

Abnormal Liver Tests

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Disclosures

- Clinical Trials
 - Genfit
 - Novo Nordis
 - Shire
 - Intercept
- Speaker/Honouraria
 - Intercept
 - Gilead



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Definitions

- **LFTs** is a misnomer
- Liver enzyme abnormalities reflect injury to either hepatocytes or cholangiocytes
- Can be referred to as liver injury tests
- Liver function tests reflect liver synthetic function(**INR, Bilirubin, albumin**)

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Liver Injury Tests

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Hepatocellular	Cholestatic (biliary)
<p>Aminotransferases</p> <ul style="list-style-type: none"> ▪ ALT (alanine aminotransferase) ▪ AST (aspartate aminotransferase) ▪ Normal <40 IU/L <ul style="list-style-type: none"> ▪ <30 for men ▪ <19 for women 	<ul style="list-style-type: none"> ▪ Alkaline phosphatase (“alk phos”) ▪ Normal is age dependent (high with growth and pregnancy) ▪ GGT (gamma-glutamyl-transferase) ▪ 5’ Nucleotidase <ul style="list-style-type: none"> ▪ Both indicate cholestasis in cases of isolated alk phos ↑

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Antimitochondrial Antibody
 Ferritin, Iron, TIBC
 A1AT Phenotype
 HCV antibody, viral load
 Ceruloplasmin, Urine Copper
 [Random] viral antibodies
 Hepatitis B sAg, viral load
 ANA, ASMA, IgG
 Ultrasound

PBC
 Hemochromatosis
 Alpha-1 Antitrypsin
 Hepatitis C
 Wilson Disease
 CMV, EBV, HSV, ABCDEFG...
 Hepatitis B
 Autoimmune Hepatitis

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Non-Hepatic Causes

- Muscle Injury: Rhabdomyolysis, seizures, dermatomyositis, long distance running
 - Check CK level
- Thyroid disease
- Celiac Disease
- Anorexia nervosa
- Adrenal Insufficiency
- Hemolysis

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Table 2
Nonhepatic cause of elevated alkaline phosphatase

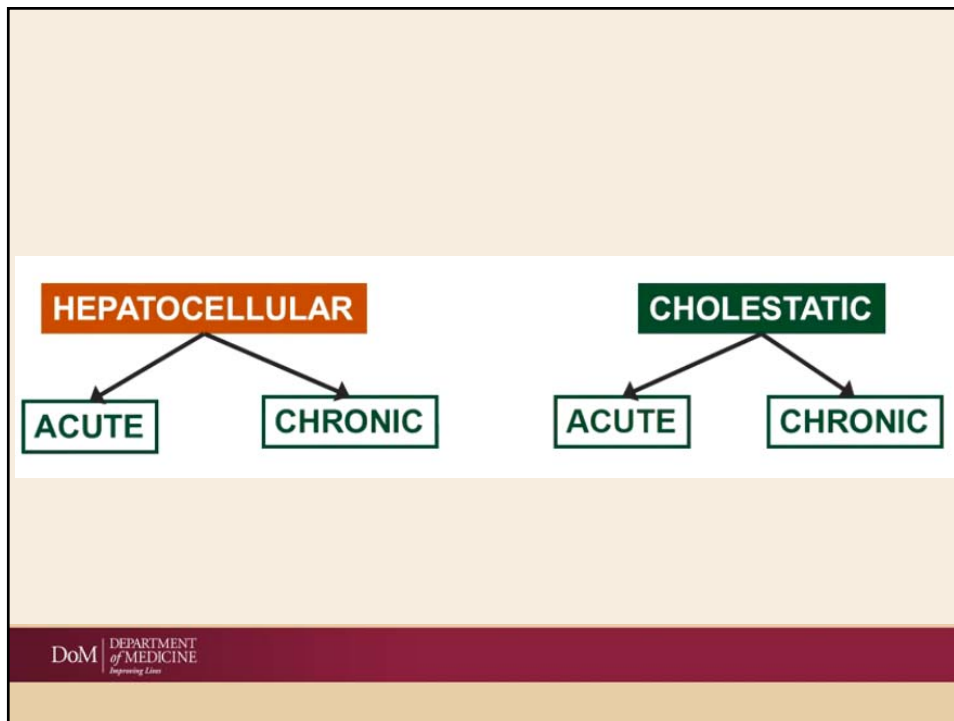
Physiologic	Pregnancy Adolescence After a fatty meal in subjects with blood group O or B
Bone disease	Healing fracture Paget disease Osteomalacia Vitamin D insufficiency Rickets Malignancy: osteogenic sarcoma, metastatic
Renal	Renal failure
Heart	Heart failure
Endocrine	Hyperthyroid Hyperparathyroid
Malignancy	Lymphoma Leukemia Renal cell carcinoma Multiple endocrine neoplasia II

