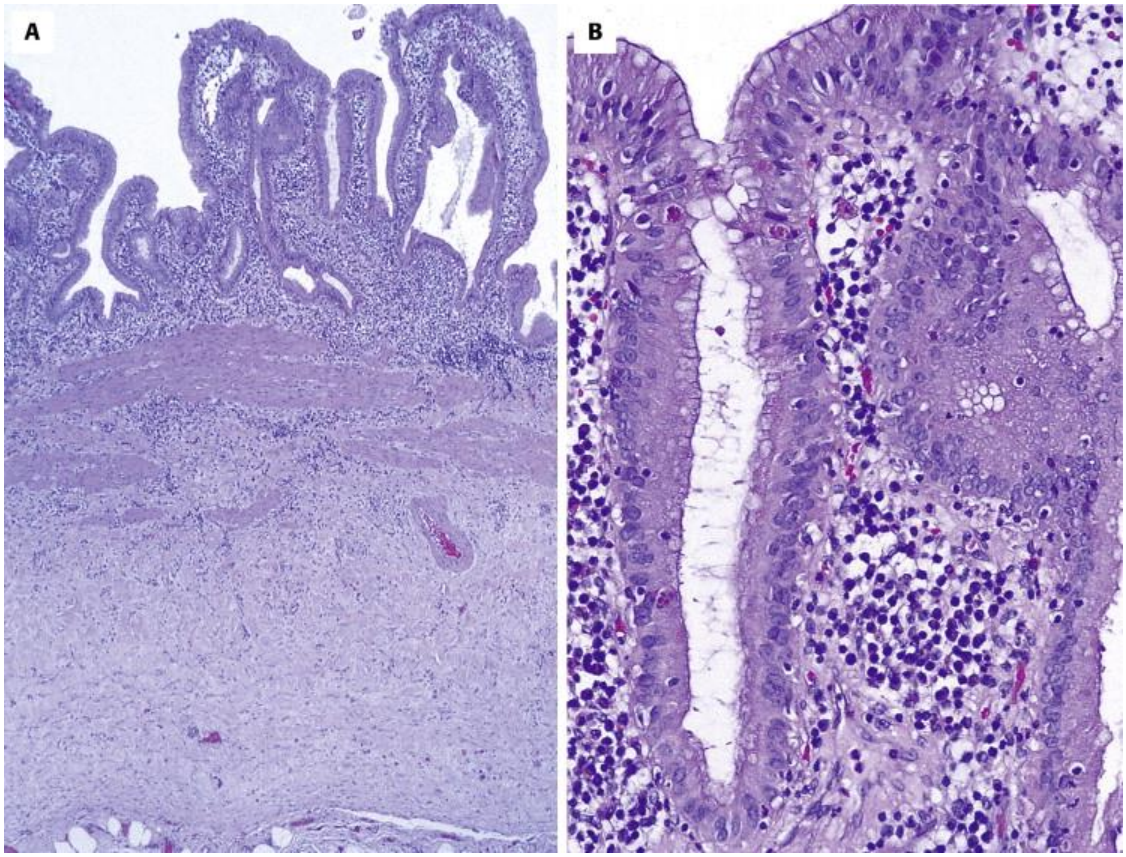
- The pathohistological features of different types of chronic cholecystitis.
  - Inflammation

Types	Minimal	↑ xantomatous macrophages	↑ eosinophils	Lymphocytic infiltration	Fibrosis	Muscular hypertrophy	Rokitansky-Aschoff sinuses
Chronic cholecystitis	+					+	+
Xanthgranulomatous		+			+		
Eosinophillic			+				
Acalculous				+			

- The histopathology of the pancreatic cystic neoplasms which have histopathologically similar biliary neoplasms mucinous cystic neoplasm (MCN).

	Hepatobiliary cystadenoma +/- dysplasia	Biliary papillomatous
○ Epithelium		
− Mucinous	+	+
− Papillary		
− Proliferation		+
− Cellular atypia	+	+
○ Stroma		
− Ovarian-like	+	
○ Localization		
− Discrete	+	
− Diffuse		+

Diffuse Acalculous Lymphoplasmacytic Cholecystitis Secondary to Bile Duct Obstruction



At low power

A) The gallbladder contains a superficial mucosal infiltration
B) These findings were once touted as being specific to primary sclerosing cholangitis, but as this case shows, they are a non-specific reflection of distal duct obstruction

Printed with permission: https://abdominalkey.com/pathology-of-the-gallbladder-and-extrahepatic-bile-ducts/ (Figure 16-7).

- The histopathological features of types of chronic cholecystitis.

Types of Cholecystitis	Histology	Associations
○ Usual chronic cholecystitis	− Muscular hypertrophy, Rokitansky-Aschoff sinuses, minimal inflammation	▪ Gallstones
○ Xanthogranulomatous cholecystitis	− Xanthomatous macrophages and fibroblastic reaction	▪ Stimulates malignancy clinically
○ Eosinophilic cholecystitis	− Eosinophils out of proportion to other inflammation	▪ Other causes of eosinophilic gastroenteritis
○ Diffuse acalculous lymphoplasmacytic cholecystitis	− Superficial lymphoplasmacytic infiltrate, no stones	▪ Obstruction of distal bile ducts (i.e., primary sclerosis cholangitis, distal bile duct tumours)

Printed with permission: https://abdominalkey.com/pathology-of-the-gallbladder-and-extrahepatic-bile-ducts/ (Figure 16-1).

Biliary Neoplasms and their Pancreatic Analogues

Histologic Features	Biliary Neoplasm	Pancreatic Neoplasm
○ Discrete cystic neoplasm that effects predominantly females, with − Ovarian-type stroma − Mucinous epithelium − Variable cytologic atypia	Hepatobiliary cystadenoma ± dysplasia	Mucinous cystic neoplasm
○ Diffuse papillary mucinous, epithelial proliferation of − Variable cytologic atypia	Biliary papillomatous	Intraductal papillary mucinous neoplasm

Printed with permission: https://abdominalkey.com/pathology-of-the-gallbladder-and-extrahepatic-bile-ducts/ (Figure 16-2).

GALLSTONES

Prevention, Diagnosis, and Treatment of Gallstones: EASL Guidelines (2016)

EASL Guidelines. J Hepatology 2016; 65: 146-181

- Primary prevention
  - Average risk
    - "Healthy food"
    - Regular physical activity

    } Maintain normal body weight
  - Increased risk
    - Ursodeoxycholic acid (UDCA)
      - Rapid weight loss
        - Post bariatric surgery
        - Very low calorie diet
        - Somatostatin analogues long term
    - Biliary sludge, recurrent bile duct stones
      - No recommendation
    - Bariatric surgery
      - UDCA may be used during interval of rapid weight loss, but elective cholecystectomy not recommended
    - Hormonic replacement therapy (HRT)
      Be aware of ↑ risk of biliary tract disease, but no prophylaxis recommended

- Clinical features suggestive of cholelithiasis
  - "…episodic attacks of severe pain in the right upper abdominal quadrant or epigastrum for at least 15-30 minutes with radiation to the right [side of the] back or shoulder…"

- Diagnostic imaging
  - Abdominal ultrasound (US) / endoscopic US
  - MRCP
    - Best suited to identify stones in the biliary tree
  - EUS
    - Suited

`

❖ Treatment

- Asymptomatic
  - Gallstones
    - Usually do not need cholecystectomy
  - Porcelain gallbladder → cholecystectomy
  - Polyps > 6 to 10 mm and enlarging, plus asymptomatic stones
  - PSC plus any size polyp
  - Asymptomatic stones found incidentally during abdominal/bariatric surgery
  - Hereditary / spherocytosis sickle cell disease plus asymptomatic gallstones
- Symptomatic
  - NSAIDs, spasmolytics, opioids
  - Antibiotics only if associated complications
    - Abscesses
    - Bacteremia / sepsis
    - Cholangitis
    - Perforation
  - Early cholecystectomy
    - Gallstones perforation becoming symptomatic early after transplantation of lung, pancreas, kidneys should be deferred whenever possible

MCQ Trick

- Cholecystectomy is **not** recommended in the asymptomatic diabetic patient with gallstones.

❖ Surgery

- Cholecystectomy, laparoscopic
  - Recommended for
    - Symptomatic gallstones (biliary colic)
    - Perform 72 h acute cholangitis from gallstones
    - Acalculous cholecystitis
    - Gallstones and bile duct stones
      - Cystectomy within 72 h after pre-op ERCP
    - Cholecystectomy as early as patient fit for surgery
    - Elderly
    - Complications
      - Acute cholecystitis
      - Gallstone pancreatitis
      - Obstructive jaundice
  - Post-cholecystectomy syndrome (persistent symptoms after cholecystectomy)

- Investigation
  - EUS, MRCPERCP plus sphincterotomy not recommended

❖ Bile duct

- Bile duct injuries
  - Clinical suspicion
    - Acute cholangitis / pancreatitis [obstructive] jaundice
  - Diagnosis type of injury
    - Type A, B, C endoscopic repair
    - Type D subhepatic drainage → early referral to centre of excellence
  - After 6 to 8 wks, hepaticojejunostomy is recommended, if type D (complete CBD transection +/- tissue loss)

Clinical Gem

- Suspect choledocholithiasis if
  - Cholelithiasis
  - Hyperbilirubinemia
  - Acute cholangitis
  - Dilated CBD

- Choledocholithiasis
  - Diagnostic imaging
    - US
    - EUS
    - MRCP
    - If intraoperative detection
      - Endoscopic clearance
      - Bile duct exploration
      - Transcystic stone extraction
  - Treatment
    - ERCP plus sphincterotomy
    - Alternatives (including for failed endoscopic treatment)
      - Laparoscopic bile duct exploration plus cystectomy, or
      - Intraoperative ERCP
      - Percutaneous / balloon-endoscopy assisted treatment (such as for bariatric surgery, previous Roux-en-Y anastomosis)

- Intrahepatic bile duct stones (IHBDS)
  - Suspected IHBDS → US, MRCP
  - Symptomatic stones during pregnancy
    - ERCP/endoscopic sphincterotomy
    - Shield and ↓ exposure area of radiation

- Acute cholangitis
  - Clinical
    - Pain, fever / chills, jaundice
  - Laboratory
    - ↑ WBC, ↑ bilirubin, ↑ transaminases
  - Diagnostic imaging
    - Abdominal ultrasound (MRCP for suspected choledocholithiasis)
  - Treatment
    - Antibiotics, IV fluids, analgesics
    - Endoscopic decompression (usually within 24 h) stone removal
    - Percutaneous drainage

- Acute biliary pancreatitis
  - Diagnosis
    - Biliary pain, ↑ WBC / ↑ lipase [↑ ALT / ↑ AST]
    - Diagnostic imaging
      - US, MRCP
  - Treatment
    - Pancreatitis (mild or severe), no bile duct obstruction
    - Severe pancreatitis, no bile duct obstruction / no cholangitis mild / severe pancreatitis, bile duct obstruction, cholangitis → ERCP, sphincterotomy, stone extraction
    - Antibiotics
    - Cholecystectomy on same admission

Primary prevention (gallstones)

Average risk

- Possible good dietary and physical activity practices would ↓ risk of cholesterol stones, symptoms complications (low quality evidence; weak recommendation)
  - Do **not** use drugs to prevent gallstones except for highly selected indicators (very low-quality evidence; weak recommendation)

- High risk
  - Short-term use of ursodeoxycholic acid (UDCA) may be useful for
    - Rapid weight loss
      - Very-low calorie diet after bariatric surgery (moderate quality evidence; weak recommendation)
  - Long term therapy
    - Use somatostatin or analogues, concomitant treatment with ursodeoxycholic acid to prevent cholesterol gallstones formation (low quality evidence; weak recommendation)
  - Do **not** do prophylactic cholecystectomy during bariatric surgery (very low quality evidence; weak recommendation)
  - No recommendation can be made re preventive measures for
    - Persons fed with total parenteral nutrition (very low quality evidence; weak recommendation)
    - Persons on hormone replacement therapy (HRT) (very low quality evidence; weak recommendation)
    - Prevention of recurrent gallstones (very low quality evidence; weak recommendation)
  - Prophylactic cholecystectomy at time of splenectomy
    - Hereditary spherocytosis
    - Sickle cell disease (very low quality evidence; weak recommendation)
    - Bariatric surgery
    - Transplantation of kidney / pancreas (very low quality evidence; weak recommendation)

❖ Clinical

- Biliary pain is characterized by episodes of
  - Severe abdominal pain in RUQ / epigastrium
  - Lasting 15-30 min
  - Reduction to right shoulder, back
  - May
    ↑ tenderness in RUQ with inspiration
    ↓ pain with analgesics

  (very low quality evidence; weak recommendation)

❖ Laboratory

- Biochemistry
  - Only in selected cases (very low quality evidence; weak recommendation)

- ❖ Diagnostic imaging
  - Do an abdominal ultrasound in person with recurrent biliary pain(high quality evidence; strong recommendation) to establish presence of cholelithiasis (moderate quality evidence; strong recommendation)
  - Do endoscopic ultrasound (EUS) if
    - Strong clinical suspicion, but
    - Negative ultrasound for cholelithiasis

    (low quality evidence; weak recommendation)

- ❖ Treatment
  - Asymptomatic
    - Do **not** do cholecystectomy for asymptomatic cholelithiasis (very low quality evidence; weak recommendation)
    - Except
    - Porcelain gallbladder polyps in patient with primary sclerosing cholangitis (PSC) (low quality evidence; weak recommendation)
      - Gallbladder polyps ≤ 5 mm

      (moderate quality evidence; strong recommendation)
  - Symptomatic
    - Biliary pain (mild acute cholecystitis), use
    - Non-steroidal anti-inflammatory drugs (NSAIDs) (moderate quality evidence; weak recommendation)
      - Antispasmodics (low quality evidence; strong recommendation)
      - Antibiotics
        - Cholangitis →
          - Abscess
          - Perforation
          - Bacteremia / sepsis

        (very low quality evidence; weak recommendation)
  - Cholecystectomy (moderate quality evidence; strong recommendation)
    - Only by experienced expert surgeons (high quality evidence; strong recommendation)
    - If possible, do not do cholecystectomy for symptomatic cholelithiasis early after heart / lung transplantation (very low quality evidence; weak recommendation)
    - Cholecystectomy as early as possible (< 72 h) after uncomplicated biliary colic
    - If both cholelithiasis and choledocholithiasis, perform preoperative ERCP and them cholecystectomy within < 72 h (moderate quality evidence; strong recommendation)

- Laparoscopic cholecystectomy
  - Standard of care for method of cholecystectomy for all indications
    - Including
      - Acute acalculous cholecystitis (high quality evidence; strong recommendation)
      - Child-Pugh A/B cirrhosis (moderate quality evidence; strong recommendation)
    - 2 ports ≥ 10 mm, and
    - 2 ports ≥ 5 mm (very low quality evidence; weak recommendation)
    - Mini laparotomy Incision < 8 cm) is an acceptable alternative to standard (≥ 8 cm laparoscopic cholecystectomy (high quality evidence; strong recommendation)
  - Do **not** do routinely
    - Give prophylactic antibiotics (very low quality evidence; weak recommendation)
    - Intraoperative cholangiography (low quality evidence; weak recommendation)
    - Switch from laparoscopic to open laparoscopy because of intraoperative loss of gallstones (very low quality evidence; weak recommendation)
    - In patients with high anaesthetic plus complications of gallstones
      - Gallbladder – Acute cholecystitis
      - Bile ducts – Obstruction
      - Pancreas – Pancreatitis

      → optimize patients status, and proceed with cholecystectomy (low quality evidence; weak recommendation)

❖ Bile Duct Injuries

- Diagnosis
  - Post-operative suspicion of bile duct (BD) injury
    - Urgent
      - Bilirubin, ALT / AST / AP / WBC
      - MRCP, CT with contrast, ultrasound

      Patient hospitalized

    Classification of the bile duct injuries

A	Cystic or aberrant bile duct leakage
B	CBD leakage, with or without stricture
C	CBD Stricture without leakage
D	Complete CBD transection with or without tissue loss

  - Intraoperative recognized BD injury
    - Type A, B, C – Primary surgical repair
    - Type D – Subhepatic drainage plus referral to “experts” / expert centre (low quality evidence; weak recommendation)
  - Post-operative recognized
    - Type A, B, C – Endoscopic management
    - Type D – Late surgical treatment

Abbreviations: AC, acute cholangitis; AP, alkaline phosphatase; BP, biliary pancreatitis; CBD, common bile duct; CT, computed tomography; ERCP, endoscopic retrograde cholangio-pancreatography; EUS, endoscopic ultrasound; HRT, hormone replacement therapy; IHBDS, intrahepatic bile duct stones; IV, intravenous; lab' chole', laparoscopic cholecystography; MRCP, magnetic resonance cholangiopancreatography; NSAIDs, non-steroidal anti-inflammatory bowel disease; OBD, obstructed bile duct; PSC, primary sclerosing cholangitis; US, ultrasound; WBC, white blood cells

- Persistent Post-cholecystectomy Symptoms
  - Perform EUS / MRCP (low quality evidence; weak recommendation)
  - Do **not** do endoscopic sphincterotomy for patient with cholecystectomy pain, but normal
    - Laboratory
    - Imaging

    (moderate quality evidence; strong recommendation)

❖ Persistent post-cholecystectomy symptoms
  - Clinical
    - Bile ducts
      - Acute cholangitis
      - Jaundice
    - Pancreas
      - Acute pancreatitis

    (high quality evidence; strong recommendation)
  - Laboratory
    - Biochemistry
      - ALT / AST / AP / WBC

    (low quality evidence; weak recommendation)
  - Diagnostic imaging
    - Abdominal ultrasound for suspected CBD stones ((low quality evidence; weak recommendation)
      - Predictors for CBD stones
        - Clinical
          - Acute cholangitis
          - Jaundice
        - Laboratory
          - Hyperbilirubinemia
        - Ultrasound
          - Cholelithiasis
          - CBD dilated

      (high quality evidence; strong recommendation)
    - "Intermediate probability" of CBD stones of CBD stones
      - EUS, or
      - MRCP

      (moderate quality evidence; weak recommendation)

- Treatment
  - Common bile duct (CBD) stones
  - Endoscopic sphincterotomy plus extraction

  (moderate quality evidence; strong recommendation)
    - High expertise required
      - Intraoperative endoscopic retrograde cholangiopancreatography (ERCP), or
      - Laparoscopic bile duct exploration, plus cholecystectomy (moderate quality evidence; strong recommendation)
      - Transcystic stone extraction
      - Endoscopic extraction

    (moderate quality evidence; weak recommendation)
  - For failed removal of gallstones, as outlined above
    - Normal anatomy
      - Extracorporeal shockwave, or
      - Lithotripsy
        - Electrohydraulic
        - Laser

      (low quality evidence; weak recommendation)
    - Altered anatomy (e.g., bariatric surgery, Roux-en-Y anastomosis)
      - Percutaneous
      - Balloon endoscopy-associated

      } CBD stone treatment (low quality evidence; weak recommendation)
  - For failed endoscopic therapy
    - Cholecystectomy plus BD exploration, or
    - Intraoperative ERCP

    (low quality evidence; weak recommendation)
  - Surgical bile duct exploration
    - Primary closure, or
    - T drainage

    } Low risk patients (low quality evidence; weak recommendation)

- Intrahepatic Bile Duct Stones (IHBD)
  - Diagnostic imaging
    - Clinical suspicion → abdominal ultrasound, or MRCP (very low quality evidence; weak recommendation)
  - Treatment
    - Asymptomatic, case-by-case discussion retreatment
    - Symptomatic
      - Multidisciplinary team

    (very low quality evidence; weak recommendation)
    - Pregnancy
      - The use of x-rays is not contraindicated [in pregnancy and for IHBD stones] provided care is taken to minimize radiation exposure
      - Expert / experienced endoscopic sphincterotomy, stenting, stone removal

- Acute cholangitis
  - Clinical suspicion
    - Abdominal pain
    - Fever / chills
    - Jaundice
    - ↑ WBC

    ▪ Diagnostic imaging
    ▪ Abdominal ultrasound

    (moderate quality evidence; strong recommendation)
  - Treatment
    - Take blood cultures x 3, then
    - Empirical antibiotics IV, IV fluids, plus
    - Bilary decompression
      - Perform in < 24 h if early non-response to antibiotics IV / fluids (low quality evidence; weak recommendation)

      ↓
    - Sphincterotomy, stenting, stone removal
      - If contraindicated
        - Later biliary stenting, stone removal (low quality evidence; weak recommendation)
      - If failed or contraindicated
        - Percutaneous bile duct drainage (low quality evidence; weak recommendation)

- Acute biliary pancreatitis (BP)
  - Clinical suspicion
    - Abdominal pain
    - ↑ lipase, amylase, WBC, bilirubin

    plus gallbladder / CBD stones (moderate quality evidence; strong recommendation)

    ↓

    EUS, MRCP (low quality evidence; weak recommendation)
  - Treatment
    - Take blood cultures x 3, then
    - Empirical antibiotics IV, IV fluids
      - Perform in < 24 h if early non-response to antibiotics IV / fluids (low quality evidence; weak recommendation)

      ↓
    - Sphincterotomy, stenting, stone removal
      - If contraindicated
        - Later biliary stenting, stone removal (low quality evidence; weak recommendation)
      - If failed or contraindicated
        - Percutaneous bile duct drainage (66) (low quality evidence; weak recommendation)

- ❖ Methods for CBD stents
  - ○ Plastic
  - ○ Metal
  - ○ Partially cover
    - − For distal bile duct
    - − For proximal malignant bile duct lesions
  - ○ Fully covered
    - − Benign lesions
    - − Removal stent
      - ▪ Post-liver transplantation
      - ▪ Chronic pancreatitis

- ○ Double duct signed (MRCP / ERCP)
  - − Stricture of CBD plus PD = pancreatic ductal adenocarcinoma

- ❖ Bile duct stricture post-liver transplantation

- ➢ Differential diagnosis
  - ○ Infection
    - − Roux-en-Y anastomosis with bacterial related cholangitis
    - − CMV infection
  - ○ Immune
    - − ABO graft incompatibility
    - − Primary sclerosing cholangitis (PSC) recurrence
  - ○ Ischemia
    - − Preservation / ischemic
    - − Hepatic artery stenosis
  - ○ Infiltration
    - − Cholangiocarcinoma
  - ○ Iatrogenic / surgical
    - − Anastomotic

- ❖ Removal of CBD stones
  - Sphincterotomy
  - Balloon extraction
  - Basket extraction
  - Mechanical lithotripsy
  - Stenting
  - Electro-hydraulic lithotripsy
  - Surgical
    - Robotic, and
    - Open surgery

Grading of Pancreatitis by EUS

Classification Findings at Endoscopic Retrograde Cholangiopancreatography

- Normal
  - Visualization of entire duct system with uniform filling of side branches without acinar opacification
- Equivocal
  - < 3 abnormal branches
- Mild
  - Normal main duct
  - > 3 abnormal side branches
- Moderate
  - Enlarged main duct (< 4 mm)
  - Enlarged gland (up to twice normal)
  - Cavities (< 10 mm)
  - Irregular ducts
  - Focal reduction in parenchymal echogenicity
  - Echogenic foci in parenchyma
  - Increased or irregular echogenicity of wall of main duct
  - Irregular contour to gland (particularly focal)
  - Enlargement
- Marked
  - Large cavities (> 10 mm)
  - Intraductal caliculi
  - Duct obstruction with stricture
  - Gross irregularity of main pancreatic duct

- ❖ Choices of Diagnostic Imaging based on Probable Etiology
  - Probability
    - Duct obstruction
    - Need for therapy

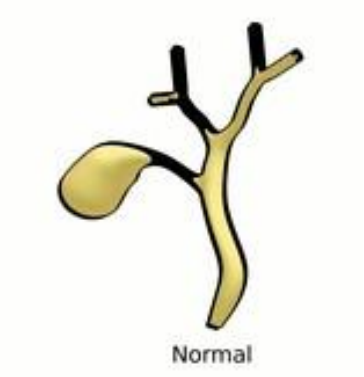
    } ▪ High – ERCP ▪ Low – MRCP / EUS
  - MRCP
    - Pancreas divisum suspected
    - Low probability of duct obstructoin

- EUS
  - Chronic pancreatitis
  - Mass / tumours
  - Low probaility of duct obstruction but ERCP not available / possible

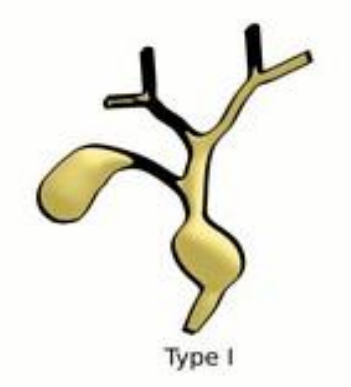
Indications for Abdominal X-ray before ERCP

- PSC
- Pseudocyst drainage
- Proximal obstruction

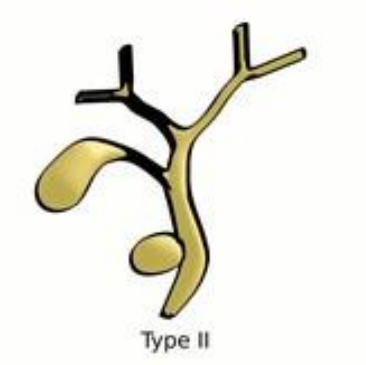
Choledochocele Cyst / Choledochocele



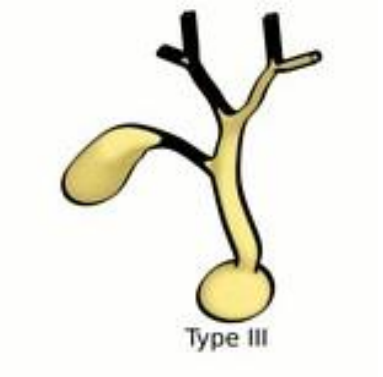
- Solitary fusiform extrahepatic



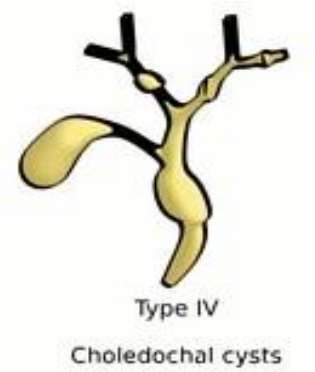
- Extrahepatic supraduodenal diverticulum