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Test		Hepatocellular Injury	Cholestasis
Liver Injury Tests	Aminotransferases (ALT, AST)	↑↑ - ↑↑↑	0 - ↑
	Alkaline phosphatase	0 - ↑	↑↑ - ↑↑↑
Liver Function Tests	Total/direct bilirubin	0 - ↑↑↑	0 - ↑↑↑
	Prothrombin time (INR)	Prolonged (does not correct with vitamin K)	Prolonged (corrects with vitamin K)
	Albumin	↓ - ↓↓↓ (chronic disease)	0

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Acute Hepatocellular Injury

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Most common	Also consider
<ul style="list-style-type: none"> ▪ Viral hepatitis ▪ Drug/toxin-induced 	<ul style="list-style-type: none"> ▪ Alcohol (AST > ALT, rarely >400 IU/L) ▪ Ischemia (AST > ALT, commonly >5,000 IU) ▪ Autoimmune liver disease ▪ Acute bile duct obstruction ▪ Hepatic vein obstruction (Budd-Chiari) ▪ Wilson's disease

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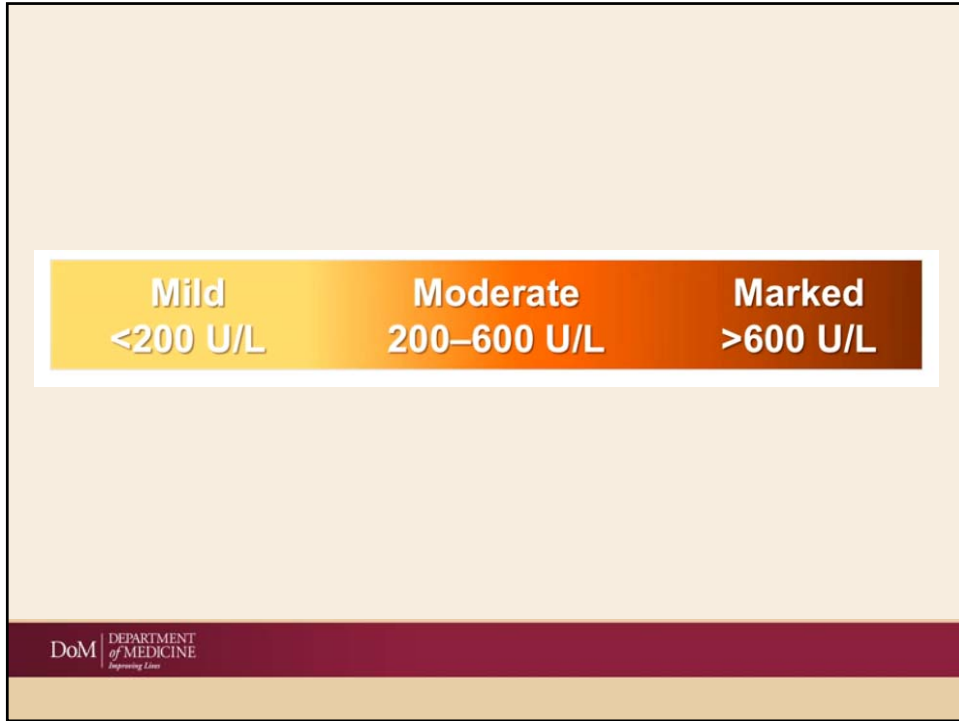
Drugs/toxins	Viral	Ischemia
<ul style="list-style-type: none"> ▪ Alcohol (AST <300 U/L) ▪ Acetaminophen ▪ NSAIDs ▪ Antibiotics: Nitrofurantoin, macrolides, minocycline, fluoroquinolones, trimethoprim/sulfamethoxazole, amoxicillin/clavulanate ▪ Anti-epileptics: Phenytoin, carbamazepine, lamotrigine, valproate ▪ Anti-tuberculosis ▪ Herbal/nutritional/dietary supplements ▪ Mushrooms 	<ul style="list-style-type: none"> ▪ Hepatitis A-E ▪ Epstein-Barr ▪ Herpes ▪ Cytomegalovirus ▪ Adenovirus 	<ul style="list-style-type: none"> ▪ “Shock liver” ▪ Budd-Chiari

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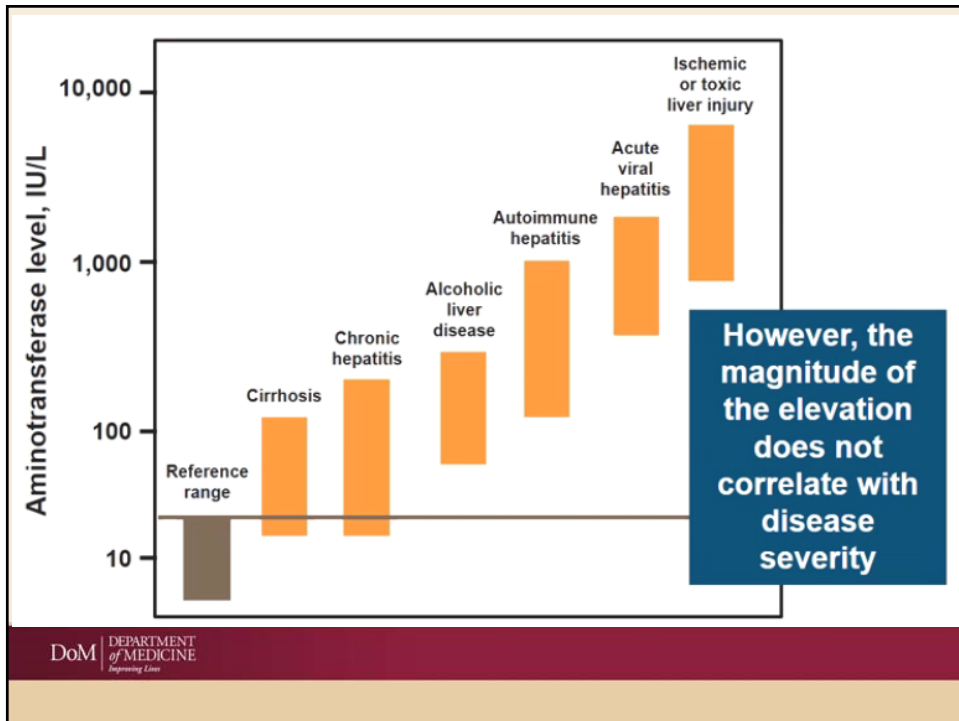
Do *not* cause acute hepatitis

- Non-alcoholic fatty liver disease
- Hemochromatosis/iron overload
- Primary sclerosing cholangitis
- Primary biliary cholangitis*
- Alpha-1 antitrypsin deficiency

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Alarm Signs

- Hospitalize patient if present:
 - Prolonged PT/INR
 - Mental status changes
 - Unable to tolerate oral fluids
 - SIRS
 - Unreliable patient

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Acute Liver Failure

- All of the following:
 - Acute hepatocellular injury
 - Coagulopathy (INR >1.4)
 - Altered mental status and/or asterixis
 - No known pre-existing liver disease