- Intraduodenal diverticulum choledochocele

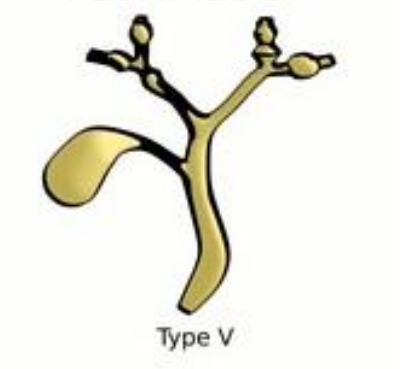


- Choledochocele



Choledochal cysts

- Fusiform and intrahepatic cysts
- Multiple extrahepatic cysts



- Multiple intrahepatic cysts: Caroli Disease

POST-CHOLECYSTECTOMY BILIARY COMPLICATIONS

Ahmad DS and Faulx A. Am J Gastroenterol 2020; 115: 1191-1198

❖ Biliary Injuries / Bile Leaks

➢ Demography

- to 3x more common with laparoscopic cholecystectomy (LC) than with open cholecystectomy (OC)
- Biliary injuries requiring surgical treatment
  - All cause mortality, 21%
  - Rate of death, ↑ 9%
  - Rate of liver transplant requires, ↑ 1%

➢ Pathophysiology / etiology

- "…inability to avoid the biliary tract and its blood supply during dissection

➢ Risk factors

- Urgent surgery / acute cholecystitis
- Choledocholithiasis
- Cystic duct not identified
- Variations in anatomy of biliary tree

➢ Types of complications

- Common (~10%)
  - Post-cholecystectomy
    - Syndrome
    - Diarrhea
- Uncommon
  - Biliary (< 1%)
    - Abscess
    - Bleeding
    - Injury
    - Leak
    - Strictures
    - Stones
  - Bowel
    - Bleeding

- Diagnosis
  - At time of surgery
  - Clinical
    - High index of suspicion
    - Fever
    - Pain
    - Nausea / vomiting
    - Jaundice

- Diagnostic imaging
  - Abdominal ultrasound / CT scan / MRI
  - Nuclear scan
    - HIDA (iminodiacetic acid)

- Classification

- Strasberg, types
  - Type A
    - Injuries leading to bile from
      - Cystic duct (CD): failure of clip occluding CD retained biliary stones
      - Liver bed: injury to small hepatic duct
      - Accessory duct: e.g., injury to duct of Luschka, when connects the right he[atic system to the gallbladder
  - Type B/C
    - Abnormal right hepatic duct joins to the main hepatic ductal system
    - If the abnormal duct is mistaken for the cystic duct, it may be damaged
      - Type B occluded
      - Type C transected

      } At point of insertion into main hepatic or common bile duct
  - Type D
    - Internal damage to the extrahepatic bile ducts
  - Type E
    - Circumferential injuries of the main bile ducts
    - The Strassberg type 3 post-cholecystectomy biliary injuries are further subdivided according to level of injury in the biliary tree, using the Bismuth classification

E1 (Bismuth type I)	Transection > 2 cm from the confluence
E2 (Bismuth type II)	Transection < 2 cm from the confluence
E3 (Bismuth type III)	Injury at the confluence; confluence is intact
E4 (Bismuth type IV)	Injury at confluence, confluence is separated
E5 (Bismuth type V)	Type C injury plus injury in the confluence

➢ Treatment

- Bile leaks, Strasberg Type A (85%), C and D
  - Up to ~25% of patients will have a bile leak post-cholecystectomy, as seen on post-operative abdominal ultrasound but many of these will not be clinically significant.
    - Significant leaks cause symptoms such as within 1 wk post-cholecystectomy such as fever, abdominal pain, and biliary ascites
  - Treatment will be influenced by the Strasberg type of injury, as well as the grade of the bile leaks seen on cholangiography
    - High grade leaks
      - Rapid early extravasation from biliary tree
      - Before small volume intrahepatic filling
    - Low grade leaks
      - Slow late extravasation from biliary
      - After complete / incomplete intrahepatic filling
  - Purpose of treatment
    - ↑ flow of bile from the liver to the duodenum, and thus to ↓ flow through the bile leak → sphincterotomy
    - ERCP transpapillary placement of stent, remove stent by EGD in 4-6 wk, or sphincterotomy plus stent
      - Superior to only sphincterotomy
    - Follow-up ERCP usually necessary if injury was to the main biliary duct to confirm healing of the leak (otherwise strictures may occur if bile leak continues)
    - If a large-bore (10 Fr) plastic stent does not stop the leak, insert
      - Multiple plastic stents, or
      - Fully covered-expandable metal stents (FC SEMS)
        - Use only for leaks from common hepatic / bile ducts or cystic duct
        - Do **not** use for leaks above the bifurcation
        - Success rate of FS SEMS, 90% - 100%
        - Adverse effects (AEs) (↑ AEs if stent left in place long term)
        - Stent
          - Migration
          - Obstruction
      - Bile duct stricture (new)

- Type B (occlusion of abnormal right hepatic duct into main ductal system)
  - When symptoms of segmental cholestasis / cholangitis develop →
    - Hepaticojejunostomy
    - When biliary enteric anastomosis not possible → segmental hepatic resection

- Type E (circumferential injuries to the main ducts (CHD / CBD), Strassberg, Bismuth I to V)
  - Surgical repair

❖ Biliary Strictures

➢ Demography

- Post-operative bile duct strictures, ~0.5%
- Initial presentation is then asymptomatic ↑ LEs (AP [alkaline phosphatase], CRP [C-reactive protein])
  - Nausea / vomiting
  - Fever
  - Abdominal pain
  - Jaundice / cholangitis

➢ Treatment

- Endoscopy serial dilation of stricture
  - Balloon
  - Dilating catheters (+/- sphincterotomy)
    - Side-by-side plastic stents, or
    - FC SEMS
  - Plastic stents, especially multiple plastic biliary stents (MPBS)
    - Resolution of strictures, 97%
    - Mean treatment period, ~12 mon
  - FC SEMS
    - Risk of stent migration (9%) and de novo strictures

❖ Biloma

- Collection of fluid in the fossa of the gallbladder in 29% of patients after cholecystectomy
- Usually asymptomatic and spontaneously resolve
- Symptoms
  - Gastric outlet obstruction
  - Pain, nausea / vomiting
  - Abscess
- Treatment
  - No loculated
    - Close the bile leak then percutaneous drainage
  - If loculated
    - Surgical drainage

❖ Retained Common Bile Duct (CBD) Stones

➢ Demography

- ~1% to 6% stones retained post-cholecystectomy within 2 yr

➢ Treatment

- Choledocholithiasis < 1.5 cm
  - Endoscopy, backet and balloons
  - Stones above a stricture
    - Dilute, stricture, extract stone, or
    - Mechanical lithotripsy (laser, or electrohydraulic)
    - Stent placement if biliary leak / stricture

❖ Migration into CBD of clips / sutures

- Foreign body in CBD
  → widens for stone formation
  → ischemic necrosis of clipped remnant of cystic duct

Abbreviations: AEs, adverse effects / events; CBD, common bile duct; CD, cystic duct; CHD, common hepatic duct; CRP, C-reactive protein; CT, computed tomography; EGD, esophago-gastroduodenoscopy; ERCP, endoscopic retrograde cholangiopancreatography; ESR, erythrocyte sedimentation rate; FC SEMS, fully covered self-expandable metal stents; Fr, French; LC, laparoscopic cholecystectomy; LEs, liver enzymes; LFTs, liver function tests; MRI, magnetic resonance injury; OC, open cholecystectomy; wk, week

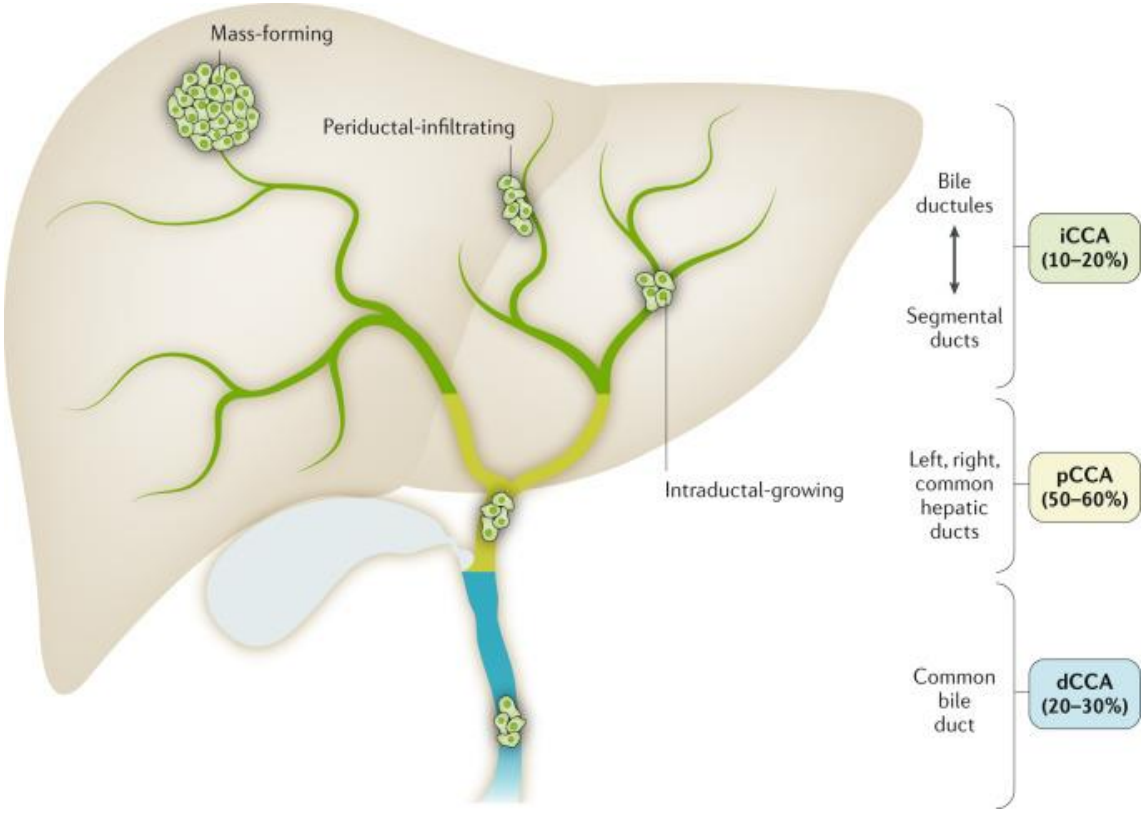
CHOLANGIOCARCINOMA (CCA) **UPDATE**

Banales JM, et al. Nat Rev Gastroenterol Hepatol 2020; 17: 557-588

- Demography
  - Incidence, 0.3 – 6/10^5 per yr
  - Mortality, 1 – 6/10^5 per yr
    - Highest in African American and Indigenous persons
  - Wide geographical variations
    - High in China, Japan, Korea
    - Low in Mexico, South America
  - Develops in non-cirrhotic liver

- Subtypes
  - Intrahepatic (iCCA; 10%) begin above the second-order bile ducts
  - Perihilar (pCCA, 60%)
  - Distal (dCCA, 30%)
    - Anatomical distinction is the point of insertion of the cystic duct (aka extrahepatic [eCCA])
      - Mutations in KRAS +/- TP53 genes mutations arise from
        - Columnar mucous cholangiocytes
        - Peribiliary glands
  - Mixed (iCCA plus HCC)
    - Arise from embryonic stem cells; biological marker: nestin
    - Epigastric changes (regenerated patterns of methylation)
    - Premalignant changes not always apparent

Anatomical classification of cholangiocarcinoma



On the basis of the anatomical site of origin,

- Cholangiocarcinoma (CCA) is classified into intrahepatic CCA (iCCA), perihilar CCA (pCCA) and distal CCA (dCCA).
  - iCCA is defined as a malignancy located in the periphery of the second-order bile ducts, pCCA arises in the right and/or left hepatic duct and/or at their junction, and
  - dCCA involves the common bile duct (that is, the choledochus).

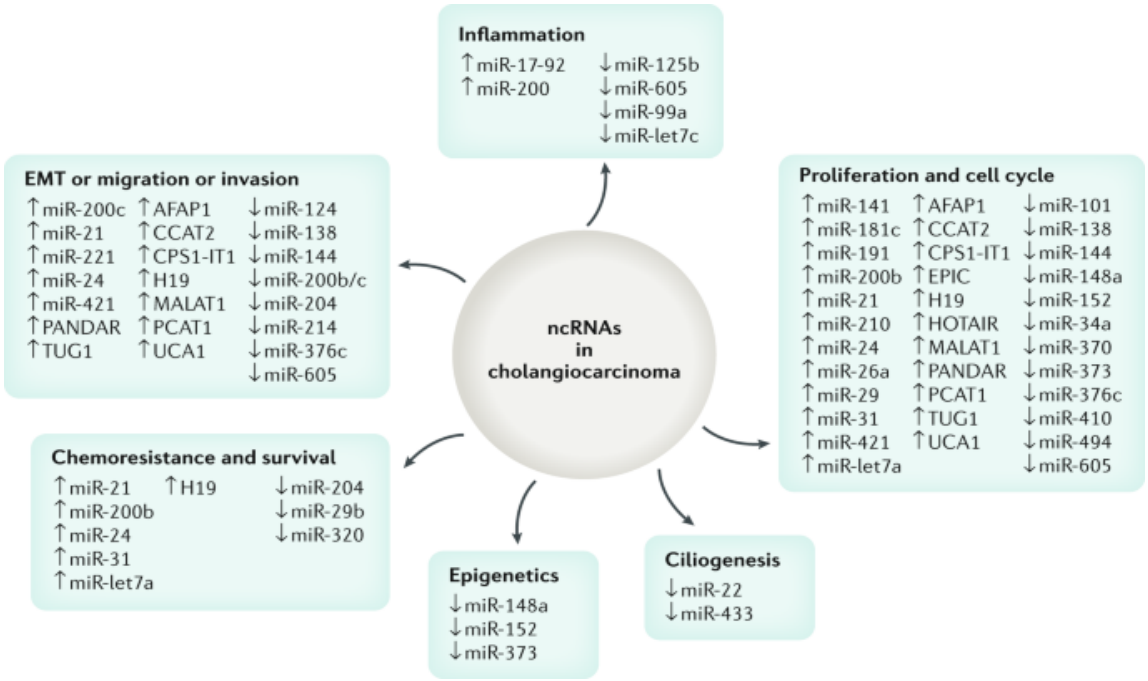
Source: Banales JM, et al. Nat Rev Gastroenterol Hepatol 2020; 17: 557-588 (Figure 1)

➢ Pathology

- Patterns of growth
  - Mass – In hepatic parenchyma
  - Infiltrating (pCCA) – Gathering along wall
  - Intraductal – Polypoid / papillary, growing into lumen of duct

- Histopathology
    - Small bile duct iCCA (including ductules)
        - Nodules
        - Tubular / acinar
        - Little mucin (few mucin-producing columnar tumour cells)
        - Mutations
            - FGFR2 fusions
            - IDH1, IDH2 mutations
        - Cells of origin
            - Hepatic stem or progenitor cells (HpSCs)
            - Cuboidal cholangiocytes
            - Abnormal histones
            - Abnormal non-coding RNAs

Non-coding RNAs in Cholangiocarcinoma and their Relationship with Different Tumorigenic Processes

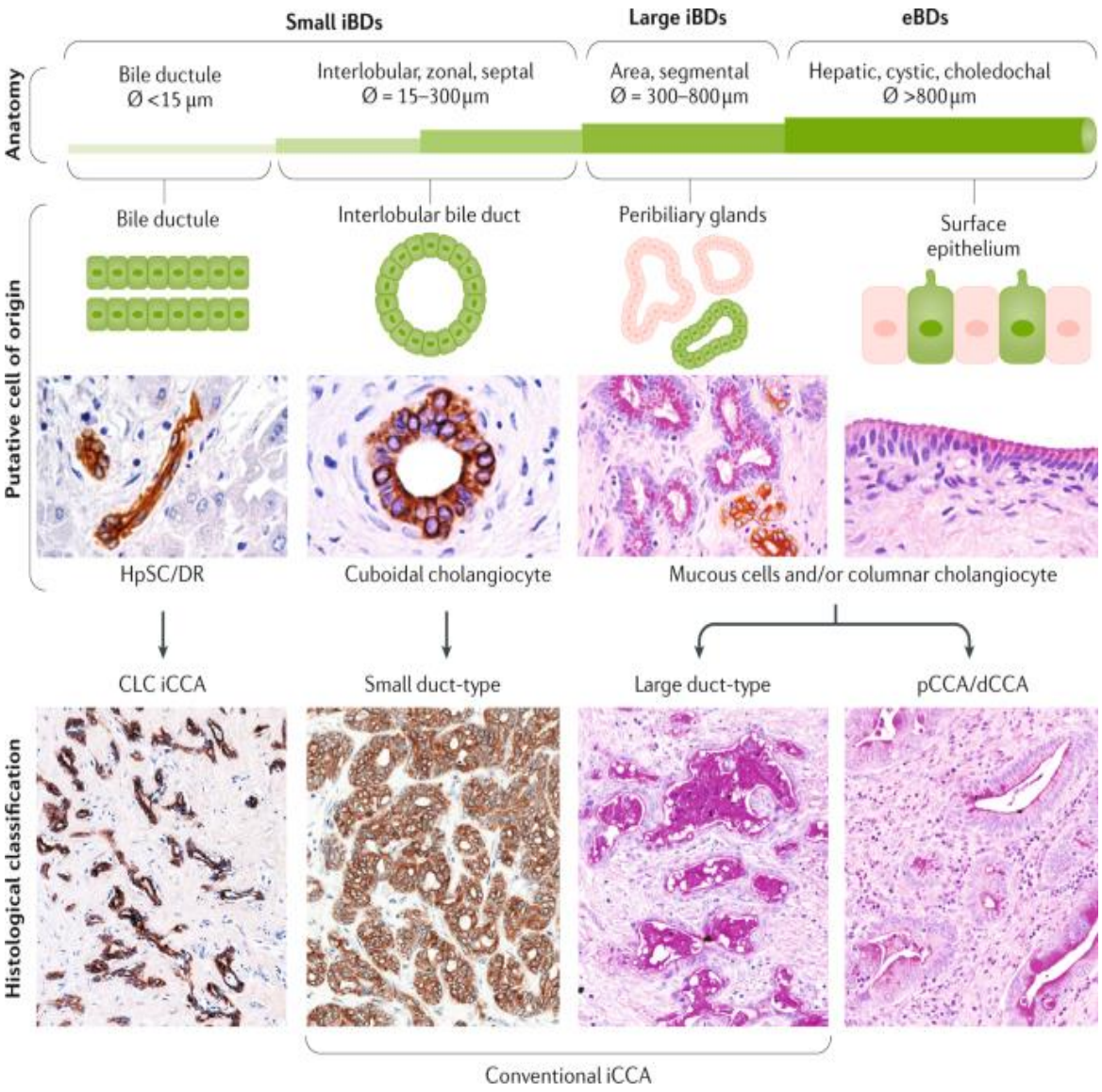


    - Non-coding RNAs (ncRNAs) that have been found to be dysregulated (up or down) in cholangiocarcinoma and that have key roles in the regulation of cellular processes, such as proliferation, cell cycle, ciliogenesis, epigenetics, inflammation, chemoresistance, survival, epithelial to mesenchymal transition (EMT), migration and invasion are shown.

Source: Banales JM, et al. Nat Rev Gastroenterol Hepatol 2020; 17: 557-588 (Figure 4)

- Large bile duct iCCA
  - Large intrahepatic ducts
  - Papillary
  - Mucin producing
  - Mutations
    - KRAS +/- TP53 genes
  - Cells of origin

Histological Classification and Putative Cells of Origin in Cholangiocarcinoma



- Based on the duct size, the intrahepatic biliary tree can be further subdivided into small and large intrahepatic bile ducts (iBDs).
- Small iBDs are lined by small cuboidal cholangiocytes whereas columnar and mucous cholangiocytes line large iBDs.
- Large iBDs contain peribiliary glands within their wall. The extrahepatic biliary tree shares anatomical features with large iBDs.
- Histological cholangiocarcinoma (CCA) variants reflect the phenotype of the involved duct and the putative cell of origin.
- Conventional intrahepatic CCA (iCCA) has two main variants
  - Small duct-type iCCA arises in small iBDs with cuboidal cholangiocytes representing the putative cell of origin, and
  - Large duct-type iCCA involves large iBDs and is considered to be derived from columnar cholangiocytes and peribiliary glands (seromucous glands; mucous acini are shown in light pink, serous acini are shown in green).
- Cholangiocarcinoma (CLC) is a frequent histological variant of iCCA and
  - Its phenotype suggests the origin from bile ductules or ductular reaction (DR) that occurs in chronic liver diseases.
  - Most perihilar CCA (pCCA) and distal CCA (dCCA) originate from the lining epithelium and peribiliary glands.

Abbreviations: eBD, extrahepatic bile duct; HpSC, human pluripotent stem cell.

Source: Banales JM, et al. Nat Rev Gastroenterol Hepatol 2020; 17: 557-588 (Figure 3)

- Risk factor
  - Infection / inflammation of biliary tree
    - Liver fluke
      - Clonorchis sinensis
      - Opisthorchis viverrini
  - Inflammation
    - Biliary tree
      - Cholelithiasis, choledocholithiasis, cholecystolithiasis
      - Choledochal cyst
      - Caroli disease
    - Liver
      - Cirrhosis
      - NAFLD
    - Pancreas
      - Chronic pancreatitis
      - Primary sclerosing cholangitis (PSC)
    - Intestine
      - IBD (UC)

- Environmental
  - Alcohol
  - HBV / HCV infection
  - Asbestos exposure
- Intake
  - Tobacco
  - Obesity
  - Drugs
    - Thorotrast contrast material
- Inherited
  - Polymorphism of genes encoding enzymes for
    - DNA repair
    - Folate metabolism
    - Immune response multidrug resistance
    - Xenobiotic
    - Detoxification
- Metabolic
  - Diabetes mellitus, type 2

➢ Pathophysiology

- Genetics
- Epigenetics
- Signalling pathways

Signalling pathways involved in cholangiocarcinoma development and progression.

- The process of cholangiocarcinogenesis, and further tumour evolution and growth, involves complex and heterogeneous processes → extracellular ligands or pro-inflammatory cytokines, growth factors and bile acids → ↑ expression and/or aberrant activation of cell surface receptors → deregulation of intracellular signalling pathways → cell proliferation, survival and migration or invasion.
- The most common genes that might be mutated or amplified resulting in the overactivation of some of these pathways are KRAS, BRAF, ARID1, PBRM1, BAP1, IDH1 and IDH2.
- The activation of these signalling pathways might also occur as a result of the interaction between the tumour epithelia and the tumour reactive stroma.