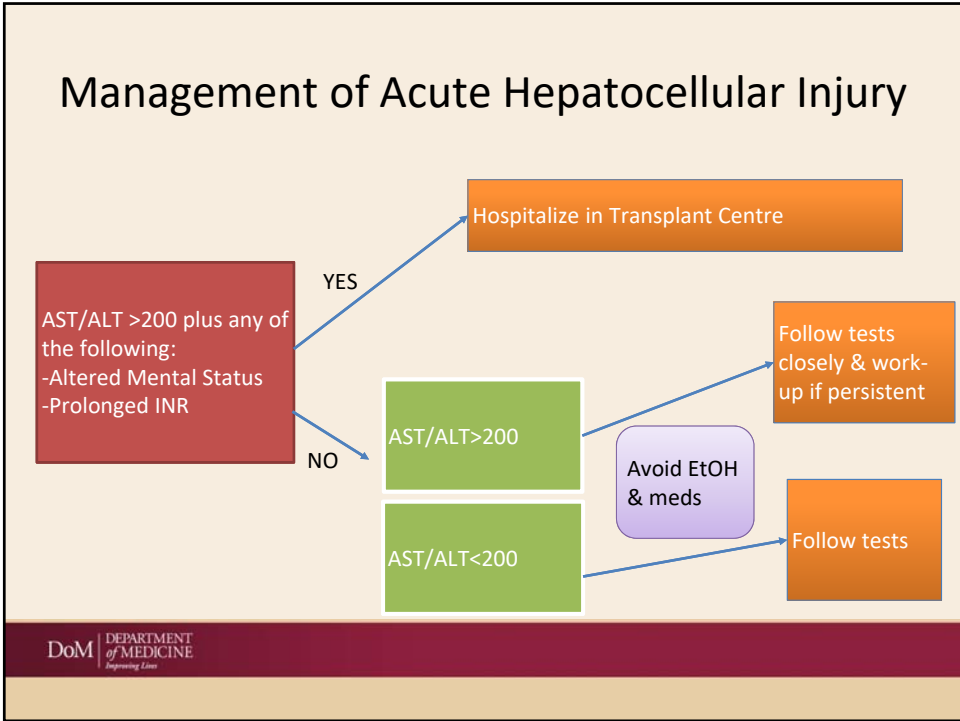
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- Most common etiology: **acetaminophen**(48%)
- Also consider: other drugs/toxins, viral, ischemia, autoimmune hepatitis, Wilson's disease
- Often critically ill, admit to ICU
- Requires urgent consultation with liver transplant service
- Death occurs from multi-organ system failure, cerebral edema/herniation and infection

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- While waiting for transfer:
- Send etiology specific labs
- Obtain Doppler ultrasound
- Start **N-acetylcysteine**(even if acetaminophen overdose is not suspected)
- Intubate if obtunded(grade 3/4 Encephalopathy)

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Case 1

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- 18 year old woman who was binge drinking on New Years Eve and seemed tired and hungover on New Year's Day
- On Jan 2, had nausea, vomiting, abdominal pain and seemed moody and sleepy
- On Jan 3, became confused, disoriented, agitated, talking to objects

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- **PMHx**...Asthma, Depression
- **Medications** ...Albuterol, Minocycline
- **Social History** ...Binge drinker, marijuana, lives with parents
- **Exam** ...Obtunded, confused, abdominal tenderness, asterixis, not jaundiced

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Labs

- Total bilirubin ... 41.4 mmol/L
- AST ... 10,299 IU/L
- ALT ... 10,651 IU/L
- ALP ... 199 IU/L
- INR ... 7.2
- Lactate ... 5.8
- Acetaminophen <10
- U/S with Dopplers - normal
- IgM anti-HAV -
- HBsAg -
- IgM anti-HBc -
- Anti-HCV -
- ANA -

Outcome

- Diagnosed with acute liver failure (markedly elevated ALT/AST, coagulopathy, altered mental status)
- Level of aminotransferases rules out alcohol as a cause of liver failure (AST <300)
- Intentional acetaminophen overdose suspected due to history of depression and alcohol intoxication

- Rapid time course and pattern of lab abnormalities strongly suggest acetaminophen toxicity (markedly elevated AST/ALT, minimal elevation in bilirubin, high INR)
- Treated with IV N-acetylcysteine
- NAC stopped when INR < 2, AST < 1000, and altered mental status resolved
- Recovered with supportive care

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Important Points

- Acetaminophen level is often negative and should never be used to rule out acetaminophen overdose
- A high degree of suspicion is needed to make the diagnosis. When in doubt start NAC; studies show that 20% of indeterminate cases of ALF are due to APAP
- NAC is most effective when started early, but can still improve survival if started > 48h after ingestion
- With aggressive supportive care, acetaminophen induced ALF has a relatively high rate of spontaneous improvement and survival

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Case 2

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- A 37 year old woman presents with a 2 day History of subjective fever, nausea, vomiting and abdominal pain
- **Jaundice** notes by her mother
- Taking aspirin but no recent acetaminophen
- Not sexually active
- Denies recent alcohol use

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- **PMHx**...hypothyroidism
- **Medications**...ASA, synthroid
- **Exam**... **Jaundice**, ill appearing, **hepatomegaly**, **diffusely tender abdomen**, no asterixis and no cutaneous stigmata of chronic liver disease

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Labs

- Total Bilirubin **262**
- Direct Bilirubin **209**
- AST **253**
- ALT 42
- ALP **227**
- Albumin 33
- INR 1.2
- WBC **20,000**
- Hgb 103
- Platelets 343,000
- Ultrasound showed **Hepatology** and an **echogenic** liver

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Alcoholic Hepatitis

- Alcohol level came back at 0.17%
- When confronted the patient reported drinking a fifth of vodka daily for the last five days

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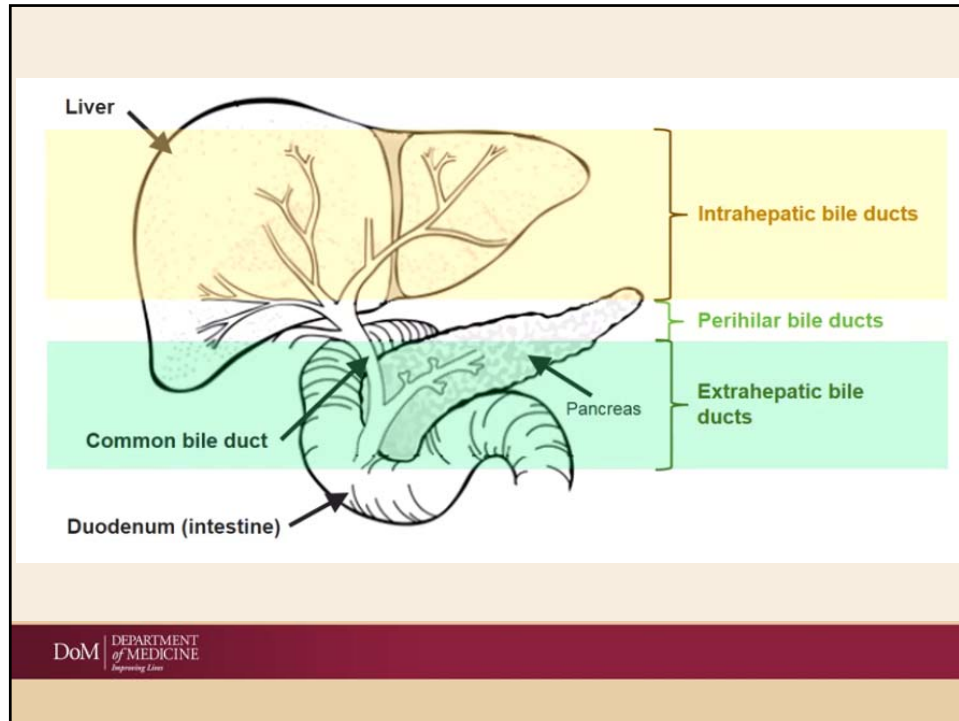
- Fever
- Abdominal pain
- Jaundice
- Hepatomegaly
- Leukocytosis
- Cholestasis
- Moderate AST elevation
- AST:ALT ratio >2
- Elevated ALP

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Management

- If Maddrey's discriminant function >31 or MELD >20 treat with prednisilone
- Need nutritional support and abstinence from alcohol