Abbreviations: 2-HG, 2-hydroxyglutarate; ECM, extracellular matrix; RTK, receptor tyrosine kinase

- Cancer-associated fibroblast (CAFs)
  - Especially CAFs which are fibroblast activation protein (FAP) positive (FAP+)

Central Role of Cancer-associated Fibroblasts in Promoting Tumour Growth and Metastasis of Cholangiocarcinoma

- Cancer-associated fibroblasts (CAFs)
  - Recruited / activated by cholangiocarcinoma (CCA) cells
  - In response to the effects of PDGF-D, and of FGF and TGFβ1
  - Released by tumour-associated macrophages (TAMs)
- CAFs → ↑ directly cell proliferation and the invasive ability of CCA cells directly, or by influencing the activity of other cells in the tumour microenvironment.
  - CAFs
    - Stimulate tumour-associated lymphangiogenesis (lymphatic endothelial cell [LEC])
    - Support M2 polarization of TAMs
    - Activate of regulatory T (Treg) cells
    - Dampen the activity of CD8+ T cells, natural killer (NK) and dendritic cells
    - ↑ heavy remodelling of the extracellular matrix (ECM) → stiffer → mechano-transduction of CCA cells → activation of intracellular pathways (YAP–TAZ).
- Immune biology / Tumour Microenvironment (TME)
  - ↑ mutational load
  - ↑ immune checkpoint molecules

  } → ↑ CD8+ T cell infiltrating TMEs; ↑ M2-like tumour-associated macrophages → ↑ WNT signalling →
    - CCA progression
    - ↑ myeloid-derived suppressor cells

Clinical

- Early
  - Asymptomatic
- Later
  - Pain / malaise
  - Nausea / vomiting
  - Jaundice
  - ↓ body weight
- Incidental finding (~20%)

➢ Biomarkers

- Nucleic acids and cell-free DNA (cfDNA) which may be formed in the blood and in other body fluids may prove to be useful for purposes of
  - Diagnosis
  - Direction of therapy
- Biomarkers which may prove to be useful for patients with CAA
  - BGJ398 (pan-FGFR inhibitor)
  - CA-19-9 / CA 19-9 plus miRNA-1537
  - Cytokeratin-19 (CYFRA 21-1)
  - FGFR2 kinase domains
  - IL-6
  - miR-21 (onco-miR)

- MMP-7
- Osteopontin and periostin
- Some bile miRNAs
- κRAS / TP53 (markers of overall survival)

➢ Management

- Surgery
  - Potentially curable in ~25% of patients with CAA
  - Staging laparoscopy recommended
    - Especially for
      - ↑ CA19-9
      - Vascular invasion (major)
  - Goal
    - Complete margin-negative resection (R_0)
      - Extended heme-hepatectomy, plus
      - Lymphadenectomy of ≥ 6 locoregional lymph nodes
  - For pCCA
    - Perform pre-operative
      - Drainage of the future liver remnant
      - Staging laparoscopy to exclude occult metastatic disease (in ~15%)
    - Extended heme-hepatectomy, including caudate lobe, plus
      - En-bloc resection of the extrahepatic duct and regional lymph nodes
    - Be aware
      - 90 day post-operative mortality, 10%
      - Half of these deaths are from liver failure (large portions of liver removed)
    - Surgery not recommended
      - Metastatic disease, **No**
      - Distant metastatic disease / aortocaval / truncal nodes positive, **No**
      - Locally advanced pCCA (Bismuth type IV, involving right / left intrahepatic ducts), no longer contraindicated
      - Local advanced pCCA to
        - Portal vein
        - Common hepatic artery (> 150% abutment)

        } ▪ Very poor prognosis, small potential benefit of surgery
    - Multiple CAA tumours: ↓ survival
      - 1 tumour, 43 mon
      - ≥ 2 tumours, 21 mon
  - Surgery with curative intent plus
    - 6 mon plus adjuvant capecitabine
  - Outcome
    - Median
      - Overall survival 51 mon
      - Relapse-free survival 24 mon
      - Relapse rate, 60%

- Consider transplantation
  - 5-yr survival ~65%
    - With no neoadjuvant chemotherapy, 83%
    - With CAA recurrence in 50%

- Palliative chemotherapy
  - Indication
    - ECOG-PS ≤ 3 (Eastern Cooperative Oncology Group Performance Status, plus
      - Molecular profiling available (for IDH 1/2, pan-IDH1-IDH2 (AG881; FGFR inhibitors), plus
      - Disease limited to liver or oligometastatic

      } Chemotherapy
  - Chemotherapy
    - Cisplatin and gemcitabine +/- nab-paclitaxel, tegafur, gimeracil, oteracil)
    - FOLFOX (folinic acid, 5-FU, and oxaliplatin)
    - Oligometastatic disease
      - Consider intra-arterial radioembolization (TARE) with Yttrium-90 plus liver chemosaturation
      - Outcome
        - Radiological response rate, 58%
        - Overall survival at 3 yr, 40%

- Targeted Therapies
  - Early success of inhibitors
    - FGFR
    - IDH
    - TRF
    - WNT

- Immunotherapy
  - Checkpoint inhibitors in persons with MMR-deficient CCA

Recommendations

- Surgical
  - Surgical resection (based on the TNM criteria) is currently a potential curative
- Medical
  - Adjuvant chemotherapy with capecitabine for 6 mon after surgical resection with curative intent is recommended for intrahepatic CCA.
  - Liver transplantation is a potential curative option for intrahepatic and perihilar CCA: promising results in terms of overall survival have been reported and it must be considered for patients with cirrhosis and intrahepatic CCA tumours ≤ 2 cm
  - Combination of cisplatin and gemcitabine is the standard of care for patients with unresected tumours, as a palliative treatment.

- FOLFOX (folinic acid, fluorouracil and oxaliplatin) can be recommended as second-line standard of care chemotherapy.
- Molecule profiling of cancer tumour tissue is highly recommended because it could provide access to effective, personalized, treatment options; phase III trial with IDH1-IDH2 or FGFR inhibitors as first- and/or second-line treatment are ongoing.

Abbreviations: CAFs, cancer-associated fibroblasts; CCA, cholangiocarcinoma; dCCA, distal CCA; FAP, fibroblast activating protein; FGFR, fibroblast growth factor receptor; FOLFOX, folinic acid, 5-fluorouracil and oxaliplatin; FXR, farnesoid X receptor; HBV, hepatitis B virus; HCV, hepatitis C virus; IBD, inflammatory bowel disease; iCCA, mixed CCA; IDH, isocitrate dehydrogenase; mon, month; NAFLD, non-alcoholic fatty liver disease; pCCA, perihilar CCA; PSC, primary sclerosing cholangitis; TARE, intraarterial radioembolization; TME, tumour microenvironment; yr, year

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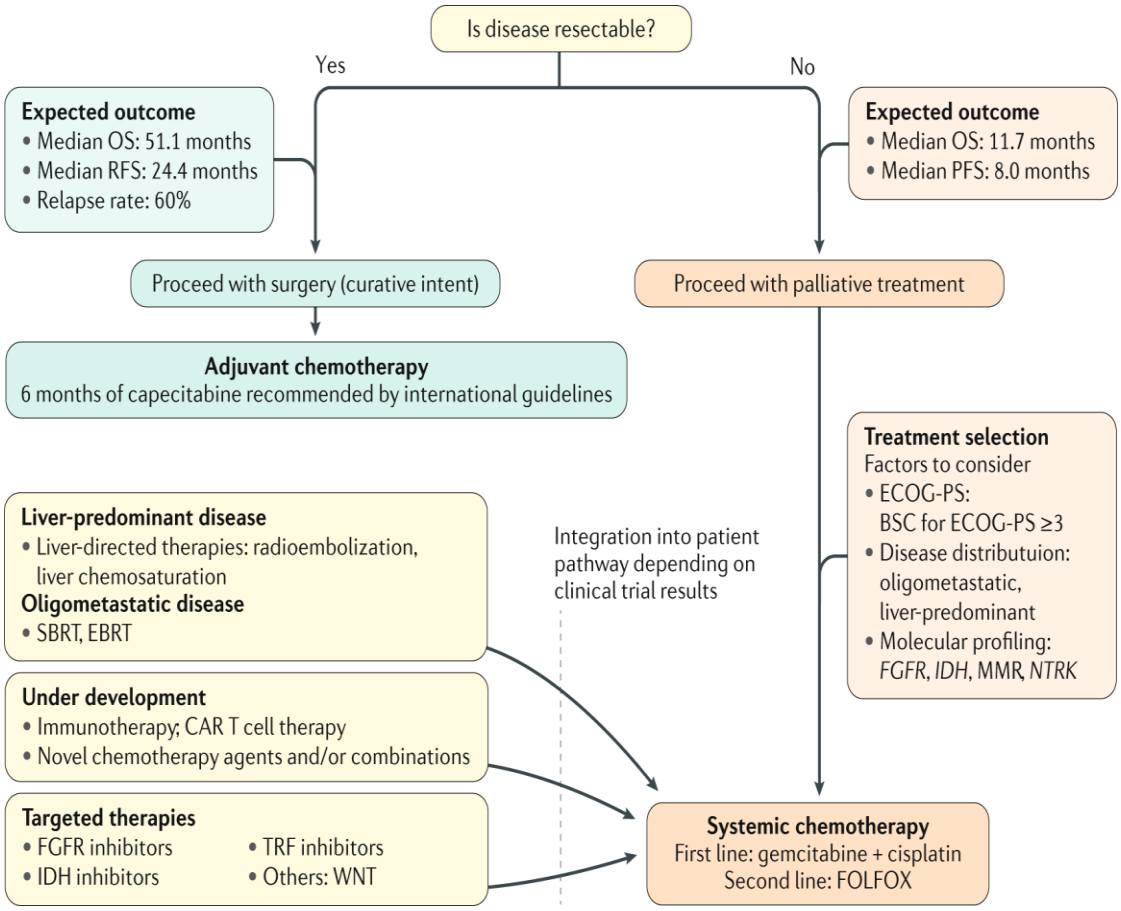
The response of cholangiocarcinomas to chemotherapy is generally poor, with alterations of relevant genes and proteins.

- Give the mechanisms of chemoresistance of drugs used to treat cholangiocarcinoma (CCA) including sorafenib.

Mechanism of Chemoresistance (MOC)			Cisplatin	Doxorubicin	Epirubicin	5-FU / targeted Drugs	Gemcitabine	Sorafenib	Tyrosine kinase inhibitors
	○	Drug	+			+	+		+
1a		− Uptake ↓							
1b		− Export ↑ (many drugs)							
2	○	Intracellular proportion of drug	+			+	+		
3	○	Altered target of drug			+	+			
4	○	DNA repair ↑	+				+		
5	○	Apoptosis ↓				+	+		
6	○	Survival ↑	+			+		+	
7	○	Altered TME		+				+	
8	○	Transition of epithelium to mesenchyme ↑					+		

Abbreviations: TME, tumour microenvironment

Current decisions and management of patients with cholangiocarcinoma



Abbreviations: BSC, best supportive care; CAR, chimeric antigen receptor; EBRT, external beam radiation therapy; ECOG-PS, Eastern Cooperative Oncology Group Performance Status; FOLFOX, folinic acid, 5-fluorouracil and oxaliplatin; MMR, DNA mismatch repair; OS, overall survival; PFS, progression-free survival; RFS, relapse-free survival; SBRT, stereotactic body radiation therapy

Source: Banales JM, et al. Nat Rev Gastroenterol Hepatol 2020; 17: 557-588 (Figure 7)

PANCREAS

Almudaires, Abdulaziz

Hudson, David

PANCREATITIS NATIONAL INSTITUTE OF HEALTH AND CARE EXCELLENCE (NICE) **GUIDELINE** (2018)
(www.nice.org.uk/ng104)

➢ Terminology

- Moderately severe
  - Moderately severe acute pancreatitis is characterized by organ failure that resolves within 48 h (transient organ failure), or local systemic complications in the absence of persistent organ failure (as defined by the revised Atlanta classification)
- Severe acute
  - Severe acute pancreatitis is characterised by single or multiple organ failure that persists for more than 48 h (persistent organ failure; as defined by the revised Atlanta classification).

➢ Patient information

- Give people with pancreatitis, and their family members or carers (as appropriate), written and verbal information on the following where relevant, as soon as possible after diagnosis.
  - Pancreatitis and any proposed investigations and procedures, using diagrams
  - Hereditary pancreatitis, and pancreatitis in children, including specific information on
    - Genetic counselling
    - Genetic testing
    - Risk to other family members
    - Advice on the impact of their pancreatitis on life insurance and travel
  - The long-term effects of pancreatitis, including
    - Effects on the person's quality of life
  - The harm caused to the pancreas by smoking or alcohol
- Advise people with pancreatitis where they might find reliable high-quality information and support after consultation, from sources such as national and local support groups, regional pancreatitis networks and information services.
- Give people with pancreatitis, and their family members or carers (as appropriate), written and verbal information on the following about the management of pancreatitis, when applicable:
  - Why a person may be going through a phase where no treatment is given
  - That pancreatitis is managed by multidisciplinary team
  - The multidisciplinary treatment of pain, including how to access the pain team and
  - Types of pain relief
  - Nutrition advice, including advice on how to take pancreatic enzyme replacement therapy, if needed
  - Follow-up and who to contact for relevant, advice, including advice needed during episodes of acute illness

- Psychological care if needed, where available (see the NICE guideline on depression in adults)
- Pancreatitis services, including the role of specialist centres, and primary care services for people with acute, chronic or hereditary pancreatitis.
- Welfare benefits, education and employment support, and disability services.

- For more guidance on giving information, including providing an individualised approach on helping people to actively participate in their care, see the NICE guideline on patient experience in adult NHS services.
- Explain to people with severe acute pancreatitis, and their family members or carers (as appropriate), that:
  - A hospital stay lasting several months is relatively common, including time in critical care
  - For people who achieve full recovery, time to recover may take at least 3 times as long as their hospital stay
  - Local complications of acute pancreatitis may resolve spontaneously or may take weeks to progress before it is clear that intervention is needed.
  - It may be safer to delay intervention (for example, to allow a fluid collection to mature)
  - People who have started to make a recovery may have a relapse
  - Although children rarely die from acute pancreatitis, approximately 15-20% of adults with severe acute pancreatitis die in hospital.
- Tell adults with pancreatitis that NICE has published a guideline on patient experience in adult NHS services that will show them what they can expect about their care.

➢ Passing information to GP

- Ensure that information passed to GPs includes all of the following, where applicable:
  - Detail on how the person should take their pancreatic enzyme replacement therapy (including dose escalation as necessary)
  - That the person should be offered HbA1c testing at least q6mon and bone mineral density assessments q2yr

➢ Lifestyle intervention

- Alcohol
  - Advise people with pancreatitis caused by alcohol to stop drinking alcohol
  - Advise people with recurrent acute or chronic pancreatitis that is not alcohol-related, that alcohol might exacerbate their pancreatitis
  - For guidance on alcohol-use disorders, see the NICE guidelines on the
    - The diagnosis and management of physical complications of alcohol-use disorders
    - The diagnosis, assessment and management of harmful drinking and alcohol dependence.

- Smoking cessation
    - Be aware of the link between smoking and chronic pancreatitis and advise people with chronic pancreatitis to stop smoking in line with NICE's guidance on stop smoking interventions and services

➢ Complications

- Acute Pancreatitis
    - People with acute pancreatitis usually present with sudden-onset abdominal pain
        - Nausea and vomiting are often present and there may be a history of gallstones or excessive alcohol intake.
        - Typical physical signs include epigastric tenderness, fever and tachycardia
        - Diagnosis of acute pancreatitis is confirmed by testing blood lipase or amylase levels, which are usually raised
        - If raised levels are not found, abdominal CT may confirm pancreatic inflammation
    - Do **not** assume that a person's acute pancreatitis is alcohol-related just because they drink alcohol
    - If gallstones and alcohol have been excluded as potential causes of a person's acute pancreatitis, investigate other possible causes such as:
        - If gallstones and alcohol have been excluded as potential causes of a person's acute pancreatitis, investigate other possible causes such as:
            - Ampullary or pancreatic tumours
            - Anatomical anomalies (pancreas divisum)
            - Autoimmune pancreatitis
            - Hereditary causes
            - Metabolic causes (such as hypercalcemia or hyperlipidemia)
            - Microlithiasis
            - Prescription drugs

- Infection
    - Do **not** offer prophylactic antimicrobials to people with acute pancreatitis.

- Fluid resuscitation
    - For guidance on fluid resuscitation, see the NICE guidelines on intravenous fluid therapy in adult in hospital and in young people in hospital.

- Nutrition support
    - Ensure that people with acute pancreatitis are not made "nil-by-mouth" and do not have food withheld unless there is clear reason for this (for example, vomiting)
    - Offer enteral nutrition to anyone with severe or moderate severe acute pancreatitis
        - Start within 72 h of presentation and aim to meet their nutritional requirement as soon as possible

- Offer anyone with severe or moderate severe acute pancreatitis parenteral nutrition only if enteral nutrition has failed or is contraindicated.

➢ Treatment

- Infected necrosis
  - Offer people with acute pancreatitis an endoscopic approach of managing infected or suspected infected pancreatic necrosis when anatomically possible.
  - Offer a percutaneous approach when an endoscopic approach is not anatomically possible.
  - When deciding on how to manage infected pancreatic necrosis, balance the need to debride promptly against the advantages of delaying intervention.
  - If a person develops necrotic, infective, hemorrhagic or systemic complications of acute pancreatitis.
    - Seek advice from a specialist pancreatic centre within the referral network and
    - Discuss whether to move the person to the specialist centre for treatment of the complications

- Pseudocysts
  - For guidance on managing pseudocysts, please see later

- Pancreatic Ascites and Pleural Effusion
  - For guidance on managing pancreatic ascites and pleural effusion secondary to pancreatitis.
  - Consider referring a person with pancreatic ascites and pleural effusion for management in a specialist pancreatic centre.

- Type 3 Diabetes
  - For guidance on managing type 3c diabetes secondary to pancreatitis.
  - Assess people with type 3c-diabetes q6mon for potential benefit of insulin therapy
  - For guidance on managing type 3c for people who are not using insulin therapy, see the NICE guidelines on type 2 diabetes in adults and diagnosing and managing diabetes in children and young people.
  - For guidance on managing type 3 diabetes for people who need insulin, see
    - The recommendations on insulin therapy and insulin delivery in the NICE guideline on type 1 diabetes in adults.
    - The recommendations on insulin therapy in the NICE guideline on diagnosis and managing diabetes in children and young people
    - NICE's technology appraised guidance on continuous subcutaneous insulin infusion for the treatment of diabetes mellitus

- For guidance on education and information for people with pancreatitis and type 3c diabetes requiring insulin, see the recommendations on education and information in the NICE guideline on diagnosing and managing type 1 diabetes in adults, and education and information in the NICE guideline on diagnosing and managing diabetes in children and young people.
- For guidance on self-monitoring blood glucose for people with pancreatitis and type 3c diabetes requiring insulin, see the recommendations on blood glucose management in the NICE guideline on diagnosing and managing type 1 diabetes in adults, and blood glucose monitoring in the NICE guideline on diagnosing and managing diabetes in children and young people.

- Chronic pancreatitis
  - People with chronic pancreatitis usually present with chronic or recurrent abdominal pain.
    - This guideline assumes that people with chronic abdominal pain will already have been investigated using CT scan, ultrasound scan or upper gastrointestinal endoscopy to determine a cause for their symptoms.
  - The guideline committee looked at evidence on diagnosing chronic pancreatitis, and the evidence review can be found in the full guideline.
  - Do **not** assume that a person's chronic pancreatitis is alcohol-related just because they drink alcohol. Other causes include:
    - Genetic factors
    - Autoimmune disease, in particular IgG4 disease
    - Metabolic disease
    - Structural or anatomical factors

- Investigation Upper Abdominal Pain
  - Think about chronic pancreatitis as a possible diagnosis for people presenting with chronic or recurrent episodes of upper abdominal pain and refer accordingly.
  - For adults with neuropathic pain related to chronic pancreatitis, follow the recommendations in the NICE guideline on neuropathic pain in adults.

- Nutrition Support
  - Be aware that all people with chronic pancreatitis are at high risk of malabsorption, malnutrition and a deterioration in their quality of life.
  - Use protocols agreed with the specialist pancreatic centre to identify when advice from a specialist dietitian is needed, including advice on food, supplements and long-term pancreatic enzyme replacement therapy, and when to start these interventions.
  - Consider assessment by a dietitian for anyone diagnosed with chronic pancreatitis.
  - For guidance on nutrition support for people with chronic alcohol-related pancreatitis, see alcohol-related pancreatitis in the NICE guideline on alcohol-use disorders.
  - For guidance on nutrition support, see the NICE guideline on nutrition support for adults.

- Pancreatic Duct Obstruction
    - Offer endoscopic ultrasound (EUS)-guided drainage, or endoscopic transpapillary drainage for pancreatic head pseudocysts
        - To people with symptomatic pseudocysts (for example, those with pain, vomiting, or weight loss).
    - Consider EUS-guided drainage for pancreatic head pseudocysts
        - For people with non-symptomatic pseudocysts that meet 1 or more of the following criteria:
            - They are associated with pancreatic duct disruption
            - They are creating pressure on large vessels or the diaphragm
            - They are at risk rupture
            - There is suspicion of infection
    - Consider surgical (laparoscopic or open) drainage of pseudocysts that need intervention if endoscopic therapy is unsuitable or has failed.

➢ Follow-up

- Pancreatic Exocrine Function
    - Offer people with chronic pancreatic monitoring by clinical and biochemical assessment, to be agreed with the specialist centre, for pancreatic exocrine insufficiency and malnutrition at least every 12 mon
        - Adjust the treatment of vitamin and mineral deficiencies accordingly
    - Offer adults with chronic pancreatitis a bone density assessment q2yr

- Pancreatic Cancer
    - Be aware that people with chronic pancreatitis have an increased risk of developing pancreatitis cancer
        - The lifetime risk is highest, around 40% in those with hereditary pancreatitis
    - Consider annual monitoring for pancreatic cancer in patients with hereditary pancreatitis

- Diabetes
    - Be aware that people with chronic pancreatitis have a greatly increased risk of developing diabetes, with a lifetime risk as high as 80%. The risk increases with duration of pancreatitis and presence of calcific pancreatitis.
    - Offer people with chronic pancreatitis monitoring of HbA1C for diabetes at least 6 mon.

ACUTE PANCREATITIS (AP)

Management of Acute Pancreatitis: ACG Guideline (2013)

Tenner S, et al. Am J Gastroenterol 2013;108(9):1400-15; 1416

➢ Definition

Atlanta Criteria (1993)	Atlanta Revision (2013)
○ Mild acute pancreatitis − Absence of organ failure − Absence of local complications	○ Mild acute pancreatitis − Absence of organ failure − Absence of local complications
	○ Moderate severe acute pancreatitis − Local complications and/or − Transient organ failure (< 48 h)
○ Severe acute pancreatitis − Local complications − Organ failure − GI bleeding (> 500 cc / 24 h) − Shock – SBP ≤ 90 mm Hg − PaO_2 ≤ 60% − Creatinine ≥ 2 mg/dL	○ Severe acute pancreatitis − Persistent organ failure > 48 h

Abbreviations: GI, gastrointestinal; SBP, systolic blood pressure

➢ Clinical

○ Acute pancreatitis (AP) is diagnosed by the patient having ≥ of the following
− Severe, characteristic pain
− Serum amylase / lipase ↑ 3x ULN
− Diagnostic imaging characteristics on US, MRI, or contrast enhanced CT (CECT)

- Prediction of severe acute pancreatitis

○ Findings associated with a severe course for initial risk assessment
− Patient characteristics
▪ Age > 55 yr
▪ Obesity (BMI > 30 kg/m^2)
▪ Altered mental status
▪ Comorbid disease

○ The systemic inflammatory response syndrome (SIRS) presence > 2 of the following criteria
− Pulse > 90 beats/mins
− Respiratory > 20 /min or PaO_2 > 32 mm Hg
− Temperature > 38°C or < 36°C
− WBC count > 12,000 or < 4,000 cells/mm^3 or 10% immature neutrophils (bands)

- ↑ BUN > 20 mg/dL
  - Rising BUN
- ↑ HCT > 44%
  - Rising BUN
- ↑ creatinine

- Diagnostic imaging
  - Pleural effusions
  - Pulmonary infiltrates
  - Multiple or extensive extrapancreatic collections of fluid

Abbreviations: BMI, body mass index; BUN, blood urea nitrogen; HCT, hematocrit; WBC, white blood cell;

- There are numerous clinical, laboratory and diagnostic imaging findings which can be used in various scoring systems to determine / score severe versus non-severe acute pancreatitis.
  - Conceptually these can be thought of as inflammation, local/systemic complications including organ failure and severe inflammatory response syndrome (SIRS)
  - Usual causes are alcohol and choledocholithiasis
    - If these are not causative, then explore other diagnosis, such as
      - Genetic mutations of patient < 40 yr
      - Metabolic causes (severe hypertriglyceridemia > 1000 mg/dL)
- Suspect AP if
  - Abdominal pain consistent with diagnosis
  - ↑ serum amylase / lipase ≥ 3x ULN
- Suspect hereditary causes
  - Family history
  - AP in persons < 30 yr
- Measure IgG4 if common causes of AP are normal

➢ Diagnostic imaging

- Perform transabdominal ultrasound (Strong recommendation; low quality of evidence)
- Patients > 40 yr suspect pancreatic duct cancer (PDCA) (Conditional recommendation; low quality of evidence)
- Contrast enhanced CT / completed tomography +/- MRI of pancreas
  - Failure of patient to improve after 3 d
  - Diagnosis unclear
  - Possible complications of acute pancreatitis

  (Strong recommendation; low quality of evidence)

- Treatment
  - Generous fluid resuscitation with NS/RL 250-500 mL/h, initially target to ↓ BUN / ↓ Cr in first 12 to 24 h
  - If choledocholithiasis suspected from ↑ bilirubin / cholangitis → ERCP and stone extraction, possibly stents
    - Appropriate antibiotics appropriate only for cholangitis / infected measures proven on culture from CT-graded FNA
      - Extrapancreatic infections, e.g., associated bacteremia, pneumonia, UTI
    - Empiric antibiotics (carbapenems, metronidazole, quinolones) for suspected infected necrosis while awaiting FNA biopsy culture results
  - Adequate pain control
  - Management of complications
  - If choledocholithiasis suspected from ↑ bilirubin / cholangitis → ERCP and stone extraction, possible stents
    - Appropriate antibiotics (only for cholangitis / infected necrosis (suspected from failure to improve after IV fluids, pain control), proven on culture) from CT-guided)
    - Empiric antibiotics (carbapenems, metronidazole, quinolones) for suspected infected necrosis while awaiting FNA biopsy culture results.
  - Nutritional support
    - Mild AP
      - Food po (clear fluids, low fat) as long as no nausea/vomiting or pain
    - Severe AP
      - Enteral nutrition, or if necessary, parenteral nutrition (PN)
      - Delivery by nasogastric (NG) or by nasojejunal (NJ) tube are comparable
  - Surgery
    - Cholecystectomy for gallstones before patient discharge for mild AP, to ↓ risk of recurrent AP
    - For severe necrotizing biliary AP, cholecystectomy after inflammation and fluid collection resolve
    - Pseudocyst and pancreatic / extrapancreatic necrosis
    - No cholecystectomy needed
    - Stable patient with infected necrosis → drainage in 4 wk
      - Symptomatic → minimally invasive necrosectomy

Abbreviations: AP, acute pancreatitis; BUN, blood urea nitrogen; Cr_s, serum creatinine; ERCP, endoscopic retrograded pancreaticocholangiography; FNA, fine needle aspiration; NJ, nasojejunal; NS, normal saline; PN, parenteral nutrition; RL, Ringer lactate; UTI, urinary tract infection

- Early ERCP in AP
  - Pancreatitis
    - Cholelithiasis, no biliary obstruction
      - No ERCP needed (Strong recommendation, moderate quality of evidence)
    - Biliary obstruction cholangitis
      - ERCP for drainage (Strong recommendation, moderate quality of evidence)
  - In high risk patient
    - Give NSAID suppository to ↓ risk of post-ERCP pancreatitis (Conditional recommendation, moderate quality of evidence)

Recommendations

- ICU admission
  - High risk category (Conditional recommendation, low quality of evidence)
  - Organ failure (Strong recommendation, low quality evidence)
  - Hemodynamic compromise (Strong recommendation, moderate quality of evidence)
- Early aggressive IV hydration
  - 250 to 500 mL/h for 24 h using lactate Ringer solution (Conditional recommendation, moderate quality of evidence), with reassessment and adjustment of rate to target ↓ BUN (Strong recommendation, moderate quality of evidence)
  - Cautions
    - Patient with severe volume depletion (tachycardia, hypotension)
      - Initial bolus infusion may be necessary (Conditional recommendation, moderate quality of evidence)
    - Slower volume infusion if patient has comorbidities such as cardiovascular / renal dysfunction
- Antibiotics
  - Prophylactic
    - Do **not** use prophylactic antibiotics (Strong recommendation, moderate quality of evidence)
  - Active infection
    - Treat associated non-pancreatic infections, e.g.
      - Bacteremia
      - Biliary tree – Cholangitis
      - GU – Urinary tract infection (catheter-acquired)
      - Lung – Pneumonia

      (Strong recommendation, moderate quality evidence)

- Infected pancreatic / extrapancreatic necrosis (Strong recommendation, moderate evidence)

↓

  - Suspect when patient fails to improve +/-
  - CT on admission shows pancreatic / extrapancreatic necrosis
  - CT-guided FNA for C/S, gram stain → sterile necrosis →
    - Stop antibiotics (Strong recommendation, moderate quality of evidence)
    - Repeat q5 to 7 d as indicated clinically (Conditional recommendation, moderate quality of evidence)

↓

  - Begin antibiotics directed by gram stain, C/S
    - Infected necrosis (carbapenem, quinolone, metronidazole) (Conditional recommendation, moderate quality of evidence)
      - If symptomatic / stable, drain/debride (endoscopically / radiologically)
      - If asymptomatic / stable → wait for ~ 4 wk to drain / debride after formation
      - Do **not** give routine administration of antifungal agents along with prophylactic or therapeutic antibiotics (Conditional recommendation, low quality of evidence)

↓

  - If empiric antibodies already started, modify depending upon C/S

- Nutrition

Recommendation

- Mild AP
  - Oral feeding, of low-fat solid diet as soon as no abdominal pain, nausea / vomiting (Conditional recommendation, moderate quality of evidence)
- Severe AP
  - Enteral feeding to meet nutritional requirements
    - Nasogastric
    - Nasojejunal

    } Delivery (Strong recommendation, moderate quality of evidence)
  - Do **not** use parenteral nutrition, unless enteral nutrition not available (Strong recommendation, high quality of evidence)

❖ Surgery

- Mild AP, cholelithiasis
  - Cholecystectomy before patient is dialysed from hospital (moderate recommendation, moderate quality of evidence)

- Necrosis, symptomatic
  - Non-infected
    - Biliary origin of AP
      - Wait for cholecystectomy until
        - Active inflammation resolved
        - Fluid collection stabilizes / resolves

    (Strong recommendation, moderate evidence)
  - Infected
    - Patient stable
      - Drainage (endoscopically, radiologically, surgically) in ≥ 4 wk so that
        - Necrosis liquifies
        - Walled-off necrosis develop from fibrosis wall around the necrosis (Strong recommendation, low quality of evidence)
    - Patient unstable
      - Urgent drainage: minimally invasive necrosectomy (Strong recommendation, low quality of evidence)
  - Asymptomatic pseudocysts and asymptomatic pancreatic and/or extrapancreatic necrosis (Moderate recommendation, high quality of evidence)

Acute Pancreatitis: Technical Review (2007)

Forsmark CE and Baillie J. Gastroenterology 2007; 132: 2022-2044

➢ Diagnosis of acute pancreatitis (AP)

- Clinical suspicion
  - Abdominal pain
    - Radiation to back
    - Peaks in 30-60 min
    - Lasts for days to weeks

- Laboratory

	Sensitivity	Specificity
↑ amylase 2x > ULN	45%	97%
↑ lipase	100%	96%

- Diagnostic imaging
  - Abdominal ultrasound
    - ↓ sensitivity if overlying goes
    - ↓ accuracy to diagnosis
      - Pancreatic necrosis
      - Peripancreatic
        - Fluid
        - Inflammation
    - Useful to diagnose
      - Cholelithiasis
      - Choledocholithiasis (↑ CBD diameter)
  - CT scan, pancreatic protocol / IV contrast-enhanced CT (CECT)
    - Useful to detect pancreatic necrosis after ~ 3d (< 30 Hounsfield units of enhancement)

➢ Predictive Scores of Prognosis

- Clinical
  - About 20% of patients with acute pancreatitis develop severe pancreatitis, necrosis of parenchyma +/- infection; SIRS, systemic inflammatory response, multiorgan system failure (MOSF), death (~10%)
  - 50% of deaths occur in weeks 1 of AP

- SIRS components
  - Heart rate > 90 bpm (beat per minute)
  - Body temperature < 36°C - > 38°C
  - Respiratory rate, 20 breaths per min, or $PaCO_2$ < 32 mm Hg (hypocarbia)
  - WBC
    - < 4000 - > 12,000 cells/μL, or
    - Band forms > 10%

  → ↑ risk of
    - MOSF
    - Mortality, 25%

- Atlantic Criteria of Severe Acute AP System (CVS)
  - Organ failure
    - Cardiovascular system (CVS)
      - Systolic blood pressure < 90 mm Hg
    - Pulmonary failure (insufficiency)
      - $PaCO_2$ < 60 mm Hg
    - Renal failure
      - Cr_s > 2 mg/dL
    - GI bleeding
      - 500 mL blood in last 24 h
  - Local pancreatic complications
    - Abscess
    - Necrosis (≥ 3% of pancreatic parenchyma, a > 3 cm)
    - Pseudocyst

- Other risk factors
  - Age
  - Comorbidities
  - Complications
    - Systemic
    - Local

➢ CT Scan (Balthazar) of Severity Index

Grade	CT Findings
A	− Normal
B	− Focal or diffuse enlargement of the pancreas, including ▪ Irregularities of contour and ▪ Inhomogeneous attenuation
C	− Pancreatic gland abnormalities in grade B, plus ▪ Pancreatic inflammation
D	− Grade C, plus ▪ A single fluid collection
E	− Grade C, plus ▪ ≥ 2 or more fluid collections and/or the presence of gas in or adjacent to the pancreas

Printed with permission: Forsmark CE and Baillie J. Gastroenterology 2007; 132: 2022-2044 (Table 5).

- 30% pancreatic necrosis or CT, ↑ risk
  - ↑ Complication
  - ↑ length of hospital stay (LOS)
  - Death

  } ▪ Sensitivity, 88%
  ▪ Specificity, 65%

- CT severity index > 5 associated with ↑ risk

Complication	↑ risk
− Necrosectomy (P = 0.001)	10x
− LOS (P < 0.001)	17x
− Death (P = 0.0005)	8x

CT severity index

% necrosis	Organ Failure
< 30	5%
30% - 50%	24%
> 50%	50%

- In patient with ↑ serum creatinine (↑ Cr_s); renal impairment)
  - Use gadolinium-enhanced MRI, **no** CT scan

- Comparison of scoring indices

Complication	Scoring System
− Necrosis − Organ failure	▪ Balthazar CT score ▪ Ranson criteria ▪ Apache II/III

Ranson's Criteria

At Admission	Within Next 48 hours
○ Age ≥ 55 yr (older than 70 yr)	− ↓ hematocrit by >10% (same)
○ White blood cell count >16,000/μL (>18,000/μL)	− Fluid sequestration estimated of >6 L (>4 L)
○ Blood glucose >200 mg/dL (>220 mg/dL)	− Serum calcium < 8.0 mg/dL (same)
○ Serum lactate dehydrogenase > 350 IU/L (>400 IU/L)	− Pa_{O_2} < 60 mm Hg (omitted)
○ Serum aspartate aminotransferase level >250 IU/L (same)	− Blood urea nitrogen level ↑ > 5 mg/dL after intravenous fluid hydration (> 2 mg/dL) − Base deficit of >4 mmol/L (>6)

NOTE.

- The criteria for non-gallstone (alcoholic) acute pancreatitis are listed first; the changes (if any) in the criteria for gallstone pancreatitis are in parentheses.

Printed with permission: Forsmark CE and Baillie J. Gastroenterology 2007; 132: 2022-2044 (Table 3).

Atlanta Criteria for Severity

Feature	
○ Organ failure	− Shock (systolic blood pressure <90 mm Hg) − Pulmonary insufficiency (Pa_{O_2} <60 mm Hg) − Renal failure (serum creatinine level >2 mg/dL after rehydration) − Gastrointestinal bleeding (>500 mL/24 h)
○ Local complications	− Pancreatic necrosis (more than 30% of the parenchyma or more than 3 cm) − Pancreatic abscess (circumscribed collection of pus containing little or no pancreatic necrosis) − Pancreatic pseudocyst (collection of pancreatic juice enclosed by a wall of fibrous tissue or granulation tissue)
○ Unfavorable prognostic signs	− Ranson's score ≥3 − APACHE II score ≥8

Printed with permission: Forsmark CE and Baillie J. Gastroenterology 2007; 132: 2022-2044 (Table 2).

➢ Laboratory Markers of Severity

- Hematocrit (hemoconcentration; Hct)
  - Hct > 44% on admission and persisting 24 h (NPV; 96%): prediction of pancreatic necrosis. Organ failure (NPV, 97%)
- ↑ Cr_s (serum creatinine)
  - Performance characteristics

Timing	Sensitivity	Specificity
Admission	72%	83%
After 24%	94%	69%

  - Unlikely to have necrosis / organ failure

➢ Causes and Associations

- Alcohol and cholelithiasis / cholelithiasis are each responsible for about 1/3 of cases of AP
- Gallstone pancreatitis
  - More common in older women
  - ↑ ALT ≥ 3x ULN is 95% accurate to diagnose gallstone acute pancreatitis (GAP)
  - ↑ bilirubin also suggests GAP
- Diagnostic imaging of cholelithiasis, dilated common bile duct, plus ↑ ALT / ↑ bilirubin indicates high likelihood of GAP

- Case questions for excessive alcohol misuse.
  - C – Cut down (“have you ever felt you should cut down on your drinking?”)
  - A – Annoyed (“have people annoyed you by criticizing your drinking?”)
  - G – Guilty (“have you ever felt bad or guilty about your drinking?”)
  - E – Eye opener (“have you ever had a drinking first thing in the morning?”

- Give less common structural causes if acute pancreatitis.
  - Bile ducts
    - Choledochal cysts
  - Pancreatic ducts
    - Pancreas divisum
    - Abnormal (pancreaticobiliary ductal union)
  - Duodenal
    - Duplication
  - Ampulla
    - Adenoma / carcinoma
    - Sphincter of Oddi spasm (SOS) / stenosis

  - Measurement of ↑ serum lipase is more specific for pancreatitis, biliary tract disease, intestinal obstruction or appendicitis

- Give other causes of ↑ amylase but normal lipase concentrations.
  - Head/neck
    - Trauma (intracranial bleed)
    - Parotitis
  - Lung
    - Carcinoma
  - GU
    - Ovarian cyst
    - Cystic neoplasm
  - Endocrine
    - Diabetic ketoacidosis
  - Infection
    - Human immunodeficiency virus (HIV)

Abbreviations: ALT, alanine aminotransferase; AP, acute pancreatitis; C, centigrade; CBD, common bile duct; CECT, contrast-enhanced CT; Cr_s, serum creatinine; CT, computed tomography; d, day; GAP, gallstone-associated acute pancreatitis; GI, gastrointestinal; h, hour; Hct, hematocrit; HIV, human immunodeficiency virus; IV, intravenous; LOS, length of [hospital] stay; min, minute; MOSF, multiorgan system failure; NPV, negative predictive value; P, probability value; SIRS, systemic inflammatory response syndrome; SOS, sphincter of Oddi; ULN, upper limit of normal; WBC, white blood cells

Management of Acute Pancreatitis: Quality Indicators (2019)

Vivian E, et al. Am J Gastroenterol 2019; 114: 1322-1342

- Please see above publication for validated quality indicators (Qis) '…which assess process, outcome, appropriateness, efficiency and structure of care metrics [which can] provide a quantitative basis for quality improvement"
- Presented there are "validity and necessarily median rating[s]", as well as suggested performance thresholds. The details of the domains are provided, including
  - Type of measure
  - Performance target
  - Quality of evidence
  - Strength of recommendation
- The implementation of these quality indicators and their incorporation into a quality improvement program is essential to achieve the maximum benefit of the guidelines outlined for patients with acute pancreatitis.

CHRONIC PANCREATITIS

Chronic Pancreatitis: ACG Guideline (2020)

Gardner TB, et al. Am J Gastroenterol 2020; 115: 322-339

- Definition
  - A paradigm shifts into the realm of precision medicine for complex disorders, which "…focuses on diagnosing the mechanistic disorder underlying the pathogenic process early in the disease course and managing the syndrome more holistically to change the natural course of the disease and minimize adverse disease effects"
    - This replaces the previously used traditional
      - Clinicopathological-based definition, as well as the
      - Cambridge definition using an ERCP-based scoring system

- Diagnosis

Recommendation

  - Use computed tomography (CT) or MRI to diagnose CP
    - Endoscopic ultrasonography (EUS) should be used only if the diagnosis of CP in question after CT/MRI is performed (Strong recommendation, low quality of evidence)

- Diagnostic Imaging
  - Performance characteristics (for diagnosis of CP)

	Mean (95% Confidence Interval [CI])	
DI Test	Sensitivity	Specificity
CT	75% (66% to 83%)	91% (81% to 96%)
MRI	78% (69% to 85%)	96% (90% to 98%)
EUS	81% (71% to 89%)	90% (82% to 95%)
US		98% (89% to 100%)
ERCP		94% (87% to 98%)

  - DI is a surrogate for histology
  - Suggestion
    - Begin DI with pancreas protocol CT (cross sectional imaging)

↓

  - EUS for suspected "minimal change disease" CP with no fibrosis

↓

Secretin stimulated MRCP (s-MRCP)

↑ visualization of MPD and SBDs changes qualification of function (duodenal filling (correlation with CP severity / exocrine dysfunction

➢ Laboratory (tests of pancreatic exocrine function)

Recommendation

- Use secretin-enhanced magnetic resonance cholangiopancreatography (s-MRCP) when the diagnosis of CP following cross-sectional imaging of EUS is not confirmed and the clinical suspicion remains high (Conditional recommendation, low quality of evidence)
- S-MRCP, "dynamic thick-slab 2-dimensional MRCP, represents a second-line (ancillary) test
- The pancreas has a large exocrine secretory reserve, and > 90% of the pancreas must be destroyed before they develop exocrine pancreatic insufficiency (EPI)
  - EPI
    - Clinical symptoms
      - Pain
      - Steatorrhea / azotorrhea
      - Fat soluble vitamin deficiency
    - Represents an imbalance of Intake
      - Digestion, fat / protein / carbohydrate
      - Needs, nutritional
      - Adaptation, small intestine

❖ Hormonal and Non-hormonal Tests of Pancreatic Exocrine Function

- Hormone stimulation direct tests
  - Secretin stimulation of pancreatic duct cells (performed with endoscopic placement)
  - Cholecystokinin (CCK) stimulation of pancreatic acinar cells (performed with placement of a Dreiling tube)
- Non-hormone tests
  - Blood — Serum trypsinogen / tyrosine
  - Breath — 13C-mixed triglyceride test
  - Stool — Fecal elastase-1

➢ Histopathology

Recommendation

- Do histological examination to diagnose CP in high-risk patients if clinical and functional evidence of CP is strong, but imaging modalities are inconclusive (Conditional recommendation, very low quality of evidence)
- Endoscopic ultrasound guided fine needle biopsy [aspiration] (EUS-FNA)
  - While histological diagnosis has been considered to be the "gold" standard for the diagnosis of CP, the histopathological changes may be patchy (sampling error), and "histological interpretation … is prone to subjectivity" → low diagnostic sensitivity
- Perform EUS-FNA in high-ris patients after first- and second-line tests (clinical history and physical, DI and laboratory testing)

FNA histology of pancreas is useful to "rule out" CP

➢ Causes / Associations

- The TIGAR-O system provides an acronym for a checklist for etiology and for risks
  - T Toxic-metabolic
  - I Idiopathic
  - G Genetic
  - A Autoimmune
  - R Recurrent acute (RAP) / severe acute pancreatitis (SAP)
  - O Obstruction
- A simpler acronym IRO
  - I Inherited
    Idiopathic
    Immune
    Injury (drugs, toxins)
  - R Recurrent acute / severe pancreatitis
  - O Obstruction

Recommendations

- Perform genetic testing in patients < 30 yr, or where the diagnosis is uncertain (Strong recommendation, low quality of evidence)
- Determine genetics in patients with early CP, when early diagnosis and treatment of CP may prevent progression to irreversible disease.
- A possible inherited disorder is important to consider in the patient with CP
  - May coexist with another cause of CP
  - Useful for establishing prevalence of CP and thus the P/NPVs
  - May help target therapy
  - Prognosis
  - Family counselling
- ACG Guidelines (2020) recommend that "… at minimum, patients with idiopathic CP should be evaluated for genetic polymorphisms" (gene mutational analysis), causing
  - Acinar cell dysfunction
    - PRSSI (cationic trypsinogen genes) [complex inheritance, low penetration]
    - SPINK1 (serine protein inhibitor Kazal type 1) [AR]
  - Ductal cell dysfunction
    - CFTR (cystic fibrosis transmembrane conductance regulator) [AR]
  - Disease-modifying genes
    - CTRC (chymotrypsin C) [complex inheritance]

➢ Treatment

❖ Lifestyle

Recommendation

- Stop all alcohol consumption in patients with CP (Strong recommendation, very low quality of evidence)

- Performing elective interventional procedure on patients who are actively using alcohol should be considered cautiously.
- Patients requiring urgent or emergent procedures for complications of CP should be considered separately.
- Abstinence from alcohol
  - ↓ pain / ↓ pain attacks
  - ↓ hospitalizations
  - Does not necessarily ↓ progression of CP
- Stop smoking

Recommendation

- Stop smoking cigarette in patients with CP (Strong recommendation, very low quality of evidence)

❖ Scoring

- Diabetes
  - The development of DM in CP is most likely related to
    - Duration of disease
    - Other etiologic factors such as body mass index and smoking status may ↑ risk
  - Type 3c DM (islet cell loss)
  - Type 2, associated with obesity
  - New-onset DM with weight loss (screen for PDAC)
- Pancreatic duct adenocarcinoma (PDAC)
  - "…there is no definitive benefit to screen patients with CP for PDAC"
    Possible exceptions: family history of PDAC, new onset DM with weight loss
- Bone mineral density
  - DEXA scan to assess presence of osteoporosis → target therapy

❖ Pain control

- Pancreatic duct obstruction
  - Exclude pancreatic duct obstruction as a cause/contributor to pain
    - Stones
    - Strictures

    } May occur together
  - Therapeutic options
    - ERCP (decompressive procedure)
      - Splenectomy
      - Stone clearance
      - Stricture dilation
      - Stenting
      - Lithotripsy
      - EUS (transluminal stent)

- Surgical
  - Decompressive procedure
    - Beger
    - Frey
    - Puestow
  - Partial pancreatectomy

- Apparent Contraindication, but be Pragmatic
  - Generally speaking, surgery provides better outcomes than do endoscopic procedures
    - Less additional drainage required
    - Less long term pain
    - Less post-operative malnutrition / ↑ post-op weight gain

Recommendation

- Use surgical intervention in patients with obstructive CP for the long-term relief of pain if first-line endoscopic approaches to pancreatic drainage have been unsuccessful (Strong recommendation, moderate quality evidence)
- Use antioxidant therapy for CP with pain (even although the benefit of pain reduction is likely limited) (Conditional recommendation, moderate quality of evidence)
- Use opiates to treat painful CP only in patients in whom all other reasonable therapeutic options have been exhausted.
- If antioxidants are going to be given a trial use in an individual patient with CP, it is suggested from clinical trials that the supplement should include
  - Ascorbic acid
  - Methionine
  - Selenium
- Do **not** use pancreatic enzyme supplements to improve pain in CP (Conditional recommendation, low quality of evidence)
- Celiac plexus blockage
  - Inject local anesthetic plus a corticosteroid into +/- around region of celiac ganglion
  - Method
    - Endoscopy
    - Interventional radiology
    - Surgery
  - Pain reduction/relief for 3-6 mon
    - Median response rate ~65%

Key concepts

- Only use TPIAT for highly selected patients with refractory chronic pain in which all other symptom control measures have failed.
- Only use experimental treatment modalities in the context of a clinical research trial.
- Perform periodic evaluation for malnutrition, including tests for osteoporosis and fat-soluble vitamin deficiency

- Pancreatic enzyme replacement therapy (PERT)

- Nutritional Improvement
    - 40,000 to 50,000 USP units of lipase with each meal
        - Balanced diet used with PERT to
            - Achieve ideal body weight
            - Minimize symptoms of steatorrhea
            - Maintain normal
                - Blood concentrations of fat soluble vitamins
                - Bone mineral density DEXA scan
            - Optimize steatorrhea →
                - ↓ fecal fat ≥ 30
                - ↓ fecal nitrogen
                - ↓ stool weight
                - ↓ flatulence improve stool consisting
    - Supplementation
        - Fat-soluble vitamins (FSV)
        - Zinc and magnesium

Clinical Gem

- Patients with CP should be considered for supplementation with fat soluble vitamins (FSV), zinc and magnesium, even if they do not have EPI (these nutrient deficiencies may occur even without EPI).

- Pain Control

Recommendation

- Use PERT in patients with CP and EPI to improve the complications of malnutrition (Conditional recommendation, low level of evidence).
    - To ↓ pain / ↑ quality of life

Abbreviation: ACG, American College of Gastroenterology; AIP, autoimmune pancreatitis; AR, autosomal recessive; CCK, cholecystokinin; CI, confidence interval; CKD, chronic kidney disease; CP, chronic pancreatitis; CT, computed tomography; DEXA, bone mineral density study; DI, diagnostic imaging; DM, diabetes mellitus; EPI, exocrine pancreatic insufficiency; ERCP, endoscopic retrograde cholangiopancreatography; ESRD, end stage renal disease; EUS, endoscopic ultrasound; EUS-FNA, endoscopic ultrasound fine needle aspiration; FSV, fat soluble vitamins; HTP, hypertriglyceridemia; MPD, main pancreatic duct; MRCP, magnetic resonance imaging; MRI, magnetic resonance imaging; NOS, not otherwise specified; NPV, negative predictive value; PDAC, pancreatic duct adenocarcinoma; PERT, pancreatic enzyme replacement therapy; PPV, positive predictive value; RAC, recurrent acute pancreatitis; SAP, severe acute pancreatitis; SBPD, side branched (pancreatic) ducts; s-MRCP, secretin-stimulated magnetic resonance imaging; US, ultrasound

AUTOIMMUNE PANCREATITIS

Advances in Autoimmune Pancreatitis (2015)

Hart PA, et al. Gastroenterology 2015; 149: 39-51

- Definitions: Autoimmune pancreatitis (AIP)
  - "…a form of chronic pancreatitis that is characterized clinically by frequent presentation with obstruction jaundice
    - Histologically by a dense lymphoplasmacytic infiltrate and fibrosis, and
    - Therapeutically by dramatic response to corticosteroids policy"

- Demography
  - Prevalence < $1/10^5$
    - Age > 60 yr
  - More common in male "blue collar workers"
  - Prognosis
    - 5 yr survival rate similar to age-/sex-matched population

- Subtypes
  - "AIP", equated with type 1 AIP (lymphoplasma sclerosing pancreatitis [LPSP])
  - "IDCP" (idiopathic duct-centric pancreatitis associated with GEL (granulocytic epithelial lesion), type 2 AIP

AIP (IgG4-related Pancreatitis)

- The pancreatic manifestation of IgG4-related disease [IgG4-RD]
- Definition (please also see above)
  - "..a multiorgan syndrome characterized by typical histology in affected organs,
  - Frequent elevations of serum IgG4 levels,
  - Abundant IgG4+ plasma cells in affected organs, and dramatic response to corticosteroid therapy"

- Clinical
  - Painless jaundice
  - Acute / chronic pancreatitis / pancreatic insufficiency / hyperglycemia
    - New onset diabetes
  - Pancreatic duct stones
  - Pancreatic mass / enlargement
  - Pancreatic duct adenocarcinoma (PDAC)
  - Other organ involvement
    - Salivary glands
    - Bile ducts
    - Renal parenchyma
    - Retroperitoneal fibrosis

- Laboratory
  - ↑↑ IgG4 in ~66% of patients with AIP
    - PPV only 10% to 15%
  - Differential of mild ↑IgG4 (1 to 2x ULN)
    - Pancreatic duct adenocarcinoma (PDAC)
    - Primary sclerosis cholangitis (PSC)
    - Cholangiocarcinoma (CCA)

- Pathogenesis

- Genetic predisposition

HLA genes	− DRB1*0405 − DQB1*0401
No-HLA genes (single nucleotide polymorphisms)	− Cationic trypsinogen (PRSSI) − Cytotoxic T lymphocyte-associated antigen 4 − Fc receptor-like 3 − Tumour necrosis factors

- Immunologic Trigger

Overview

Th2 / Treg activation →	− ↑IL-4, -5, -13 → eosinophil activation → ↑ IgE → allergy-like features − ↑ TGF → activation of ▪ Fibroblasts ▪ Macrophages ← Fc receptors, Immune complexes, Non-IgG4 ↓ − Extracellular remodeling
B cell activation →	− ↑ Bregs − ↑ oligoclonal expansion of plasmablasts − Differentiation of plasma cells − ↑↑ IgG4

- Autoimmunity

Autoantibodies (non-specific)	− Lactoferrin, 75% − Carbonic anhydrase II, 55% − Anti-nuclear antibodies, 40% − Pancreatic secretory trypsin inhibitor, 33%

- Molecular mimicry
  - Homology between
    - Human carbonic anhydrase, and
    - H. pylori α-carbonic anhydrase
    - Human pancreatic acinar ubiquitin-protein ligase E3 component, n-recognon-2, and
    - H. pylori plasminogen-binding proteins

- Environmental factors
  - In persons with AIP +/- IgG4-related sclerosing cholangitis
    - 88% were “blue-color workers”

- Immunologic trigger
  - ↑ lymphotoxin α/β (TNF family) abnormally expressed by pancreatic acinar cells
  - Innate immunity: Toll-like receptor ligands stimulate peripheral blood mononuclear cells from AIP patients → ↑ IgG4 / ↑ IL-10
    - “activation and expansion of B cells that are already committee to production of IG4
  - ↑ Breg (peripheral blood) CD19+ CD24+ high CD38 high
    - ↓ Breg CD19+ CD24 high CD27+
    - ↑ IgG4 switched B cells, and ↑ CD19+ CD20- high CD38 or CD19 low CD27+ CD20- CD38+ plasmablasts
    - ↑ IgG4+ plasmablast (share some surface markers with Bregs
  - T cells and cytokines
    - Activation of Th1/Th2 → ↑ cytokine (Th2 > Th1)
    - ↑ IL-4/-5 (TH2 cytokines) in bile
    - ↑ IL-21 → ↑ IgG4 and IgG4 class switching (involving CCL1 and CCL8)
  - Treg
    - ↑ pancreatic tissue Treg (FOXP3+ CD4+ CD25+),
    - Treg in blood cells correlate to ↑ IL-10 / ↑ TGFβ
    - ↑ TGFβ / ↑ macrophages → fibrosis
    - IL-4 plus IL-10 → ↓ IgE / IgG4 (selective induction of IgG4 by IL-10)
  - IgG4+ plasma cells
    - ↑ in tissue (histological hallmark) often as IgG4/G3 immune complexes
    - Suggestion: the ↑ IgG4 in AIP represents a primary tissue-destructive property in AIP, rather than an inflammatory antibody.