Acute Cholestatic Liver Injury

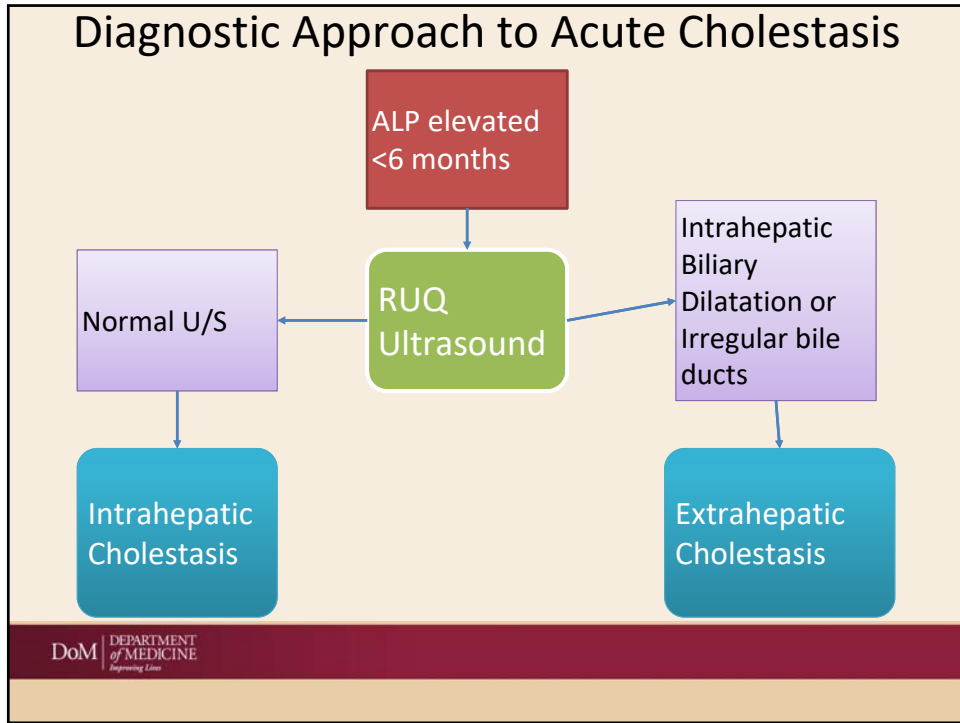


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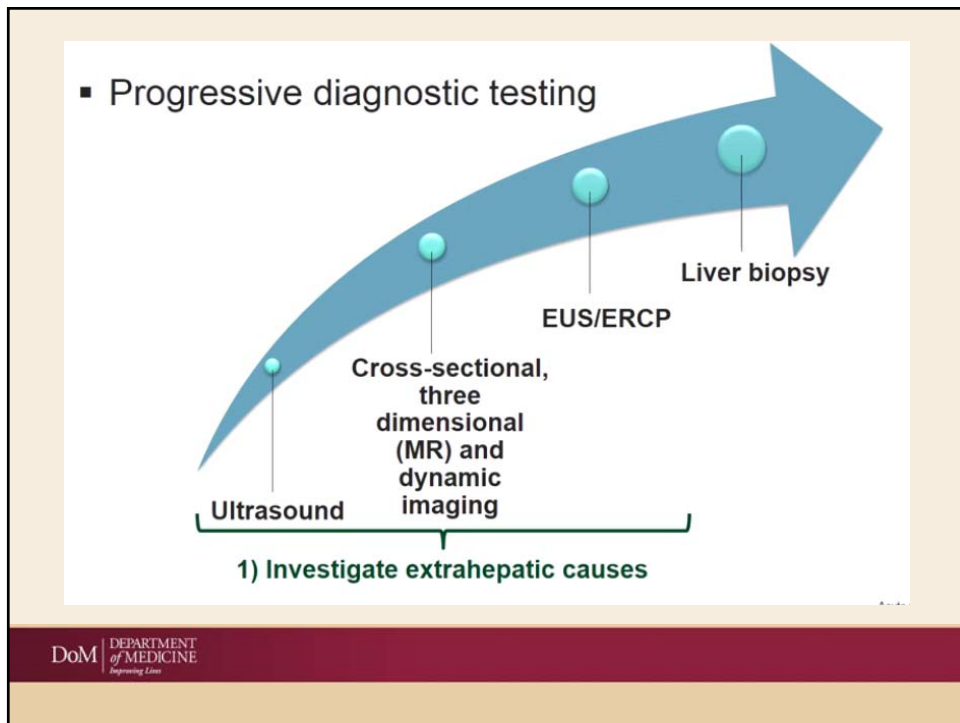
Symptoms of Acute Cholestasis

- Jaundice
- Fatigue/listlessness
- Pruritis
- Fever
- RUQ pain

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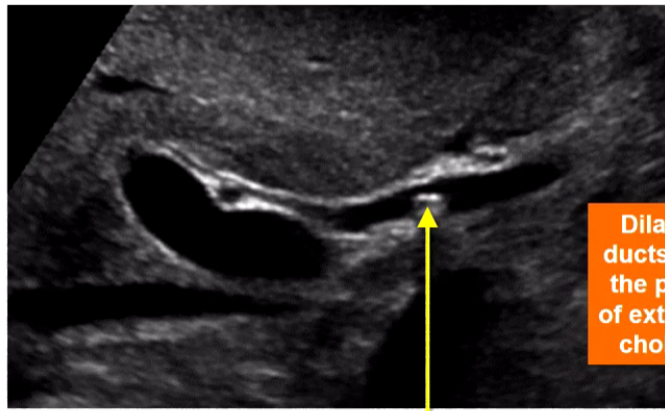


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Ultrasound: First Diagnostic Test in Evaluation of Acute Cholestasis