SO YOU WANT TO BE A GASTROENTEROLOGIST!

- Give reasons why IgG4 likely has a role other than inducing inflammation (non-inflammatory antibody).
  - In AIP, the properties of ↑ IgG4 do not support the role of being proinflammatory
    - ↓ ability to fix complement
    - ↓ ability to bind Fc receptors
    - Provides for “Fab-arm exchange (exchange of a pair heavy and light chains) → IgG4 molecules to become: anti-inflammatory”
      - ↓ cross-linking
      - Behave like monovalent antibodies
      - ↓↓ formation of large immune complexes

- Complement system
  - ↓ C3 / ↓ C4 (complement immune-mediated complement activation)
    - Complement usually activated by
      - Classic pathway
      - Mannose-binding pathways
    - IgG4 cannot bind to the classic pathway
      - This suggests that in AIP complement is fixed by other classes of IgG and not by IgG4
  - Chemotactic factors
    - CCL1 / CCL8 → ↑ recruitment of Th2 cells and Tregs in AIP
    - "…CCL1 – CCL8 interaction may cause a microenvironment in which Th2 cells and Tregs are abundant, leading to an IgG4 class switch through IL-4 and IL-10
  - Mislocation of cystic fibrosis transmembrane conductase (CFTR) is dislocated from the cell membrane of the duct epithelium of the normal pancreas → cytoplasm of duct epithelium in AIP
    - The mislocation of CFTR from pancreatic duct cell membrane to cytoplasm may be caused by "unbalanced expression of claudin-1 and -2

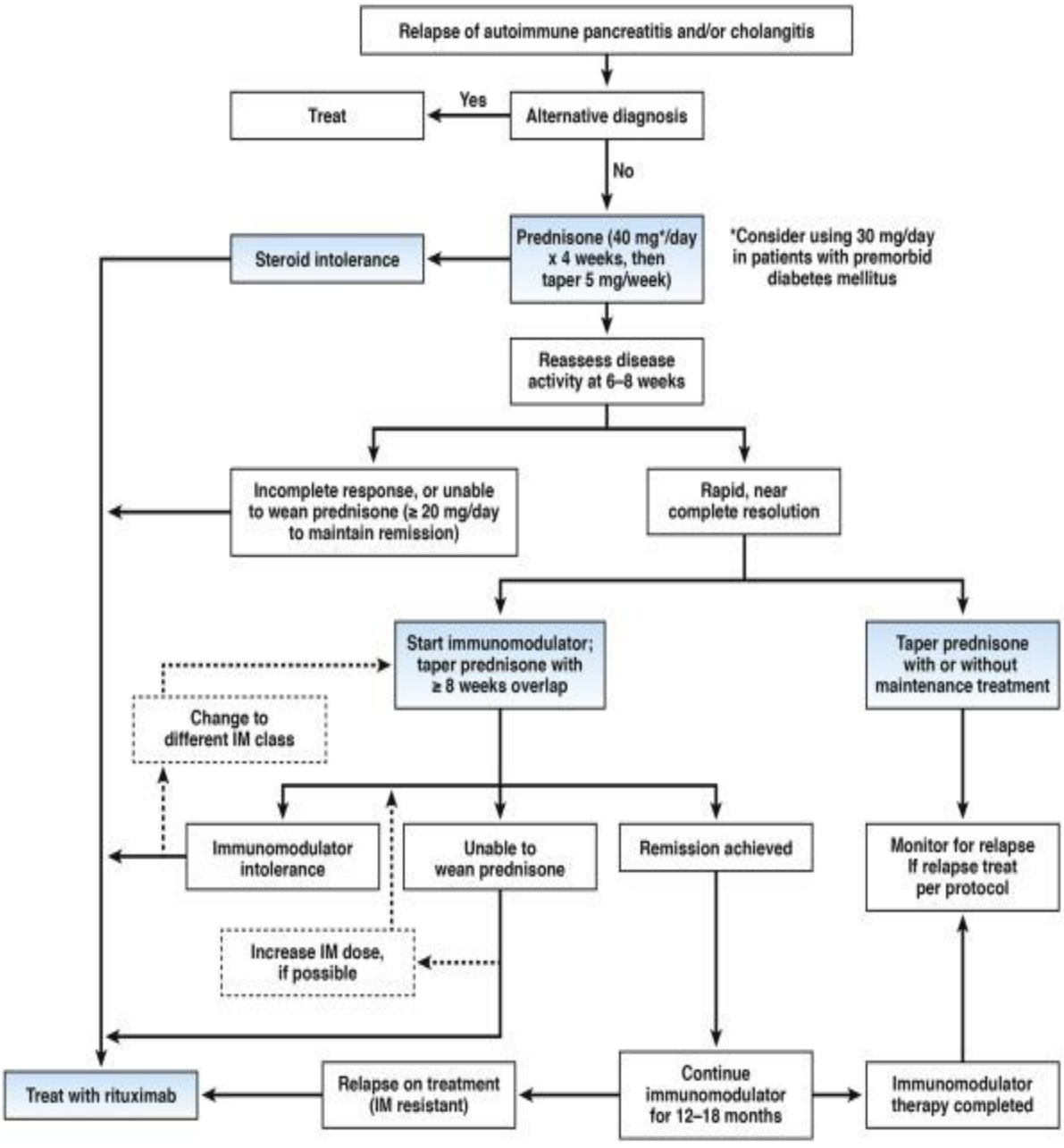
❖ Pancreatic ducts

- MRCP / ERCP
  - Magnetic resonance cholangiopancreatography {MRCP] is not substitute for endoscopic retrograde cholangiopancreatography [ERCP] if ductal changes are to be used for diagnosis of AIP
  - Ducts strictures
    - Long (> 1/3 length of pancreatic duct [PD]), or
    - Multiple
  - No presence of
    - Upstream dilation of ducts > 5 mm
    - Side branches coming of strictures part of PD

➢ Treatment

  - Corticosteroid
    - Early use to ↓ inflammation before irreversible development of fibrosis
    - Prednisone, 30 mg to 40 mg po/d for 4 wk, then reassess for high of relapse,
    - High risk features
      - Pancreas
        - Diffusely enlarged
      - Bile ducts
        - Involvement of intrahepatic and extrahepatic, suprapancreatic portion
    - If non-high risk, taper prednisone by 5 mg per wk until discontinued, or
    - If high risk for relapse, consider maintenance
      - Low lose corticosteroid +/- immunosuppression (successful in > 95%)
      - Rituximab
      - 375 mg/m2 body surface area q1wk x 4 wk, then q2-3 mon (induction of remission in 83%; very high cost)

A proposed treatment algorithm for management of disease relapses for patients with firmly established AIP (i.e., malignancy has been excluded).

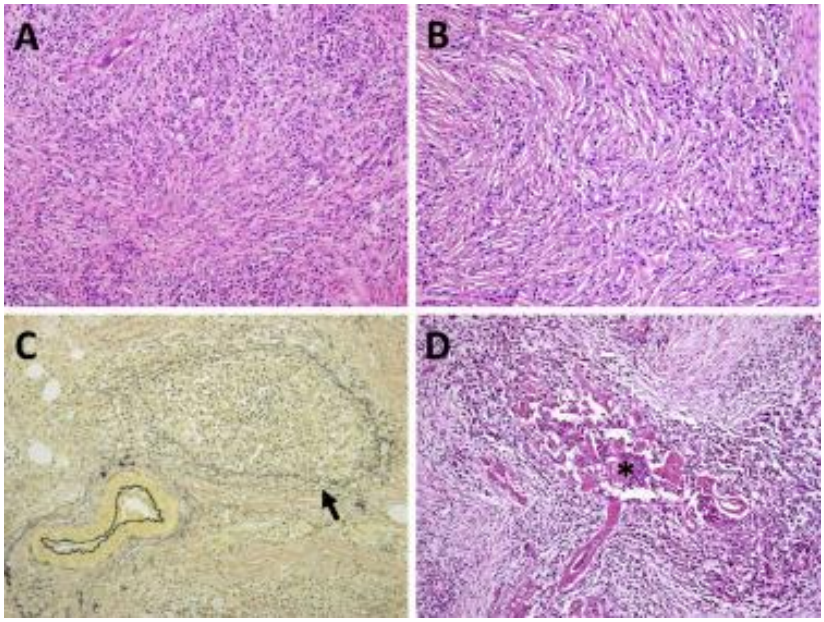


Printed with permission: Hart PA, et al. Gastroenterology 2015; 149: 39-51 (Figure 6A).

Idiopathic Duct-Centric Pancreatitis (IDCP)

- Definition
  - "…a corticosteroid-responsive form of pancreatitis with clinical and histological feature distinct from AIP (laboratory and diagnostic imaging changes may be similar in AIP and in IDCP"
  - Clinical
    - Younger age of onset, M=F, no extrapancreatic organ involvement (15% have IBD)
    - Presentation
      - Acute pancreatitis, jaundice from extrinsic compression of distal CBD from compression of head of pancreas
      - Low risk of relapse
  - Histology
    - Pancreatitis resembling "duct destructive pancreatitis"
    - Involves
      - Pancreatic acini, as well as pancreatic ducts
      - Usually periductular inflammation > acinar
    - Marked lobular infiltration of neutrophils into epithelium of pancreatic ducts
    - Granulocytic epithelial lesions (GEL)

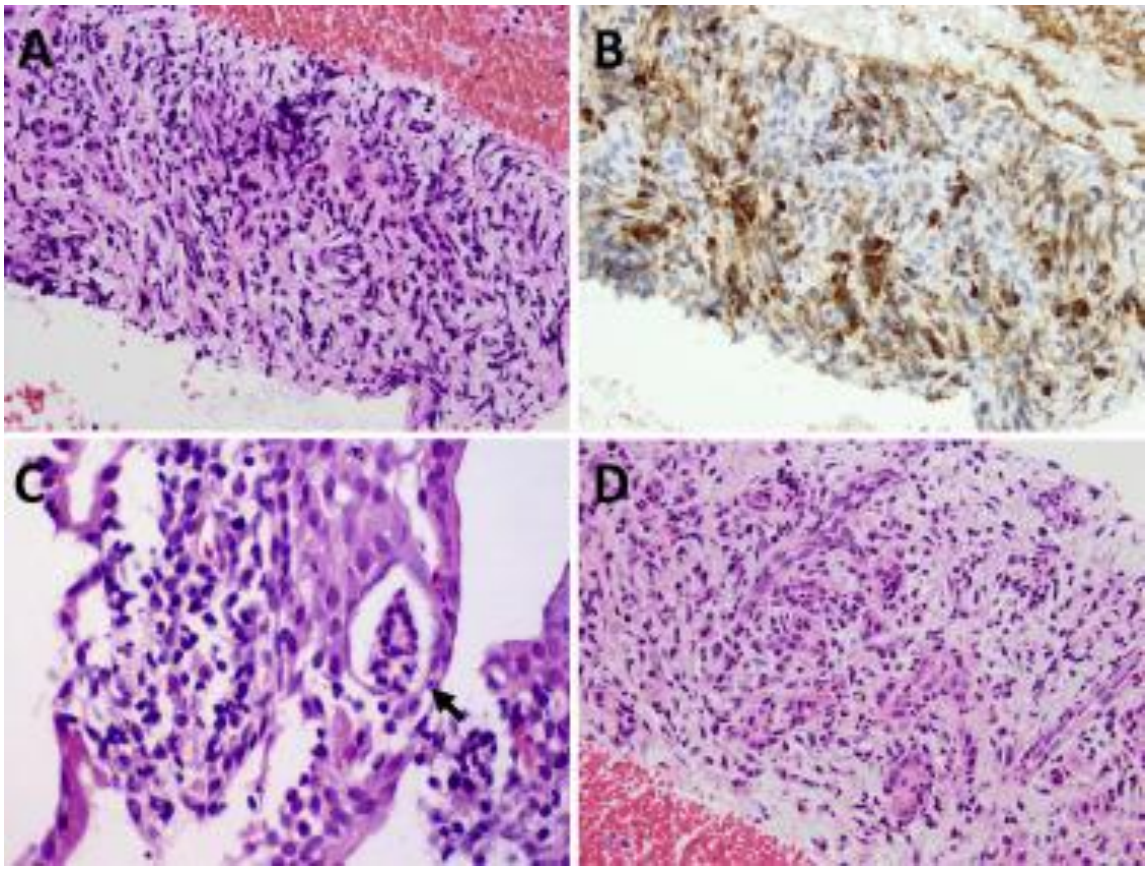
Representative histopathologic features in resected pancreatic specimens from patients with (A–C) AIP and (D) IDCP



Including (A) lymphoplasmacytic inflammation, (B) storiform fibrosis (in a swirled pattern), (C) obliterative phlebitis (arrow, Elastica van Gieson stain), and (D) GEL (asterisk).

Printed with permission: Hart PA, et al. Gastroenterology 2015; 149: 39-51 (Figure 2).

Histological findings in patients with (A and B) AIP and (C and D) IDCP obtained from endoscopic ultrasonography–guided core biopsies



(A) a prominent fibroinflammatory process. (B) Immunostaining for IgG4 highlights infiltration of IgG4+ plasma cells (>10 cells in this field). (C) Neutrophils infiltrate the epithelial layer of the pancreatic duct, forming a small aggregate (arrow). This change is in keeping with a GEL. (D) Involved ductules are infiltrated by many neutrophils, another suggestive feature of IDCP.

Printed with permission: Hart PA, et al. Gastroenterology 2015; 149: 39-51 (Figure 3).

Comparison of AIP and IDCP

	AIP	IDCP
• Clinical		
○ Age at diagnosis, mean	7th decade	5th decade
○ Male sex	75%	50%
• Laboratory		
○ Elevation of serum IgG4 level	~ 66%	~25%
○ Other organ involvement	50%	No[a]
○ Histological findings		
− Lymphoplasmacytic infiltration	++	++
− Periductal inflammation	++	++
− Storiform fibrosis	++	+
− Obliterative phlebitis	++	+
− GEL	−	+++
− IgG4 tissue staining	Abundant (≥10 cells/high-power field)	Scant (<10 cells/ high-power field)
• Treatment		
○ Response to corticosteroids	~100%	~100%
○ Risk of relapse	High (20%–60%)	Low (<10%)
○ Associated with IgG4-RD	Yes	No

[a] Inflammatory bowel disease is seen in approximately 10% to 20% of patients with IDCP but may also occur in patients with AIP.

Printed with permission: Hart PA, et al. Gastroenterology 2015; 149: 39-51 (Table 1).

Abbreviations: AIP, autoimmune pancreatitis; Breg, regulatory B cells; C, compliment; CCA, cholangiocarcinoma; CFTR, cystic fibrosis transmembrane conductance regulator; ERCP, endoscopic retrograde cholangiopancreatography; GEL, granulocytic epithelial lesion; H, Helicobacter; HLA, human leukocyte antigen; IBD, inflammatory bowel disease; IDCP, idiopathic centric pancreatitis; IgG4-RD, IgG4-related disease; IL, interleukin; m, meter; MRCP, magnetic resonance cholangiopancreatography; PDAC, pancreatic duct adenocarcinoma; po, per OS (by mouth); PPV, positive predictive sclerosing pancreatitis; TNF. Tumour necrosis factor; Treg, regulatory T cells; UC, ulcerative colitis; wk, week; yr, year

PANCREATIC CYSTS

Diagnosis and Management of Non-familial Pancreatic Cysts: AGA Guideline (2018)

Elta GH, et al. Am J Gastroenterol 2018; 113: 464-479

- Demography
  - Prevalence
    - Asymptomatic, 2% to 14%
    - > 70 yr, 40%
    - Cysts > 2 cm, 0.8%
  - Risk of malignant transformation
    - Malignancy at time of imaging, 0.25%
    - Annual transformation rate to cancer, 0.24%
    - Considering just IPMNs
      - Overall risk of pancreatic duct adenocarcinoma (PDAC), 2.8%, 0.7% per yr
    - Considering high risk IPMNs (normal nodule, dilated MPD)

	Pooled Cumulative Incidence	
	Low Risk Group (HGD, PDCN)	High Risk Group
1	0.02%	2.0%
5	3.1%	9.8%
10	7.8%	~25%

Abbreviations: CEA, carcinogenic antigen; DI, diagnostic imaging; EUS-FNA, endoscopic ultrasound with fine-needle aspiration; F, female; HGD, high grade dysplasia; IPMNs, intraductal papillary mucinous neoplasms; M, male; MCNs, mucinous cystic neoplasia; PD, pancreatic duct; PDAC, pancreatic duct adenocarcinoma; PNGT, pancreatic neuroendocrine tumours; SCA, serous cystadenomas; SPNs, solid pseudopapillary neoplasia; YoA, years of age; yr, year

- Pathology

Common Neoplastic	Non-neoplastic
○ Mucin-producing − Mucinous cystic neoplasm (MCNs) − Intraductal papillary mucinous neoplasms (IPMNs) ○ Solid-pseudopapillary ○ Pancreatic neuroendocrine ○ Serous cystadenocarcinoma (0.1%) − Solid pseudopapillary neoplasm (10%) risk of HGD/PDAC; metastases, 8%	○ Pseudocysts

❖ Pseudocysts
- Associated with acute/chronic pancreatitis
  - Exclude cystic neoplasm causing first episode of pancreatitis
- No malignant transformation
- Treatment required for symptoms
  - No treatment
  - No surveillance

- Intraductal Papillary Mucinous Neoplasms (IPMNs)

➢ Types
- Main pancreatic duct
- Side branch pancreatic duct (PD)
  - Risk of malignancy, 38% to 68%
  - Most common type of pancreatic cysts
  - Low risk of malignancy
  - May cause pancreatitis due to mucin-associated obstruction of PD
- Mixed
  - Mucous may be seen on ERCP/EGD coming out of patulous papillary orifice
- Macrocystic
- Usually communicate to pancreatic duct

- Mucous Cystic Neoplasms (MCNs)

➢ Demography
- F>M
- Age 50-60 yr

➢ Pathology
- Macrocystic
- Cyst
  - Does not communicate with PD
  - Lined by columnar epithelium
  - Surrounded by ovarian-type stroma
- Usually in body/tail of pancreas
- HGD/PDAC in 10% at time of surgical resection
  - HGD/PDAC rare if
    - Size < 3 cm
    - CA19-9 normal
    - Diagnostic image concerning feature, none

➢ Laboratory
- Cystic fluid analysis
  - ↑ CEA
  - CA19-9 normal
  - ↑ viscosity

- Serous Cystadenomas / SCAs

➢ Demography
  - W > M (3:1)
  - Usually age 50-60 YOA
  - Usually asymptomatic

➢ Pathology

- Microscopic
  - Malignant potential (serous cystadenocarcinoma), 0.1%

➢ Diagnostic imaging
  - Microcytic/honeycomb
  - Central scar (pathognomonic), 30%

Diagnostic Imaging Alert
  - SCAs are usually microcystic, but a few may be macrocystic
    - When SCA is macrocystic, it may resemble IPMNs/MCNs, and so to distinguish it from IPMNs/MCNs, the cyst fluid must be assessed for CEA.

➢ Laboratory
  - Cyst fluid
    - ↓↓ carcinoembryogenic antigen (CEA)
    - ↓ viscosity

- Mucinous

High-risk Characteristics for Mucinous Pancreatic Cysts
  - Symptoms
    - Jaundice secondary to the cyst
    - Acute pancreatitis secondary to the cyst
    - Elevated serum CA19-9 when no benign cause for elevation is present
  - Imaging findings
    - Mural nodule or solid component with the cyst or pancreatic parenchyma
    - Main pancreatic duct diameter of > 5 cm
    - Charge in main duct caliber with upstream atrophy
    - Size ≥ 3 cm
    - Increase in cyst size ≥ 3 mm/year
  - Cytology
    - High-grade dysplasia or pancreatic cancer

Adapted from: Elta GH, et al. Am J Gastroenterol 2018; 113: 464-479 (Table 3)

- Solid-pseudopapillary Neoplasm

➢ Demography
  - F > M (10:1)
  - 20s
  - 5 yr survival rate, 98%

➢ Pathology
  - Small-solid
  - Larger-solid plus cystic
  - Malignant behaviour, 10%

- Cystic Pancreatic Neuroendocrine Tumours

➢ Demography
  - F=M
  - Presentation in 60s
  - Associated with MEN-1 (multiple endocrine neoplasia type 1)

➢ Pathology
  - Types
    - Solid
    - Cystic
    - Mixed
  - Usually non-functioning

➢ Diagnostic Imaging
  - EUS-FNA for aspiration/cytology

➢ Clinical
  - Pancreatic cysts often asymptomatic/incidental finding
  - Symptoms
    - Non-specific
    - ↑ likelihood of malignancy (OR, 1.6; 95%CI, 1.0-2.6)

Clinical Alert

- New onset diabetes
- Unexplained acute pancreatitis

} – Exclude neoplastic cysts / PDCA, especially when > 40 yr

Recommendation

- Use caution when attributing symptoms to a pancreatic cyst
  - The majority of pancreatic cysts are symptomatic and the non-specific nature of symptoms requires clinical discernment (Conditional recommendation, very low quality of evidence)

➢ Laboratory

- Please see Diagnostic Imaging, EUS-FNA plus cystic fluid analysis

➢ Diagnostic Imaging (DI)

- MRI/MRCP

	CT	MRI	EUS
Performance characteristics			
– Cyst detection	20%	3%	
– Accuracy to distinguish			
▪ Benign from malignancy cysts	70-80%	~75%	
– Sensitivity to identify communication between MPD and cysts (distinguish IPMN from other types of cysts)			
MRI superiority			
– Sensitivity to			
▪ Detect cysts			86-96%
▪ Distinguish benign from malignant	70-80%	55-75%	86-96%
▪ Distinguish IPMN from other types of cysts (communication between cyst and MPD)	80%	96%	86-96%
– Better assent of internal morphology, e.g., mural nodule			
– MRI superior to CT scan			
▪ ↓ identification of calcification			
– Secretin-stimulated MRCP			
▪ Extra visualization of communication of cysts to MPD, 5%			

- Combination of

Diagnostic Imaging (DI)	Diagnostic Accuracy	Predicting Malignancy
− PET/CT	94%	97%
− MDCT	77%	
− MR	87%	76%

DI Gem

- "A consensus statement be radiologist recommended is dedicated MRI with MRCP as the imaging modality of choice for pancreatic cysts"

- ERCP
  - Inferior to MRCP, EUS
    - Only role is for evaluation of MPD in IPMN

Recommendations

- Magnetic resonance cholangiopancreatography (MRCP) is recommended as first-line investigation
  - Pancreatic protocol CT or EUS (endoscopic ultrasound) recommended if MRI/MRCP cannot be performed
- If cyst is considered to be "indeterminant"
  - Perform a second modality (e.g.,
  - EUS plus aspiration of cysts fluid

  (Conditional recommendation, very low quality of evidence)

- Caution
  - The performance characteristics of the MRI/MRCP, CT, EUS are poor in diagnosing
    - Types of cyst, 40% to 50%
    - Distinguishing benign from malignant, 55% to 75%

  (Conditional recommendation, very low quality of evidence)
- Criteria for
  - Regular surveillance (no high-risk characteristics)
    - Guided by size of cyst
  - ↑ frequency of surveillance
    - High risk characteristics

  (Conditional recommendation, very low quality of evidence)