Dilated bile ducts indicate the presence of extrahepatic cholestasis

Gallstone within common bile duct

Acute Extrahepatic Cholestasis

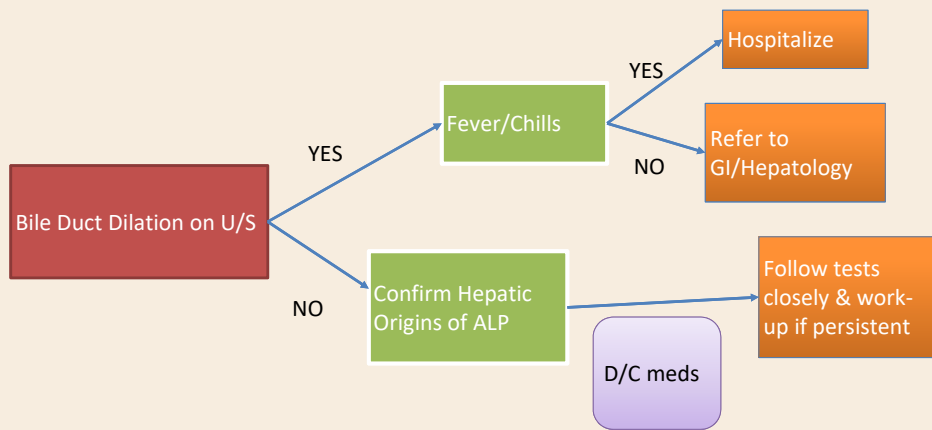
Most common	Also consider
<ul style="list-style-type: none"> ▪ Cholelithiasis (stone in common bile duct) 	<ul style="list-style-type: none"> ▪ Pancreatitis ▪ Stricture ▪ Bile duct/pancreatic cancer ▪ Postoperative bile duct injury

Acute Intrahepatic Cholestasis

Most common	Also consider
<ul style="list-style-type: none"> ▪ Drug-induced ▪ Viral hepatitis 	<ul style="list-style-type: none"> ▪ Alcohol ▪ Infiltration <ul style="list-style-type: none"> ▪ Malignant (eg, lymphoma) ▪ Non-malignant (eg, sarcoidosis) ▪ Pregnancy

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Management of Acute Cholestatic Injury



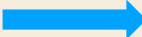
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Case 3

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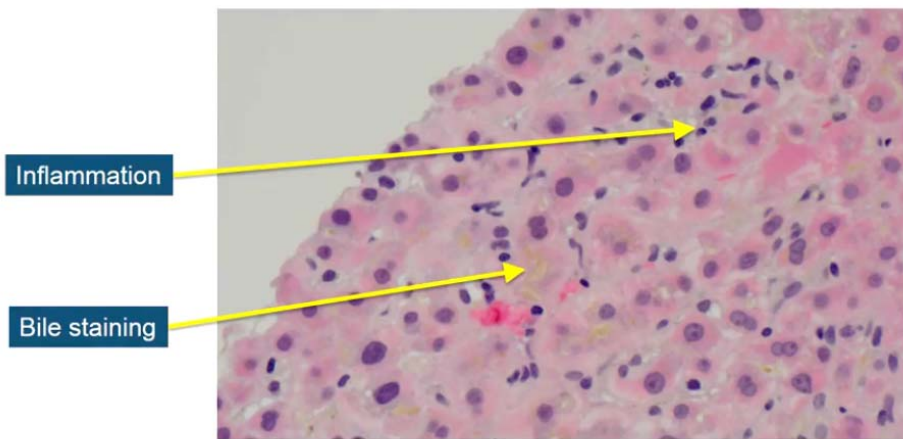
- 58 year old man with a history of prostatitis
- Treated with amoxicillin-clavulanate for 14 days
- On day 12 of treatment, he noted the onset of malaise and jaundice

DAY 12	Discontinued A-C	DAY 42
Alk Phos 150		Alk Phos 450
AST 54		AST 44
ALT 100		ALT 30
Direct Bilirubin 77		Direct Bilirubin 710

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- HAV IgM, HBsAg, HCV RNA, ANA, ASMA negative
- Ultrasound – No dilated ducts
- Liver Biopsy performed