- EUS-FNA plus cyst fluid analysis

➢ Establish type of cyst

- Differentiating benign vs. malignant EUS
  - Sensitivity, 85% to 96%
  - Specificity, 30% to 99%
- Differentiating true solid cyst from mucin

	Mural Nodules	Mucin
– Border	▪ Poorly defined	▪ Well-defined
– Echoic	▪ N/↑ centre	▪ ↓ centre

- Performance characteristics to distinguish IPMNs or MCNs from other types of cysts vary depending upon cut-off used for fluid measurements
- CEA in cystic fluid

	Cyst Fluid Cut-off	
	192 ng/mL	> 800 ng/mL, or < 5 ng/mL
– Sensitivity	63%	50%
– Specificity	95%	95%

  - ↑ amylase in cystic fluid < 250 IU/L excludes 98% of pseudocysts
  - Cytology
    - Sensitivity, 54% to 63%
    - Specificity, 88% to 93%
  - Genetic profiles, KRAS +/- GNAS mutation
    - Sensitivity, 84% to 96%
    - Specificity, 100%

➢ Establish HGD/PDAC

- CEA
  - Poor performance
    - Sensitivity, 65%
    - Specificity, 65%
  - Cytology
    - Sensitivity, 65%
    - Specificity, 90%
- Endoscopic equipment
  - Cytology
    - Impaired brush
  - Needle
    - Microbiopsy forcep
    - Confocal microscopy
      - Performance characteristics for
        - Distinguishing

	Sensitivity	Specificity
− SCAs from other types of cysts	59% to 69%	100%
− IPMNs/MCNs from other types of cysts		80%

Abbreviations: GNAS, guanine nucleotide-binding protein, KRAS, k-RAS 2 Kirstein rat sarcoma viral oncogene homology

Recommendations

- EUS-FNA plus analysis of cyst fluid: indications
  - Cysts diagnosis which are not clear, or when type of cyst will change treatment
    - CEA (cyst fluid) to differentiate IPMNs/MCNs from other cysts
    - Do **not** do CEA or identify IPMNs/MCNs with high grade dysplasia/cancer

    (Conditional recommendation, very low quality of evidence)
  - Cytology of cyst fluid to determine if the cyst has high grade dysplasia/cancer when
    - "…imaging features alone are insufficient to warrant surgery

    (Conditional recommendation, very low quality of evidence)
  - Molecular markers
    - To identify IPMNs/MCNs when diagnosis is unclear
    - When making a diagnosis would change treatment

    (Conditional recommendation, very low quality of evidence)

➢ Treatment

- Patient Fitness for Pancreatic Surgery
  - Predicting death from non-PDAC causes vs. PDAC
    - Charlson comorbidity index (CCI) at 5 yr, 78% of deaths not sue to IPMNs
      - Chance of non-IPMNs-related death at 3 yr CACI > 7
        - ↑ IIX median survival 43 mon
      - CACI may be useful to predict which patient would not likely to benefit from surgical resection of IPMN (would die from non-IPMN comorbidities)
    - Adult Comorbidity Evaluation 27 (ACE-27) score moderate/severe, plus age of patient at diagnosis may also predict when patient with IPMN more likely to die of their comorbidity than from the IPMN

➢ Surveillance

Clinical Laboratory Consideration

- IPMNs/MCNs
  - May be present in pancreas for years before there is malignant transformation
    - Malignant transformation occurs in 15% to 45%

      The value of surveillance is not proven for IPMNs/MCNs
  - Surgery can be offered to patients with IPMNs/MCNs who are
    - Asymptomatic
    - Fit for pancreatitis surgery

- SCA, pseudocysts
  - Do **not** require surveillance
  - Symptoms/signs
    - New onset diabetes in patients > 50 yr, 1% develop PDAC in 3 yr
    - Acute pancreatitis secondary to the cyst
    - Development of obstructive jaundice
  - Laboratory
    - CA19-9 > 37 U/mL predicts malignant transformation to HGD/PDAC (in IPMNs)
      - Sensitivity, 40%
      - Specificity, 89%
      - OR, 4.34 (95% CI, 2.65 t0 7.10)

- Image considerations (high risk cysts (IPMNs/MCNs) (↑ risk HGD/PDAC)
  - Size of IPMN cyst ≥ 3 cm
    - Surrogate for HGD/PDAC or for HGD/PDAC 2.97 (95%CI, 1.82-4.85); other data or 62.4 (95%CI, 30.8-126.3)
  - Rapid ↑ size of IPMN ≥ 3 mm/yr (range, 2 to 5 mm per yr)
    - Repeat MRI/EUS +/- EUS +/- FNA in 6 mon
  - Mural nodule / solid component OR 9.3 (95%CI, 5.3-16.1)
    - Patients with IPMNs, but not patients with MCNs are at risk of developing malignancy in the preventive parenchyma anatomically sperate from the cyst" (a "concomitant" PDAC; develops in 4% to 8% of persons with IPMNs
    - Implication: in patient with IPMN, and the rest of the pancreatic parenchyma
  - Main pancreatic duct (MPD) > 6 mm (dilation)
    - OR 7.25 (95%CI, 3.0-17.4) for HGD/PDAC
    - ↑ risk
      - HGD, ~60%
      - PDAC < ~44%
    - Suggestion of ACG Guideline Committee
      - "We recommend use of a consecutive duct diameter [of] > 5 mm
      - A sudden change in the caliber of the MPA is also of concern
    - Focal dilation/obstructing lesions

Recommendations

- Asymptomatic cysts on initial investigation
  - Patient not fit for surgery
    - Even large cysts do not investigate extensively
      (Strong recommendation, low quality of evidence)
  - Pseudocysts on clinical history/initial investigation (which have very low risk of malignant transformation
    - Do **not** investigate extensively
      (Conditional recommendation, low quality of evidence)
  - Initial investigation suggests MCN/IPMN in patient who is surgically fir offer cyst surveillance
    (Conditional recommendation, very low quality of evidence)

- Ablation of Pancreatic Cysts
  - Alcohol +/- paclitaxel, or radiofrequency ablation → ↓ size of cyst, however
    - There is no evidence that ↓ size of IPMN/MCN reduces the risk of
      - Progression to HGD/PDAC
      - Development of PDAC in a patient of the pancreas away from the cyst

Recommendations

- Asymptomatic cysts on initial investigation
  - Patients no fit for surgery
  - Pseudocysts on clinical history/initial investigation (which have very low risk of malignant transformation do not investigate extensively
    (Conditional recommendation, low quality of evidence)
  - Initial investigation suggests MCN/IPMNs in patient who is surgically fit offer cyst surveillance
    (Conditional recommendation, low quality of evidence)
- MRCP is the best diagnostic imaging modality for surveillance of pancreatic cysts
  - EUS is performed for surveillance when MRCP cannot be performed
    (Conditional recommendation, very low quality of evidence)

Postsurgical resection

- MSNs surgically resected MCNs (regardless of presence of dysplasia [even HGD])
  - Do **not** develop a new MCN in remainder of post-surgical pancreas, but
  - 25% risk of recurrence of original cancer
    - Surveillance for 5 yr
- IPMNs high risk of recurrence of IPMNs including PDAC in remnant pancreas (10% to 65%)
  - Follow guidelines for PDAC (e.g., Tamera K, et al. Ann Surg 2014; 259: 360-368)

- HDG resected
  - Recurrence 13% to 31%
  - Median time to recurrence, 19 to 47 mon
  - Surveillance (MRI/EUS) q6mon
- Low/intermediate grade dysplasia resected
  - Recurrence in 0% to 22%
  - Surveillance q2yr
- Solid-pseudopapillary neoplasm with negative margins
  - Recurrence in 4% within a median time of ~50 mon
  - Surveillance imaging q1yr for 5 yr

Recommendations

- Patients with surgically resected benign cysts (e.g., SCA, pseudocyst), do not require post-operative surveillance or resected MCNs without cancer (Strong recommendation, low quality of evidence)
- Surveillance
  - IPMNs
    - Post-operative surveillance
  - Solid pseudopapillary
  - Neoplasm
    - Surveillance q1yr for ≥ 5 yr

    (Strong recommendation, very low quality of evidence)
- If patient becomes a non-surgical candidate
  - Stop surveillance (Strong recommendation, very low quality of evidence)
  - Assess patients > 75 yr for suitability for surgery (Conditional recommendation, very low quality of evidence)

Non-Inflammatory Pancreatic Cysts (Pancreatic Cystic Neoplasm [PCNs])

Phan J and Raman Muthusamy VR. Curr Gastroenterol Rep 2018; 20(7):32.

- Demography
  - Incidental findings in 3% to 20% of all abdominal CT/MRIs
  - Prevalence ↑ with age
  - W > M, except for IPMN
  - Risk of cyst seen on MRI becoming PDAC 0.24%
  - Malignant potential
    - Low: non-mucinous
      - Serous cystic neoplasms (SCNs)
      - Solid pseudopapillary epithelial neoplasms (SPEN)
    - High: mucinous
      - Mucinous cystic neoplasm (MCN)
      - Intraductal papillary mucinous neoplasms (IPMN)
  - Surgical
    - Morbidity and mortality, 30%

- Clinical
  - Asymptomatic or symptomatic e.g., jaundice (biliary obstruction)

- Diagnostic imaging (DI)
  - CT/MRI useful to demonstrate non-inflammatory pancreatic cyst
    - May not indication which type, or benign vs. malignant
  - Typical DI features
    - SCN
      - Clusters
      - Microcysts
      - Central radiation
      - Stellate calcifications
    - Present in only 20% of SCNs
      - Multiple septations (accuracy for SCN > 90%)

- Endoscopy
  - Endoscopic ultrasound (EUS)
    - Incremental diagnostic yield of EUS to CT scan, 19% to 36%
    - Sensitivity for detecting cysts < 1 cm EUS > CT
    - Presence of mural nodules
      - Diagnostic accuracy mucinous cysts (MCN/IPMN), 83%
      - Associated with dysplasia/cancer

- EUS plus FNA
  - Performance characteristics for detecting mural nodules
    - Sensitivity, 2x > CT
    - Specificity, 35% to 58%
    - EUS, 63%
    - EUS plus FNA (cytology plus fluid analysis), 86%
  - Identify cancer
    - Sensitivity, 30% to 63%
    - Specificity, 100%
- Septations
  - Multiple septations suggests SCN (accuracy > 90%)
- Fluid markers
- Carcinoembryonic (CEA) secreted by mucinous cells
  - CEA > 300 ng/mL predictive of MCN/IPMN
    - Sensitivity, 48%
    - Specificity, 98%
  - CEA < 5 ng/mL predictive of SCN/pseudocyst
    - PPV, 95%
    - Accuracy, 67%
- Limited use for CA124, CA72-4, CA19-9
- Amylase
  - Present if fluid in cyst arises from communication between cyst and main pancreatic duct (MPN), e.g., in IPMN
  - Amylase < 250 U/L rules out pseudocysts
    - Sensitivity, 44%
    - Specificity, 98%
  - However, inconsistent predictability
  - Amylase < 350 U/L plus CEA < 30 ng/mL predicts SCN in 85%
- Fluid viscosity / “string sign”
  - Used to predict presence of mucinous cyst (MCN, IPMN)
  - CEA > 2000 ng/mL plus ↑ viscosity predicts MCN/IPMN with diagnostic accuracy of 89%
  - GNAS, sensitivity for IPMN, 66%
- Molecular changes
  - KRAS plus GNAS mutations, sensitivity 96%
    - Sensitivity, 12% to 50%
    - Specificity, 80% to 96%
  - “..when compared against CEA or cytology, there was no significant difference in the accuracy of comprehensive DNA analysis in detecting mucinous cysts”
  - Perhaps the role of identifying molecular changes is to improve NPV of the analysis of cyst fluid for dysplasia/cancer (MCN, IPMN)

➢ Treatment

❖ Mucinous cysts: algorithms for cyst diagnosis and treatment

- Sendai guidelines to predict malignant potential (i.e., ↑ risk factors)
  - Cyst
    - Size > 3 cm (resect all cysts > 3 cm)
    - Mural nodule
  - PD dilation
    - MD-IPMN > 5 mm
    - BD-IPMN > 6 mm
  - Symptoms
    - E.g., jaundice, pain, pancreatitis
  - FNH
    - Cytology positive

Treatment Teaser

- Give the negative issue for using the Sendai guidelines to identify high risk and need to resect a PCN.
  - The size of the cyst > 3 cm is an issue for malignancy prediction, since ~50% of PCN > 3 cm are benign
  - < 3 cm PCN, ~25% are malignant
  - PPV, 11% to 52%
  - NPV, 71% to 100%

❖ Fukuoka guidelines

- Resection
  - All MCN / MD-IPMN, mixed
  - BD-IPMN
    - Symptoms obstructive jaundice from PCN at level of pancreas
    - Solid component, enhancing on diagnostic imaging
    - MPD > 10 mm
    - EUS-FNA cytology suspicious

Concern for Fukuoka Guidelines

- MPD > 6 mm, ↑ risk of malignancy, pooled or 7.27 (95%CI: 3.0-17.4)

❖ AGA Guidelines

○ Indication for EUS (≥ 2 of the following)	Indications for Surveillance
− Cyst size ≥ 3 cm	▪ < 3 cm
− Solid component	▪ No solid
− MOD dilated (no specific measurement)	▪ No MPD dilation
↓	↓
Surgery	MRI at 1 yr, then q2yr x2 if concerning features develop → EUS-FNA

○ Prediction of advanced neoplasia

Performance Characteristics	AGA	Fukuoka
Sensitivity	28%	35%
Specificity	96%	94%

○ Features of AGA guidelines
- − Good
  - ▪ 60% ↓ unnecessary surgery
- − Bad
  - ▪ 5% of patients selected for surveillance had missed cancer

○ Contrast-enhanced EUS (CE-EUS)
- − Colour flow image microbubbles to detect ↑ vascularization in mural nodules
- − Detection of PDAC vs. focal pancreatitis, neuroendocrine tumour (NET)
  - ▪ Sensitivity, 94%
  - ▪ Specificity, 89%
  - ▪ Overall accuracy, 92%

○ Direct intracystic biopsy

○ Confocal laser-induced endomicroscopy (CLE)
- − Identifies villous epithelial pattern in IPMNs

○ MCN
- − Grey band with a thin dark line (mucin-producing epithelium with “interwoven” fibrous tissue”

○ SCN
- − Superficial vascular network (“necklace”) of subepithelial cells along wall of cyst
- − Production of SCN
  - ▪ 100% specific, 100% PPV!

Abbreviations: AGA, American Gastrointestinal Association; BD, branch duct; CEA, carcinoembryonic antigen; CE-EUS, contrast-enhanced endoscopic ultrasound; CLE, confocal laser-induced endomicroscopy; CT, computed tomography; EUS, endoscopic ultrasound; FNA, fine needle aspiration; M, men; MD, main duct; MRI, magnetic resonance imaging; NPV, negative predictive value; PD, pancreatic duct; PPV, positive predictive value; W, women; yr, year

INFLAMMATORY PANCREATIC FLUID COLLECTIONS

Endoscopy in the Diagnosis and Management of Inflammatory Collections of Pancreatic Fluid (PFCs): **ASGE Guideline** (2016)

Muthusamy VR, et al. Gastrointestinal Endoscopy 2016; 83: 481-486

Inflammatory Pancreatic Fluid Collections (PFCs)

- Types
  - Acute peri-PFCs
    - Multiple, homogenous collection of fluid
    - No wall to the collection of fluid
    - Retroperitoneal fascial planes are normal
  - Pseudocysts
    - PFCs arising from pancreatic and peripancreatic fluid
    - Persist > 4 wk
    - May develop necrotizing pancreatitis
    - Well-defined non-epithelial wall
    - Fluid rich in amylase/lipase
  - Acute necrotic collections (ANCs)
    - Multiple, loculated collections of fluid and necrotic debris (< 4 wk)
    - Occur in 20% of patients with acute pancreatitis (AP)
    - Often associated with disruption of the main pancreatic duct (MPD)
    - Secondary infection in 30%
  - Walled-off necrosis (WON)
    - Collection of pancreatic / peripancreatic necrotic debris
    - Enhancing encapsulated wall (reactive tissue)
    - WON develops ≥ 4 wk after necrotizing pancreatitis
    - May become infected
    - Predicts severity and progression of pancreatic inflammation"
    - Diagnose by MRCP/MRI, EUS, contrast enhanced CT scan
    - Perform again before endoscopic drainage or surgery

➢ Definitions of inflammatory pancreatic fluid collections

Term	Definition	Contrast-enhanced CT findings
○ Acute peripancreatic fluid collection (peri-PFC)	− Peripancreatic fluid associated with interstitial edematous pancreatitis with no associated peripancreatic necrosis. This term applies only to areas of peripancreatic fluid seen within the first 4 wk after onset of interstitial edematous pancreatitis and without the features of a pseudocyst.	▪ Homogeneous collection with fluid density ▪ Confined by normal peripancreatic fascial planes ▪ No definable wall encapsulating the collection ▪ Adjacent to the pancreas (no intrapancreatic extension)
○ Pancreatic pseudocyst	− An encapsulated collection of fluid with a well-defined inflammatory wall usually outside the pancreas with minimal or no necrosis. This entity usually requires >4 wk after onset of interstitial edematous pancreatitis to mature.	▪ Well circumscribed, usually round or oval homogeneous fluid density ▪ No non-liquid component Well-defined wall (completely encapsulated) ▪ Maturation usually requires >4 wk after onset of acute pancreatitis ▪ Occurs after interstitial edematous pancreatitis
○ Acute necrotic collection	− A collection containing variable amounts of both fluid and necrosis associated with necrotizing pancreatitis; the necrosis can involve the pancreatic parenchyma and/or the peripancreatic tissues.	▪ Occurs only in the setting of acute necrotizing pancreatitis ▪ Heterogeneous and non-liquid density of varying degrees in different locations (some appear homogeneous early in the course) ▪ No definable wall encapsulating the collection ▪ Can be intrapancreatic and/or extrapancreatic
○ Walled-off necrosis	− A mature, encapsulated collection of pancreatic and/or peripancreatic necrosis that has developed a well-defined inflammatory wall. This usually occurs >4 wk after the onset of necrotizing pancreatitis.	▪ Heterogeneous with liquid and non-liquid density with varying degrees of loculations (some may appear homogeneous) ▪ Well-defined wall (completely encapsulated) ▪ Intrapancreatic and/or extrapancreatic location ▪ Maturation usually requires 4 wk after onset of acute necrotizing pancreatitis

Printed with permission: Muthusamy VR, et al. Gastrointest Endosc 2016; 83: 481-486 (Table 2).

- Give why MRCP / contrast enhanced CT. EUS should be reported before endoscopic / surgical drainage.
  - The differential will give several conditions which do not need to be drained (non-inflammatory fluid collection)
    - Cystic neoplasm
    - Duplication cyst
    - Pseudoaneurysm
  - Differentiating infected from non-infected necrosis
    - Infection most common at 2-4 wk
      - Fever
      - Gas bubbles on imaging
      - Clinical deterioration

- Give why EUS-FNA of WON not recommended to differentiate infected from non-infected WON.
  - False-negative rate high
  - ↑ risk of contamination (introduction of bacteria into previously sterile WON)

Recommendations

- We recommend drainage of all infected PFCs in patients who fail to improve with conservative management alone (Quality of evidence, high)
- We recommend drainage of symptomatic sterile necrosis lasting more than 8 wk after the onset of acute pancreatitis (Quality of evidence, moderate)
- We suggest that routine FNA of PFCs is not required to diagnose infected necrosis (Quality of evidence, low)

➢ Treatment

Recommendations

- We recommend that endoscopic drainage of PFCs be performed only after sufficient exclusion of alternative diagnoses, such as cystic pancreatic neoplasms and pseudoaneurysms (Quality of evidence, high)
- We recommend waiting for maturation of the cyst wall of PFCs before endoscopic intervention (Quality of evidence, moderate)
- We recommend drainage of symptomatic pancreatic pseudocysts (Quality of evidence, moderate)

- Acute peri-PFCs / ANCs
  - Do **not** usually require treatment
- Pseudocysts, WON-treated after 4 wk (encapsulation)
  - Treated after 4 wk (encapsulation)

} The later the timing of drainage, the better

Time (days) from hospital admission	Mortality rate
0-14	56%
14-29	26%
> 29	15% (P < 0.001)

- Pseudocysts, WON treated after 4 wk (encapsulation)
- Pseudocytes endoscopic (ERCP) drainage (transmural)
- Outcomes
  - Drainage successful, ~80% to 100%
  - Adverse events, ~5% to 15%
  - Recurrence, 18%
    - Better outcomes when transmural stent is combined with placement of nasocystic tube (NCT)

Recommendations

- We suggest drainage of rapidly enlarging pancreatic pseudocysts (Quality of evidence, low)
- We recommend that endoscopic drainage be considered for initial therapy before surgical drainage of pancreatic pseudocysts (Quality of evidence, moderate)
- WON
  - Indications (after 8 wk)
    - Pain, refractory
    - Anorexia / ↓ weight
    - Obstruction
      - Stomach
      - Bile duct
    - Systemic illness
      - Peridrainage care
        - Antibiotics
        - CO_2 insufflation
        - Deep sedation
  - Comparison of endoscopic is surgical drainage: ↓ risk of
    - Inflammation
    - Multiple-organ failure (MOF), new onset
    - Fistulae

❖ ENDOSCOPIC METHODS OF DRAINAGE OF PSEUDOCYSTS

- Transmural
  - Make an endoscopically assisted women in wall of stomach / duodenum
    - Dilate puncture incision with a balloon
  - Insert ≥ 1 stents
    - Double-pigtailed
    - Plastic
    - Self-expandable metal stent (SEMS; lumen-apposing, covered)
    - SEMS plus plastic double pigtail

Recommendations

- We recommend that endoscopic drainage of PFCs be performed only with the availability of surgical and interventional radiology support (Quality of evidence, high)
- We suggest using CO_2 when performing transmural drainage procedures (Quality of evidence, low)

SO YOU WANT TO BE A THERAPEUTIC ENDOSCOPIST!

- Give when it is recommended to use EUS-guidance for endoscopic drainage of PFCs.
  - When there is no compression / indentation of the lumen of the stomach or duodenum from the PDC to be drained endoscopically visible

Recommendations

- We recommend using EUS for transmural drainage of PFCs in the absence of a luminal bulge or when portal hypertension is suspected (Quality of evidence, high)
- PFC in unusual location
- Varices closely which might complicate the procedure
- "…prior failed direct endoscopic approach"

- Transpapillary
  - For pseudocysts which communicate with MPD, perform sphincterotomy and pass the stent towards the tail of the pancreas, placing the stent across any area of disruption of the MPD (↑ rate of successful drainage in pancreatis body / tail)
  - Adverse outcomes of transpapillary drainage
    - Parenchyma
    - Duct
    - Fluid
    - Post-ERCP pancreatitis
    - Stent-induced scarring
    - Slower / incomplete drainage
    - Infection

❖ WALLED OFF NECROSIS (WON)

- Place 2 transmural plastic pigtail stents
  - Lumen opposing large-diameter metal stents nasocystic drainage (NOD)
  - If inadequate clinical benefit from NCD within 48-72 h
    → endoscopic transmural necrosectomy (ETN)
    → repeat ETN q48-72 h as needed to remove all necrotic debris

- Outcomes
  - Success rate ~75%
  - Adverse events, 36%
  - Mortality, 6%
- Other methods
  - Combined endoscopic plus radiological drainage
  - Multiple transluminal gateway technique (MTGT)
    - Transmural tract for nasocystic lavage
    - Tract for drainage of necrotic debris

    } ↑ rate of clinical success vs. conventional single tracts, 92% vs. 52%

Recommendation

- We recommend initial endoscopic transmural and/or percutaneous drainage of WON before consideration of endoscopic transmural necrosectomy or surgical drainage (Quality of evidence, high)

- After-procedure Care
  - Antibiotic prophylaxis
  - Repeat / follow-up CT scan at 4-6
  - Remove internal stents endoscopically when diagnostic imaging suggests resolution
  - In patient with chronic pancreatitis (CP)
    - Perform endoscopic therapy of any obstruction of the MPD
  - In patient with WON plus disconnected pancreatic duct syndrome / disruption of MPD
    - Insert long term indwelling transmural stent to ↓ risk of recurrence of PFC
    - Infection in site of transpapillary drainage may be resolved with
      - Conversion to a transmural approach
      - Exchange smaller for larger stent

➢ Adverse events of endoscopic therapy of PFCs

- Pancreas
  - Infection
  - ↑ risk
    - Inadequate drainage of fluid / necrotic debris
  - Hemorrhage, obstruction, perforation (damage to MPC)
- Stent
  - Migration
- Patient
  - Aspiration, sedation complications, mortality

PANCREATIC NEOPLASMS

Endoscopy in the Diagnosis and Treatment of Cystic Pancreatic Neoplasms: ASGE Guideline (2016)

Muthusamy VR, et al. Gastrointest Endosc 2016; 84: 1-9

- Demography
  - Found incidentally in 2.5% persons by diagnostic imaging undertaken for other reasons incidence in persons ≥ 70 yr, 10%

- Types

- Neoplastic (epithelial)
  - Serous cystic neoplasms (SCNs) (16%)
  - Mucinous cystic neoplasms (MCNs) (20%)
  - Intraductal papillary mucinous neoplasms (IPMNs) (38%)

- Non-neoplastic
  - Pseudocysts
  - Other types of pancreatic tumours which may have cystic component
    - Neuroendocrine tumours (NET), cystic component (7%)
    - Pancreatic duct adenocarcinoma (PDAC)
    - Solid pseudopapillary neoplasms

- Endoscopy: Endoscopic Ultrasound
  - Do **not** use EUS to distinguish
    - Benign from malignant IPMN< or
    - Mucinous from non-mucinous pancreatic neoplasms
  - Do **not** use size of cysts to distinguish benign from malignant pancreatic cystic tumours
    - Of cystic lesion ≤ 2 cm
      - Malignant, 20%
      - Malignant potential, 45%

      } However, ~95% of these were symptomatic
  - Microcysts
    - Multiple small (< 3 cm) compartments within a cystic lesion suggests a serous cystic lesion
    - Accuracy 92% to 96%
  - Pancreatitis
    - Atrophy
    - Calcifications
    - Change in echo texture

    } ▪ Plain cysts → Septations
    ▪ Plus, cysts with no → Solid components

    } − Pseudocyst
      ▪ Sensitivity, 94%
      ▪ Specificity, 85%

- Distinguish intracystic mucus from epithelial nodule
  - Intracystic mucus
    - RIM
      - Smooth, well-defined
    - Centre
      - Hyperechoic
      - Hypoechoic
  - Epithelial nodules
    - RIM
      - Poorly defined
    - Centre
      - Hyperechoic
- Predictors of malignant vs. benign IPMN
  - Cyst > 3 cm
  - Enhancing solid component in cyst
  - MPD walls thickened
  - Enhancing solid component in cyst
- "Worrisome features
  - MPD
    - 5-9 mm
    - Sudden change in diameter of duct
  - Parenchyma
    - Atrophy upstream to duct
  - Peripancreatic lymphadenopathy

- Contrast enhanced EUS
  - Assess ↑ vascularity

Recommendations

- ERCP, pancreatoscopy, and intraductal US may be helpful in the diagnosis and characterization of suspected main duct IPMNs (Quality of evidence: low)

- EUS plus FNA
  - Perform cystological / histological examination of
    - Aspirated solid material
    - Regional lymph nodes
  - Performance characteristics of cytology to distinguish mucinous from neuromucinous pancreatic cysts
    - Sensitivity, 54% to 63%
    - Specificity, 88% to 93%
  - Adverse events ~3%
    - Pancreatitis
    - Bleeding
    - Infection
  - "…current ASGE guidelines suggest administration of antibiotics for 3 to 5 d after EUS-FNA of pancreatic cyst lesion

Recommendations

- Administer of prophylactic antibiotics for patients undergoing EUS-FNA for the evaluation of cystic pancreatic neoplasms (Quality of evidence, low)
- Clues
  - Cuboid cells
    - Glycogen-ride → serous neoplasm
  - Histocytes
    - Macrophages, neutrophils → pseudocyst
  - Mucin
    - Mucinous neoplasm
- Use EUS-FNA of any pancreatic cystic lesion over 3 cm in diameter or when cross-sectional or EUS imaging confirms an epithelial nodule, dilated main pancreatic duct, or suspicious mass lesion (Quality of evidence, medium)
- EUS-FNA is optional in asymptomatic patients in whom cross-sectional imaging demonstrates a cyst <3 cm and without either a mass and/or epithelial nodule or associated dilated main pancreatic duct (Quality of evidence, low)

- New Endoscopic Techniques
  - Confocal laser endomicroscopy plus IV fluorescein
  - Cholangioscopy
  - Pancreatography

- ERCP **not** usually recommended, except if
  - Signs suggestive of
    - MPD IPMN
      - Mucus coming out of patulous pancreatic orifice (pathognomonic, seen in 20% to 55%)
    - Pancreaticoduodenal fistula, with mucous seen in IPMN with malignant invasion
  - Narrow MPD
    - Pancreatitis
    - PDAC
    - Pancreatic trauma
  - Communication with MPD
    - IPMN
    - Pseudocyst
      - SCN
      - MCN

    } Rare

➢ Characteristics of pancreatic cystic lesions

	Pseudocyst	IPMN	Mucinous cystic neoplasm	Serous cystic neoplasm	Cystic endocrine neoplasm	Solid pseudopapillary neoplasm	Ductal adeno-carcinoma with cystic degeneration
Clinical features	History of moderate to severe pancreatitis	History of pancreatitis, abdominal pain, or found incidentally	Usually found incidentally but can cause abdominal pain and a palpable mass if large	Usually found incidentally but can cause abdominal pain and a palpable mass if large	May have clinical features of solid pancreatic endocrine neoplasm	Usually found incidentally; rarely causes abdominal discomfort	Presents with painless jaundice, abdominal/back pain or rarely pancreatitis
Morphology/ EUS findings	Anechoic, thick-walled, rare septations, regional inflammatory nodes may be seen	Dilated main pancreatic duct or side branches; may appear as a septated cyst; may have a solid component	Macrocystic, occasionally septated; peripheral calcifications, solid components and regional adenopathy when malignant	Microcystic with a "honeycomb" appearance; rarely has a macrocystic component; central calcification	Unilocular cyst occupies most of neoplasm	Solid and cystic components	Primarily solid mass with cystic spaces
Fluid characteristics	Thin, muddy-brown	Viscous or stringy, clear	Viscous or stringy, clear	Thin, clear to serosanguineous	Thin, clear	Bloody + necrotic debris	Bloody ± debris
Fluid chemistries	↑ amylase, low CEA	↑ amylase and CEA	↑ CEA, low amylase	↓ CEA and amylase	Variable	Variable	Variable
Cytology	Neutrophils, macrophages, histiocytes; negative staining for mucin	Mucinous columnar cells with variable atypia; fluid stains positive for mucin	Mucinous columnar cells with variable atypia; fluid stains positive for mucin	Cuboidal epithelium that stains positive for glycogen	Monomorphic endocrine tumour cells; stains positive for chroma granin and synaptophysin	Monomorphic cells with round nuclei and eosinophilic or foamy cytoplasm; stains positive for vimentin and a-1-antitrypsin	Malignant adenocarcinoma may be seen, but varying degrees of atypia may be present in the specimen
Malignant potential	None	Yes	Yes	Almost none (rare reports)	Yes	Yes	Already present

Abbreviations: *IPMN*, Intraductal papillary mucinous neoplasm; *CEA*, carcinoembryonic antigen

Printed with permission: Muthusamy VR, et al. Gastrointest Endosc 2016; 84: 1-9 (Table 2).

- Laboratory (cystic fluid)
  - Amylase < 250 U/L
    - Excludes a pseudocyst with specificity of 98%
  - CEA > 192 ng/mL
    - Differentiates mucinous from non-mucinous from non-mucinous cyst with
      - CEA plus ↑ CEA plus cytology plus EUS (hypoechoic mass +/- macrocystic mutation)
        - Sensitivity, 63% to 75%
        - Specificity, 84% to 88%
        - Sensitivity, 91%
        - Specificity, 31%

- Pancreatic cyst fluid
  - Molecular markers
    - KRAS mutation mucinous cysts
    - ↓ KRAS plus allelic loss
      - Malignancy (specificity, 96%)
    - Duodenal collection of pancreatic juice after administration of secretinin
    - GNAS mutations of 64% of patients with IPMNs
  - MPD – Dilated → CP
  - SB – Blunted → IPMN

Recommendations

- Initially test the aspirated pancreatic cyst fluid for CEA, amylase, and cytology (Quality of evidence, medium)
- Do molecular testing of the cyst fluid for cytology and for carcinogenic antigen (CEA) if the initial testing is inconclusive, and when test results may alter management (Quality of evidence, low)
- Pancreatographic findings in MPA suggestive of IPMN
  - Dilation
    - Segmental, or
    - Diffuse
  - Filling defects stones, mucus
  - Communication
    - Correct diagnosis (versus surgical findings) ~75%
    - Other pooled studies show
      - Sensitivity, 35%
      - Specificity, 97%

- Treatment (endoscopic treatment of cystic lesions of pancreas)
  - Ablation ethanol +/- paclitaxel (chemotherapeutic agent, which improves response to ethanol alone)
    - Indications
    - Success rate
    - Optimal outcome predictors
      - < 3 to 4 cm in size
      - < 3 to 6 locules
      - No communication with MPD
  - Surveillance imaging follow-up
    - “patients achieving cyst ablation are thought to be at continued risk of developing ductal adenocarcinoma and should undergo continued surveillance imaging”

Diagnosis and Management of Asymptomatic Neoplastic Pancreatic Cysts: AGA Guidelines (2015)

Vege SS, et al. Gastroenterology 2015; 148: 819-822

- Surveillance
  - Patient must understand risks and benefits of surveillance program
  - Cyst < 3 cm, no solid component, no dilated pancreatic duct (PD)
    - If no change in cyst size, solidity or PD → surveillance MRI at years 1, 3, and 5
    - If changes in cyst → EUS-FNA
  - Cyst with ≥ 2 of the following
    - Size ≥ 2 of the following
    - Solid component
    - Dilated PD

    → EUS/FNA → MRI surveillance at 1, 3, and 5 yr
    - Has concerning features
    - Concerning features → surgery

- Surgery
  - Resection if above diagnostic features applying at a centre with "…demonstrated expertise in pancreatic surgery"
  - After resection of pancreatic cyst containing dysplasia/cancer, perform post-surgical surveillance of any remaining pancreas with MRI q2yr
    - Otherwise, no surveillance required

- Surveillance
  - ↑ risk factors for pancreatic cysts
    - ≥ 3 cm diameter
    - Solid component
    - ↑ pancreatic duct size

    (Conditional recommendation, very low quality evidence)
  - Prepare patient with a pancreatic cyst with "…a clear understanding risk and
    - ↓ risk (size < 3 cm, no solid component, no ↑ pancreatic duct size)
    - Repeat MRI in 1 yr, therapy 2 yr x 2 (total of 5 yr)
    - ≥ 2 high risk factors > EUS-FNA → repeat MRI in 1 yr, then q2yr
    - MRI repeat at 1 yr, then q2yr (to total of 5 yr)

    (Conditional recommendation, very low quality evidence)
  - If concerning factors conformed → surgery (Conditional recommendation, very low quality evidence)

- EUS with no concerning findings → repeat MRI in 1 yr, then q2yr
  - MRI repeat at 1 yr, then q2yr (to total of 5 yr)

  (Conditional recommendation, very low quality evidence)
  - If no significant change in cysts characteristics after 5 yr surveillance, or
    - Patients no longer a surgical candidate, stop surveillance

  (Conditional recommendation, very low quality evidence)

❖ Surgery

- Perform pancreatic cyst surgery in a centre of excellence in pancreatic surgery (Strong recommendation, very low quality evidence)

❖ Surveillance after pancreatic cyst surgery

- No cyst high-grade dysplasia/cancer
- No routine surveillance (Conditional recommendation, very low quality evidence)
- With high-grade dysplasia / invasive cancer
  - MRI q2yr remaining pancreas q2yr

  (Conditional recommendation, very low quality evidence)

Endoscopy in Benign Pancreatic Disease: ASGE Guideline (2015)

Chandrasekhara V, et al. Gastrointest Endosc 2015; 82: 203-214

- Methodology
  - This guideline may be revised as necessary to account for changes in technology, new data, or other aspects of clinical practice. The recommendations were based on reviewed studies and were graded on the strength of the supporting evidence by using the GRADE criteria.
  - This guideline is intended to be an educational device to provide information that may assist endoscopists in providing care to patients. This guideline is not a rule and should not be construed as establishing a legal standard of care or as encouraging, advocating, requiring, or discouraging any particular treatment.
  - Clinical decisions in any particular case involve a complex analysis of the patient's condition and available courses of action.
    - Therefore, clinical considerations may lead an endoscopist to take a course of action that varies from these guidelines.

GRADE system for rating the quality of evidence for guidelines

Quality of Evidence	Definition
○ High quality	− Further research is very unlikely to change our confidence in the estimate of effect.
○ Moderate quality	− Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
○ Low quality	− Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
○ Very low quality	− Any estimate of effect is very uncertain.

❖ Acute Pancreatitis (CP)

➢ Causes/Associations

- Most common
  - Cholelithiasis
  - Ethanol
  - Idiopathic
- Role of endoscopy to establish other causes
  - Biliary tree
    - Choledocholithiasis
    - Sludge
  - Pancreas
    - Congenital abnormalities
    - Pancreas divisum
    - Cysts
    - Neoplasms
    - Acute exacerbation of chronic pancreatitis
  - Ampulla
    - Masses
    - Dysfunction of sphincter of Oddi (SOD)

➢ Endoscopy

- Endoscopic Ultrasound (EUS)
  - Determines cause of first episode of pancreatitis in ~30%
    - ↓ diagnostic yield after cholecystectomy
  - Pancreatic duct adenocarcinoma (PDAC) may be detected by EUS in persons with first episode of otherwise unexplained acute pancreatitis (AP)
    - Mean age of onset of AP from PDAC 60 yr (some authorities suggest investigation of all persons ≥ 40 yr who present with unexplained AP)

Abbreviations: AIP, autoimmune pancreatitis; AP, acute pancreatitis; ASGE, American Society of Gastrointestinal Endoscopy; CP, chronic pancreatitis; CT, computed tomography; ePFT, endoscopic pancreatic function testing; ERCP, endoscopic retrograde cholangiopancreatography; EUS, endoscopic ultrasound; FNA, fine-needle aspiratory; HCO_3^-, bicarbonate; IDCP, idiopathic duct centric pancreatitis; MPD, main pancreatic duct; MRCP, magnetic resonance cholangiopancreatography; NPV, negative predictive value; PD, pancreatic duct; PDAC, pancreatic duct adenocarcinoma; SOD, Sphincter of Oddi

➢ Endosonographic criteria for chronic pancreatitis

	Parenchymal changes	Ductal abnormalities
○ Major A	− Hyperechoic foci with shadowing	▪ MPD calculi
○ Major B	− Lobularity with "honeycombing": ≥3 contiguous lobules measuring at least 5 mm in length	
○ Minor criteria	− Lobularity without honeycombing	▪ Irregular/ectatic MPD contour
	− Hyperechoic foci without shadowing	▪ ≥3 dilated side branches
	− Cysts	▪ MPD dilation >3.5-mm body; >1.5-mm tail
	− Hyperechoic stranding	▪ Hyperechoic MPD margin

- ○ Consistent with chronic pancreatitis:
  - − 1 major A feature and ≥3 minor features
  - − 1 major A and major B features
  - − 2 major A features
- ○ Suggestive of chronic pancreatitis
  - − 1 major A feature and ≤3 minor features,
  - − 1 major B feature, and ≥3 minor features
  - − Any ≥5 minor features.
- ○ Indeterminate for chronic pancreatitis
  - − 3 or 4 minor features,
  - − Major B feature alone or with <3 minor features
- ○ Normal: ≤2 minor features without major features.

Abbreviation: MPD, Main pancreatic duct

Printed with permission: Chandrasekhara V, et al. Gastroentest Endosc 2015; 82: 203-214 (Table 2).

MRCP is usually used to diagnose, whereas ERCP is used for treatment of hepatobiliary lesions

- Give examples of the therapeutic role of ERCP.
  - ○ Sphincterotomy
    - − Obstruction / drainage / gaining access
  - ○ Papillotomy
    - − Minor papilla (pancreas divisum)
  - ○ Placement of biliary/pancreatic stent
  - ○ Drainage of pancreatic pseudocyst, walled off necrosis (WON)
  - ○ Necrosectomy

Recommendations

- If patient > 40 yr with acute pancreatitis (AP) with clinical, laboratory, and diagnostic (MRI or CT) not revealing cause of AP (idiopathic) → perform endoscopic ultrasound (EUS). (Quality of recommendation, low)
- Do **not** perform ERCP to investigate one / first episode of AP (Quality of recommendation, moderate)
- In the patient with acute recurrent pancreatitis and normal EUS +/- MRCP (no biliary tract stones / sludge and no chronic pancreatitis → ERCP plus empiric biliary +/- pancreatic sphincterotomy, or manometry of Sphincter of Oddi (Quality of recommendation, low)
- In the patients with ↑ risk of post-ERCP pancreatitis who require ERCP → give rectal indomethacin +/- stenting of PD (Quality of evidence, high).

❖ Choledocholithiasis / microlithiasis

- Terminology
  - Stones ≥ 3 mm
  - Microlithiasis < 3 mm
  - Sludge, biliary: suspicion of
    - Cellular debris
    - Glycoprotein
    - Mucin
    - Proteinaceous material
- Sampling/examination
  - Sample duodenal fluid
  - Polarized microscopy to detect biliary crystals
- Congenitally acquired anatomical variant resulting in lack of fusion of dorsal and ventral pancreatic ducts
- Diagnose by MRCP, treat (papillotomy +/- stenting and rectal indomethacin) recurrent pancreatitis with ERP
  - Relief
    - Early, 60%
    - Recurrence in 6 mon, 1/2 of these persons

❖ Sphincter of Oddi dysfunction (SOD)

Types	Pancreatic Type Pain	↑ amylase/lipase on two occasions	Dilated Pancreatic Duct
1	+	+	+
2	+	+	+
3	+	-	-

- Perform sphincterotomy for type 1 SOD
  - Biliary, pancreatic, common sphincters
  - 50% response to biliary sphincterotomy, as well as biliary plus pancreatic sphincterotomy
  - ↑ risk of recurrent acute pancreatitis (AP) with pancreatic SOD

Recommendations

- For patients with type 1 or type 2 Sphincter of Oddi dysfunction (confirmed by myotomy) → perform ERCP sphincterotomy (Quality of evidence, moderate).
- In the patient with chronic abdominal pain which is though to be due to SOF type 3, do **not** do ERCP (Quality of evidence, high)

❖ Autoimmune Pancreatitis (AIP)

➢ Demography

- Type 2 AIP idiopathic duct-centric pancreatitis (IDCP) is more common than AIP in Europe / United States

➢ Diagnosis

- Clinical, laboratory, diagnostic imaging, histopathology
- Some guidelines recommend inclusion of pancreatography for diagnosis, others do not (e.g., Mayo Clinic “HISTORE” criteria)

➢ Endoscopy

- MRCP
  - Features of AIP
    - Pancreatic duct stricture
      - Long/narrow. > 1/3 the length of the main pancreatic duct
      - Multiple
      - No dilation (upstream, < 5 mm)
      - Side branches from structural duct
  - Some patients with AIP will have strictures of both pancreatic and biliary stricture (IgG4-related disease [RD])
    - Need to perform MRCP/ERCP and not just ERP

- Endoscopic Ultrasound (EUS)
  - EUS findings of AIP
    - Pancreatic gland
      - Diffuse enlargement
    - Parenchyma
      - Hypoehoic
      - Patchy
      - Heterogenous

      } Seen in 57%
    - Duct wall
      - Thickened
    - Margins
      - Hypoehoic
    - Distinguish AIP from pancreatic duct adenocarcinoma (PDAC): features more common in EUS of PDAC gland enlargement, focal duct dilation pancreatic duct / biliary duct (PD/BD

MCQ Gem

- Role of EUS-FNA to diagnose type of pancreatic mass (AIP vs. POAC)
  - To exclude PDAC
  - Not to diagnose AIP
- However, negative EUS-FNA does not exclude PDAC, since false-negative rate of EUS-FNA for ≥ 3 cm diameter
  - A core tissue sample may be obtained using a large caliber cutting biopsy needle

Recommendation

- In patients with suspected autoimmune pancreatitis (AIP), perform
  → EUS-guided tissue biopsy (to exclude pancreatic duct adenocarcinoma [PDAC], or
  → Larger gauge core biopsy
  (Quality of evidence, moderate).

❖ Chronic Pancreatitis (CP)

- Diagnostic imaging
  - MRCP, CT, EUS
  - Endoscopic pancreatic function testing (ePFT)
    - Peak HCO_3- < 80 mEq/L indicated pancreatic insufficiency
    - HCO_3- > 80 mEq/L excludes CP with insufficiency high negative predictive value (NPV)
- ERCP
  - To assess BD/PD, not the parenchyma of the pancreas
  - To relieve obstruction of PD/BD – Strictures
  - Replace by EUS/MRCP for diagnosis – Stone
  - For diagnosis id non-invasive imaging is non-diagnostic / equivocal to diagnose CP
    - High resolution of pancreatic parenchyma / ducts
- EUS
  - Drain pancreatic fluid
  - Perform anaesthesia of pain by uni-/bilateral injection around celiac plexus
  - Features of CP on EUS
    - Hyperehoic parenchyma
      - Cysts
      - Foci
      - Lobulus
      - Strands
    - Ducts
      - Dilation
      - Irregular
      - Margins hyperechoic
      - Stones
      - Side branches

Clinical Suggestion

- The Rosemont classification of EUS features of CP does not "…increase interobserver agreement for the diagnosis of CP"
  - Non-EUS features of CP must also be present on MRCP/ERCP, ePFT before diagnosing CP (e.g., use EUS plus ePFT)

Recommendations

- In patient suspected as having chronic pancreatitis which has not been diagnosed by MRCP → endoscopic ultrasound (EUS) +/- endoscopic pancreatic function tested (ePFT) (Quality of evidence, low)

- PDAC in CP
  - 2% of patients with new diagnosis of CP also have PDAC
  - Differentiate CP from PDCA, or CP plus PDCA
  - Pancreatic protocol CT scan (triple phase) recommend to detect PDAC, even in patient with CP ("standard CT scanning is insensitive for the deletion of pancreatic adenocarcinoma [PDAC] in patients with chronic pancreatitis [CP]")
  - Other testing is not sufficiently sensitive to detect the PDAC
    - EUS
      - Accuracy, < 75%
    - EUS plus FNA
      - Sensitivity ~80% to 90%

- Strictures of Pancreatic Duct (PD)
  - PD strictures from CP inflammation / fibrosis
    - Diagnose with
      - ERCP +/- brushings for cytology
      - Confocal microscopy
  - ERCP (transpapillary route) to dilate PD strictures, then stent
    - Remove intraductal stones
    - Abdominal pain ↓ 65% to 85% when no intraductal stones
      - Pain relief may persist after PD dilation, stenting then removal of stent, even if strictures remain
    - Change stents frequently to ↓ risk of obstruction
    - Use 10F single stents, or multiple plastic stents
  - EUS-guided access / drainage of obstructed main PD indicated for
    - Anatomy abnormal (e.g., previous surgery)
    - Unsuccessful transpapillary (ERCP/ERP) approach
    - Retrograde transpapillary drainage ("Rendezvous" technique)
    - Anterograde
      - Duct puncture and transmural drainage
      - Passage of transpapillary stent
    - Technical success ~85%
      - Symptom relief in ~80% of these

Recommendation

- In patients with symptomatic dominant strictures of the pancreatic duct
  - undertake multidisciplinary review of the patient's case

  → perform ERP with dilation of stricture +/- placement of stent
  (Quality of evidence, high)

❖ Pancreatolithiasis (chronic calcific pancreatitis)

- Extracorporeal shock wave lithotripsy (ESWL)
  - Variable results of ↓ pain short / long term
  - May require multiple (> 10) sessions of endotherapy
  - Better success if ERP done > 2d after ESWL (82%), vs. 16% when ERP < 2d alter ESWL

Recommendation

- In patients with stones in the pancreatic duct (pancreatolithiasis) who continue to have pain despite endoscopic extraction of the stones → perform extracorporeal shock wave lithotripsy) (Quality of evidence, moderate)

❖ Pain from CP

- Pancreatic surgery may be "…more effective and durable than endoscopic treatment for pain relief in patients with CP and PD obstruction"
  - Factors predicting success of endotherapy for pain relief
- Patients
  - Short duration of CP
  - Less frequent attacks of pain
  - No alcohol/smoking
- Pancreas
  - Stone in head of pancreas
  - No main PD stricture at initial ERP

❖ Peripancreatic Fluid Collection

➢ Causes/associations

- Acute pancreatitis
- PD disruptions / leaks

  - Ascites
  - Pseudocysts

➢ Treatment

- Endoscopic drainage
  - Transpapillary non-bridging stent +/- sphincterotomy

❖ EUS-guided Celiac Block

- Celiac plexus
  - Network of ganglia (1 to 5) and interconnecting fibers located near vertebrae T12 to L2
  - Transit pain sensation from pancreas
  - Injection of an anesthetic agent ↓ pain in ~55% of patient with CP, but pain relief tests < 24 wk

Pancreatic Ductal Adenocarcinoma (PDAC): **The Importance of KRAS**

Buscail L, et al. Nat Rev Gastroenterol Hepatol 2020; 17: 153-168

- Demography
  - Median survival, 12 mon
  - 80% of persons with PDAC have mutations of KRAS
  - 5-yr survival rate, < 3%
- Treatment
  - Chemotherapy standard
    - Gemcitabine
    - Gemcitabine plus nab-paclitaxel
    - Folfirinox
      - 5-fluorouracil
      - Folinic acid
      - Irinotecan
      - Oxaliplatin
  - Surgery
  - Palliation
  - New KRAS target drugs
    - Biologicals / monoclonal antibodies
      - Anti-eGFR
      - Anti-eGFR2
    - Small molecules

KRAS Protein and Mutations

- The KRAS gene encodes the protein KRAS
  - KRAS is a GTPase which is a molecular switch for coupling cell membrane receptors for growth factors to
    - Intracellular signalling pathways
    - Transcription factors
  - KRAS binds to
    - GTP → activation
    - GDP → inactivation

    } Regulated by
    - Guanine nucleotide exchange factor (GEF)
    - GTPase activating proteins (GAPs)
  - KRAS-GTP affects effector proteins / signalling pathways and nuclear transcription factors e.g.,
    - Mitogen-activating protein kinase (MAPK)
    - Mechanistic target of rapamycin (mTOR)
    - Rapidly accelerated fibrosarcoma (RAF)

Abbreviations: eGFR, estimated glomerular filtration rate; GAPs, GTPase activating proteins; GEF, guanine nucleotide exchange factor; MAPK, mitogen-activating protein kinase; mon, month; mTOR, mechanistic target of rapamycin; RAF, rapidly accelerated fibrosarcoma

- KRAS mutation in PDAC
  - "An activating point imitation of the KRAS oncogene on codon 12 (EXON 2) ….
    - Triggers replacement of the GGT sequence (which encodes glycine)…" by various sequences

➢ Methodology

- Tissue (EUS-FNA, endoscopic ultrasound-fine needle aspiration)
  - Assessment of FNA has
    - Sensitivity, 65% to 95%
    - Negative predictive value, 50% to 70%
  - "A negative EUS-FNA in cases in which PDAC is strongly suspected continue to pose a problem"
  - New methods, such as digital polymerase chain reaction (dPCR) may ↑↑ sensitivity, particularly to differentiate benign from malignant tumour
- Blood circulating tumour DNA (ctDNA) may prove to be useful in future

- Cell metabolism reprograming.
  - KRAS promotes glycolytic flux → glucose uptake and lactate production through glucose transporters
  - Macropinocytosis is the uptake of nutrient via endocytosis, which leads to an accumulation of catabolite intermediates that's stimulate carbon metabolism and sustain cell proliferation.
  - Autophagy is the process by which cytoplasmic components are degraded and recycled through lysosomes and is critical during the late stages of pancreatic cancer.
  - Reactive oxygen species (ROS) are regulated by KRAS.

- Interactions with the microenvironment
  - Tumour cells expressing oncogenic KRAS secrete molecules that act in a paracrine manner on microenvironment components such as
    - Fibroblast
    - Innate and adaptive immune cells
    - Blood microvessels
  - KRAS-induced chemokine secretion promotes
    - Macrophage recruitment
    - Lymphocyte / myeloid cell infiltration (including myeloid-derived suppressor cells that inhibit anti-tumour immune responses

- Cancer-associated fibroblasts (also called pancreatic stellate cells) regulated the tumour stroma, including
  - Extracellular matrix
  - Collagen fibres
  - Hyaluronic acid
- Pro-angiogenic factors stimulate tumour angiogenesis
- All these cells and structures from the microenvironment → ↑ tumour cell growth

Abbreviations: COX2, cyclooxygenase 2; CXC, CXC chemokine; GM-CSF, granulocyte macrophage colony-stimulating factors; Shh, sonic hedgehog; TGF-β, transforming growth factor-β; VEGF, vascular endothelial growth factor

- Different Therapeutic Strategies Targeting the KRAS Gene and KRAS Protein
  - RNA interference to suppress mutant KRAS expression (mainly G12D mutant)
  - Farnesyltransferase inhibitors prevent farnesylation of KRAS protein on the C-terminal motif of KRAS site of farnesylation (CAAX) (reticulum of Golgi apparatus) (tipifarnib, lonafarnib)
  - Inhibition of phosphodiesterase 6δ (PDEδ), which assists in the translocation of farnesylated KRAS to the membrane (deltarasin)
  - Inhibition of RAS signalling by dislodging farnesylated KRAS from the membrane (farnesyl thiosalicylic acid; salirasib)
  - Vaccination against KRAS using mutated peptide at the amino-acid level (amino-acid substitution of various KRAS mutants)
  - Targeting the pocket RAS-GDP complex and interfering with KRAS-son of Sevenless (SOS) interaction and subsequent SOS-mediated nucleotide exchange (small molecules)
  - Blocking the interaction between GTP and KRAS and consequent inhibition of rapid accelerated fibrosarcoma (RAF) interaction
    - Hyaluronic acid
  - Targeting RAF-mitogen-activated protein kinase (MEK)-extracellular signal-regulated kinase (ERK) pathway and phosphoinositide 3 kinase (PI3K)-AKT-mechanistic target of rapamycin (mTOR) pathway (small molecule inhibitors)

Abbreviations: GAP, GTPase-activating protein; GEF, guanine nucleotide exchange factor; GRB2, growth factor receptor-bound protein 2

- Activation of KRAS Protein and Its Downstream Intracellular Pathways
  - After the binding of growth factor receptors (tyrosine kinase or G-coupled receptors)
    - Growth factor receptor-bound protein 2 (GRB2) combines with the guanine nucleotide exchange factor Son of Sevenless (SOS)
    - Interacts with KRAS protein
  - The KRAS protein attaches to the cell membrane to be active
  - A farnesyl isoprenoid is covalently linked to the cysteine residue by farnesyltransferase on the C-terminal motif of KRAS site of farnesylation (CAAX)
  - Once this membrane association is effective, KRAS can be activated when bound to GTP.
  - Intrinsic KRAS, GTP-GDP cycling is regulated by guanine nucleotide exchange factors (GEFs) → stimulate nucleotide exchange
  - By GTPase-activating proteins (GAPs) that accelerate the intrinsic GTP hydrolysis activity of KRAS
  - Mutation of KRAS
    - ↓ intrinsic activity of GTPase activity
    - Prevents GAPs from promoting the conversion of GTP to GDP → KRAS bound to GTP → ↑ downstream signalling pathways → ↑ nuclear transcription factors leading to
      - Cell proliferation
      - Survival and transformation
  - RAS-like (RAL)A-RALB pathway (1)
    - Nuclear factor-κB (NF-κB) pathway (2)
    - Phosphoinositide 3-kinase (PI3K) pathway (3)
    - p38 pathway (4)
    - JUN N-terminal kinase (JNK) pathway (5)
    - Mitogen-activated protein kinase (MAPK) pathway (6)

Abbreviations: ERK, extracellular signal-regulated kinase; MEKK, mitogen-activated protein kinase; mTOR, mechanistic target of rapamycin; PLC, phospholipase C; RAF, rapid accelerated fibrosarcoma

Pancreatic Ductal Adenocarcinoma (PDAC): **the Importance of Extracellular Matric** (ECM) **Proteins, Vasculature, and Cancer-associated Fibroblasts** (CAF)

Hosein AN, et al. Nat Rev Gastroenterol Hepatol 2020;17(8):487-505.

- The activated stroma / desmoplastic stromal subtype of pancreatic ductal adenocarcinoma (PDAC) reflects molecular changes which may signal beneficial therapeutic strategies
- The tumour microenvironment (TME) of the PDAC include
  - The extracellular matric (ECM)
  - Vasculature
  - Fibroblasts (cancer-associated fibroblasts, CAFs)

  } ▪ As well as endothelial cells, pericytes, neurons, immune cells

➢ Extracellular Matric (ECM)

- Pancreatic tumour cells → B1 integrin / STAT3 stimulate stroma fibroblasts → ↑ collagen type I, III, and IV; ↑ hyaluronic acid; ↑ fibronectin } ▪ Desmoplasia
- Pancreatic tumour cells → ↑ proteolytic enzymes → ↑ remodelling of stroma
- ↓ vasculature diameter in PDAC from ↑ intestinal fluid pressure (IFP)

- Therapeutic Targets
  - Enhance
    - Hyaluronic acid (HA) → ↓ IFP in tumour → ↑ dietary of chemotherapy
  - Inhibit
    - Rho-associated protein kinase (ROCK): ECM remodeling
    - ↓ matric metalloproteinase (MMPs)
    - ↑ microvascular density (MVP)
    - Focal adhesion kinase (FAK) →
      → ↑ infiltration of CD8+ T cell
      → delivery of chemotherapy
    - Discoid in domain receptor 1 (DDR1)

- Vasculature
  - Improve poor PDAC vascularization (a therapeutic target)
    - ↑ pericyte coverage
    - ↑ tumour perfusion
    - ↑ O2 tension
    - ↑ chemotherapeutic delivery
  - The pancreatic ductal adenocarcinoma (PDAC) tumour microenvironment features an inefficient, leaky vasculature with poor pericyte coverage
    - Associated with poor tumour perfusion leading to hypoxia and suboptimal drug delivery
  - Tumour vasculature normalization by blocking the vascular endothelial growth factor (VEGF)–VEGFR2 axis106 → ↑ pericyte coverage and tumour perfusion, leading to
    - ↓ hypoxia
    - ↑ drug delivery and CD8+ T cell trafficking into the tumour through the action of the leukocyte adhesion molecules ICAM and VCAM

Adapted from: Hosein AN, et al. Nat Rev Gastroenterol Hepatol 2020;17(8):487-505 (Figure 3)

- Cancer-associated Fibroblasts (CAF)

➢ Therapeutic targets in the extracellular matrix of PDAC.

- Hyaluronic acid
  - Hyaluronic acid degradation by pegylated recombinant human hyaluronidase 20 (PEGPH20) → ↓ intratumoral pressure, → ↑ chemotherapy
- ROCK
  - Activated Rho-associated protein kinase (ROCK) in the PDAC tumour → extracellular matrix remodelling (↑ matrix metalloproteinases (MMPs). This process favours metastasis and decreased microvessel density (MVD), which then leads to poor tumour perfusion and decreased tumour drug delivery. Fasudil is a small-molecule inhibitor of ROCK with anti-PDAC activity in preclinical models.
- FAK
  - Activated, focal adhesion kinase (FAK)
    - ↓ CD8+ T cell infiltration into the PDAC tumour microenvironment
    - ↑ desmoplastic response
    - ↓ drug delivery to the tumour
  - Defactinib is a small-molecule inhibitor of FAK under clinical evaluation for the treatment of PDAC in combination with an immune checkpoint inhibitor

Abbreviations: CAF, cancer-associated fibroblast

Adapted from: Hosein AN, et al. Nat Rev Gastroenterol Hepatol 2020;17(8):487-505 (Figure 2)

- Intratumoral fibroblast heterogeneity in PDAC
  - Protumour inflammatory cancer-associated fibroblasts (iCAFs) and antitumour myofibroblastic cancer-associated fibroblasts (myCAFs) are produced when resident pancreatic fibroblasts receive paracrine and cell-contact cues from pancreatic ductal adenocarcinoma (PDAC) cells, respectively, within the tumour microenvironment.
  - Tumour cell-derived IL-1α aids in the generation of iCAFs, which secrete LIF and propagate the iCAF phenotype.
    - IL-1β also acts to maintain the iCAF phenotype through autocrine signalling.
  - iCAFs upregulate a host of inflammatory cytokines (such as IL-6 and granulocyte colony-stimulating factor [G-CSF])
    - Contribute to local collagen deposition
  - Putative markers for iCAFs are platelet derived growth factor receptor-α (PDGFRα) and CXCL12.
  - When IL-1 receptor (IL-1R) is activated by IL-1 ligands, IL-1 receptor-associated kinase 4 (IRAK4) is also activated, which in turn leads to the activation of IKKβ.
    - These events lead to the liberation of nuclear factor-κB (NF-κB) from inhibitory proteins, enabling it to translocate to the nucleus → acts as a transcription factor for a host of inflammatory genes that drive the iCAF phenotype125,133.
  - iCAFs have also been shown to signal through the JAK–STAT signalling pathway. Cell contact between PDAC cells and juxtatumoural fibroblasts generates myCAFs through transforming growth factor-β (TGFβ) signalling.
  - Putative markers for myCAFs are fibroblast-specific protein 1 (FSP1) and/or α-smooth muscle actin (αSMA).
  - Mesenchymal stem cell-derived cancer-associated fibroblasts (mscCAFs) are recruited from the bone marrow and produce granulocyte–macrophage colony-stimulating factor (GM-CSF) locally in the tumour microenvironment → polarization of macrophages towards an immunosuppressive phenotype → blunting of a robust T cell response against the tumour.
  - mscCAFs are positive for CD44, CD49, CD73 and CD90.
  - Major histocompatibility complex (MHC) class II-expressing CAFs (apCAFs) present antigen to CD4+ T cells. Shh, sonic hedgehog.

- Therapeutic targets in pDaC CaFs.
  - IGF1R and AXL
    - Signalling of insulin-like growth factor 1 (IGF1) receptor (IGF1R) and AXL → invasive and metastatic behaviour of pancreatic ductal adenocarcinoma (PDAC) tumour cells.
  - Vitamin D
    - PDAC cancer-associated fibroblasts (CAFs) have ↑ vitamin D receptor (VDR) expression and ↓ expression of lipid storage genes.
    - When treated with calcipotriol (a synthetic form of vitamin D), these CAFs → ↑ lipid storage gene expression and hinder epithelial-to-mesenchymal transition (EMT) (chemoresistance and the action of myeloid-derived suppressor cells [MDSCs]).
  - Retinoic acid
    - Retinoic acid signalling
      - PDAC CAFs are induced to assume a lipid storage phenotype when treated with all-trans retinoic acid (ATRA) →
        - ↓ β-catenin nuclear localization and
        - ↓ invasion of cancer cells.

Adapted from: Hosein AN, et al. Nat Rev Gastroenterol Hepatol 2020;17(8):487-505 (Figure 6)

Abbreviations: αSMA, alpha smooth muscle actin; CAF, cancer-associated fibroblast; DDR1, discoid domain receptor 1; ECM, extracellular matrix; FAK, focal adhesin kinase; FSP, fibroblast specific protein 1; GCSF, granulocyte stimulating factor; IFP, intestinal fluid pressure; MHC, major histocompatibility complex; MMP, matric metalloproteinase; mscCAF, mesenchymal stem-cell derived cancer-associated fibroblasts; MVP, microvascular density; NFκB, nuclear factor κB; PDAC, pancreatic duct adenocarcinoma; PDGF, platelet-derived growth factor; PEG PH20, pegylated recombinant human hyalonidase 20; ROCK, Rho-associated protein kinase; Shh, Sonic hedgehog

Pancreatic Ductal Adenocarcinoma (PDCA): **A Review** (2016)

Fogel EL, et al. Am J Gastroenterol 2017; 112: 537-554

- Prognosis
  - Proportion of patients with PDAC, who are surgical candidates
    - 15% to 20%
    - 5 yr survival rate for distant, metastatic disease, 2%
    - 5 yr survival; rate after pancreaticoduodenectomy (patients diagnosed with advanced, unresectable disease)
      - Lymph node
        - Negative, ~25%
        - Positive, ~10%

- Demography
  - M > F, age > 65 yr, African origin > Caucasians

- Risk factors
  - Older men with African ancestry
  - Smoking
  - ↑ BMI (obesity)
  - Chronic pancreatitis (pooled relative risk [pRR], 13.3 (95%CI: 6.1-28.9)
    - Even higher pRR for
      - Hereditary
      - Tropical

    } Pancreatitis → Genetic changes
      - BRCA2
      - PALB2
      - P16
      - STR11/LKB1
  - Diabetes mellitus, long-standing type 2
  - H. pylori infection
  - Genetic mutations

- Definition
  - "Borderline resectability"
    - To disease
      - Venous invasion advanced
      - Hepatic invasion early

    } Good response to trial of neoadjuvant chemotherapy

- Resectability
  - Invasion
    - Veins (patient; no involvement of veins branches e.g., jejunal veins)
    - Arteries (major)
  - Metastases
- Vessel invasion
  - 180^{o} circumference of vessel is contagious with tumour
  - Performance characteristics to detect PDAC on CT/MRI
    - Sensitivity, 45% to 84%
    - Specificity, 98% to 100%
  - Teardrop sign (deformity of vessel)
    - Even if < 180% circumference of vessel contiguous of tumour
- Dilation of peripancreatic vein
  - Anterior / superior pancreaticoduodenal vein
  - Gastrocolic trunk formation of vascular arcade invasion of arcade by tumour → engagement of veins

➢ Diagnostic Imaging

- CT
  - Pancreas protocol computed tomography (ppCT) for pancreatic parenchyma
    - Late arterial phase (parenchyma)
      - Hypodense mass (10% of PDAC are isodense, i.e., no mass seen)
      - Poorly defined
    - Venous phase
      - Hepatic metastases
      - Arteries
        - Celiac
        - Common hepatic
        - Peripancreatic
        - Superior mesenteric
      - Veins
        - Portal
        - Splenic
        - Superior mesenteric

      } Use coronal and sagittal reformations to ↑ sensitivity for local invasion

    - Sensitivity to diagnose PDAC
      - Overall, 89% to 97%
      - < 2 cm, 65% to 75%
  - Stages
    - Isolated venous invasion / locally advanced but potentially resectable, T3 stage
    - Arterial invasion → non-resectable. T4

- Limitations of CT (↓ sensitivity)
  - Detection of nodal metastases: threshold

	Sensitivity
10 mm	15%
5 mm	~70%

  - Hepatic / peritoneal metastases miss rate for detection of overall metastases, ~30%

❖ Magnetic resonance imaging (MRI)

- Precontrast / early postcontrast MRI
  - Hypodense
- Late postcontrast
  - Enhancement, or isodense
- Superior to CT + distinguish metastatic disease vs. cyst / hemangioma
- Duct penetrating sign (patent duct in pancreatic mass)
  - Suggests chronic / autoimmune pancreatitis

➢ Endoscopic ultrasound (EUS)

- Sensitivity for pancreatic lesions (begin a malignant), > 95%
  - Even useful to detect small lesions in pancreas
    - "…a normal pancreas by EUS examination essentially rules out PDAC…"
      In the patient with chronic pancreatitis and no mass seen on EUS
- False negative EUS
  - Pancreas
    - Recent (< 4 wk) acute pancreatitis
    - Diffuse infiltrating cancer
  - Biliary tract
    - Biliary stent
- Determine surgically resectability
  - EUS = ppCT

Specific for PDAC

- Double duct sign (dilated bile and pancreatic ducts)
- Intrahepatic lesions +/-
- Lymphadenopathy

Note: "…however, a degree of uncertainty will remain as benign disease at the time of pancreatico-duodenostomy found in up to 15% of patients", e.g., autoimmune pancreatitis type I, inflammatory pseudo tumour

- EUS-FNA
  - Diagnosis of malignancy
    - Sensitivity, 85% to 90%
    - Specificity, ~99%

    } ▪ Standard of care

➢ Staging

- TNM method can be used but more clinically useful is to stage PDAC as

Definition	Vascular	Spread	
− Resectable	-	-	▪ Resection
− Borderline	PV+	Stomach	▪ Remove vein partial gastrectomy, plus resection
− Locally advanced	CA+		▪ Non-curative by surgery
− Metastatic		Lung Liver	▪ Surgically incurable

- Biliary obstruction
  - Obstruction of bile duct
  - Hepatic metastases

➢ Treatment

❖ Endoscopy

- Even if there is biliary obstruction
  - Proceed with surgical resection if lesion is resectable and patient is fit
  - Do **not** routinely just do ERCP in patients with "non-deep" jaundice related complications which might delay surgery (cholangitis, pancreatitis, occlusion of tent, bleeding (↑ rate of surgical complications too)
- If patient who was thought preoperatively to be operative turns out to be operative, then post-operatively perform ERCP plus biliary drainage
- Indications for biliary drainage
  - Deep jaundice
  - Inoperability
  - Planned chemotherapy

MCQ Gem

- Give the reason why drainage of obstructed bile duct in patient with PDAC must be performed before administering chemotherapy.
  - Jaundice / hyperbilirubinemia / biliary obstruction → ↑ risk of adverse effects of chemotherapy
    - Thus, correct BD obstruction before pre-operative chemotherapy

- ERCP successful for decompression of malignant strictures in > 90%
  - Requires high level of expertise, and
  - Use plastic (polyethylene) stents
  - Stent replacement may become necessary because of development of biofilm → recurrent BD obstruction
  - Consider using uncovered or covered (preferred) self-expandable metallic stents (USEM, SEM respectively) for longer potency of stent
  - For pre-operative neoadjuvant chemotherapy, use self-expanding metal stents
- When ERCP drainage fails
  - Percutaneous transhepatic biliary drainage (PTBD)
    - ↑ rate of success if biliary radicals are dilated
  - EUS-guided
    - Hepaticogastrostomy
    - Choledochoduodenostomy
  - Sonographic antegrade advancement of guideline across papilla
- Percutaneous transhepatic biliary drainage (PTBD), after initial percutaneous transhepatic cholangiography (PTC)
  - When ERCP cannot be performed
  - Contraindications to PTBD
    - Ascites, severe
    - Bleeding diatheses (coagulopathy)
    - Duct obstruction, intrahepatic
      - Chronic liver disease
      - Hepatic metastases
- Types of devices for PTBD
  - External biliary drainage
    - Drainage into bag, for high-grade biliary obstructions
    - Internal decompression before staged internalization once edema resolved, or
    - Temporary decompression before surgery
  - Internal-external drainage
    Approach obstruction through liver and through papilla / biliary-enteric anastomosis
  - Internal SEMS
    - Drainage into bowel lumen
  - Use antibiotic prophylaxis
    - Possible to treat tumour ingrowth / overgrowth
    - Do **not** place SEMS

- Complications
  - Hematobilia from injury to hepatic arteries / portal veins which run adjacent to the bile ducts
    - Pseudoaneurysm
  - Contaminated segments of the biliary tree are successful drained or until patients are a febrile for 48 h after discontinuing antibiotics"
  - Bile leakage
    - Catheter occlusion
    - Migration of catheter
- Other therapeutic choices
  - Combined intervention radiology and ERCP Rendes-Vous procedures

❖ Surgery

- Selection of patients for surgery based upon pancreatic protocol CT (high-resolution with dual-phase contrast enhancement
  - Artery / abnormal tissue plane between
    - Celiac artery (CA)
    - Common hepatic artery (CHA)
    - Superior mesenteric artery (SMA)
- Resectable
  - No
    - When obstruction of superior mesenteric vein (SMV) or portal vein (PV)
    - Extrahepatic cancer
    - Resection +/- adjuvant
      - Chemotherapy / chemoradiotherapy
    - Neoadjuvant chemotherapy, then resection

} Possible extended lymphadenectomy and vascular resection (SMV, PV)

	Borderline Resectable	Locally Advanced
SMV/PV		
Patent / short segment, possible reconstruction	+	
Obstructed, no possible reconstruction		+
CHA / SMA Invasion		
< 180°, or 50% vessel circumference	+	
> 180°, or 50% vessel circumference		+

- Resectable PDCA
  - No evidence of extra-pancreatic disease
  - Patent superior mesenteric vein (SMV) / portal vein (PV)
  - Normal tissue plane between tumour and the celiac common hepatic artery (CHA), or superior mesenteric artery (SMA)
  - ↑ survival with adjuvant chemotherapy / chemoradiotherapy
  - Of patients who are eligible to be "resectable" based on radio criteria, at surgery only 70% are actually resectable
    - Neoadjuvant, gemcitabine-based chemoradiotherapy plus resection extended OS to 34 mon, with 5 yr survival rate of 36%

- Borderline resectable / locally advanced unresectable PDCA
  - Borderline Resection
    - Involvement of SMV/PV but patent, or short segment occlusion with vein reconstruction option
    - Evidence of tumour abutment (< 180º or 50% vessel circumference) against celiac, CHA, or SMA
  - Locally advanced
    - Artery / abnormal tissue plane between
    - SMV / PV occlusion with no option for reconstruction
    - Arterial encasement (> 180o or 50% vessel circumference) of celiac, CHA or SMA
  - Chemoradiotherapy to cause significant regression of tumour so that resection is possible

- Metastatic
  - Evidence of metastatic spread (typical to the liver, peritoneum or lung)
  - FOLFIRINOX →
    - ↑ progression-free survival (PFS) by 3 mon (from 3.4 mon to 6.6 mon)
    - ↑ overall survival (OS) by 5 mon (from 6.7 mon to 11.1 mon)
  - Nab-paclitaxel (nanoparticle albumin-bound paclitaxel plus gemcitabine) →
    - ↑ progression-free survival by 2 mon (from 3.3 mon to 5.5 mon)
    - OS by 2 mon (from 6.7 mon to 8.5 mon)

Approach to patients with pancreatic ductal adenocarcinoma after complete staging by computed tomography (CT)

- Complications of pancreatectomy (~35%)
  - ↓ rate of gastric emptying
  - PDAC recurrence
  - Fistula
    - Gastrojejunostomy
    - Hepaticojejunostomy
    - Pancreaticojejunostomy

    } Frequency, resection
    - Head, 15%
    - Tail, 25%
  - Treatment of severe / uncontrolled fistula drainage after distal pancreatectomy
    ERCP plus stent undrained intrahepatic collections of fluid
    May also consider percutaneous interventional drainage of collections of fluid

❖ Radiotherapy (RT) / Chemotherapy

Rationale for neoadjuvant therapy

- Increase likelihood of truly negative surgical margins
- Increase likelihood of completion of all intended multimodality therapy
- Declaration of distant metastases and early progression of disease
- Declaration of patient's functional status and inability to tolerate operation
- Opportunities for in vivo and in vitro testing for chemo-responsiveness
- The role of radiotherapy / chemotherapy is controversial
- Some centre will offer RT in patients with PDAC which does not progress after 5 cycles of adjuvant chemotherapy +/- erlotinib
- Others suggest postoperative RT in patients with
  - Positive resection margins, or
  - Multiple positive lymph nodes

  } No metastases
- Locally advanced PDAC-chemotherapy follow by RT
  - Stereotactic hypofractionate body radiation therapy may become a method of delivery

➢ Complications

- Pancreatic Insufficiency
  - Occurs
    - When 80% of exocrine function lost
    - In 80% of patients with pre- and post-operatively)
  - Predictors of maldigestion
    - Pancreatico-duodenostomy
    - Pre-surgery MPD > 10 mm

- Mechanisms
  - ↓ acinar tissue
  - ↓ gastric emptying
  - ↓ mixing
  - ↓ release / secretion of CCK
  - ↓ vagus innervation

- Pain control
  - Palliative care service
  - Oral, dermal, systemic analgesia
  - Celiac ganglion block
    - Percutaneous
    - EUS-CPN (EUS-guided celiac plexus neurolysis with local anaesthetic plus alcohol)
    - Surgical

- Gastric Outlet Obstruction
  - Occurs in 10% to 25% of patients with unresectable PDAC
  - Treatment
    - Dietary, prokinetics
    - Enteral self-expanding metal stents (SEMS)
    - If appropriate, perform biliary drainage before placing duodenal SEMS
  - Surgical
    - Gastrojejunostomy

INDEX

Note: Page number followed by f and t indicates figure and table respectively.