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Outcomes

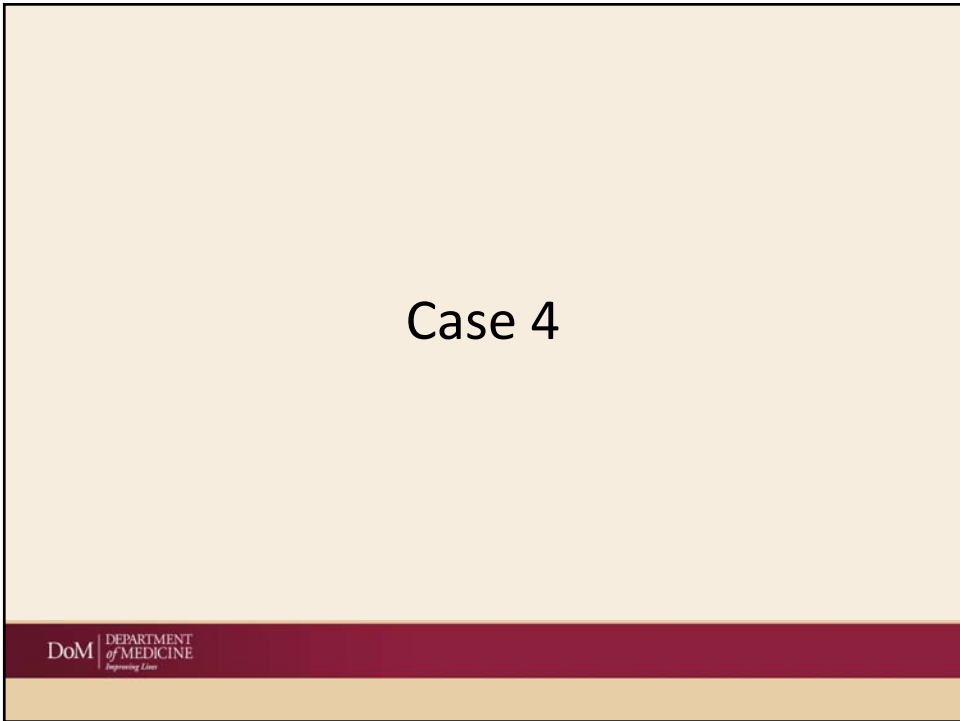
- The patient experienced progressive jaundice, fatigue, inanition, but with minimal pruritis
- Symptoms and jaundice peaked at 42 days following onset
- Progressive resolution of jaundice without specific treatment
- Patient's bilirubin normal by day 65 following onset

Drug-Induced Cholestasis

- Drug-induced cholestasis can have normal alkaline phosphatase at onset
- It can progress after discontinuation of offending drug
- It can be prolonged; 3 months not atypical
- Resolution is common with cessation of the drug
- Liver biopsy: confirms diagnosis but unlikely to change management



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- 60 year old female, obese, diabetic
- One day history of **fever, right upper quadrant pain**
- Examination shows **RUQ tenderness** on percussion

LAB TESTS

Alk Phos 165

AST 348

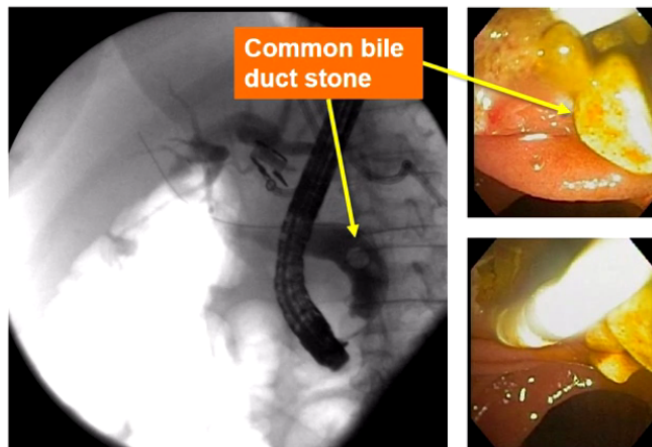
ALT 589

Direct Bilirubin 77

WBC 24,000

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- Ultrasound – dilated ducts, gallstones
- ERCP



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Choledocholithiasis with Cholangitis

ERCP-Stone Removed



LAB TEST	Day 1	Day 2	Day 4
Alk Phos	165	450	265
AST	589	144	45
ALT	348	130	108
Direct Bilirubin	42	700	22
WBC	12,000	24,000	13,000

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Outcome

- The patient experienced progressive improvement in pain following ERCP
- Liver enzymes normalized by day 5 post ERCP; WBC normal
- Patient was referred for cholecystectomy as inpatient

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Choledocholithiasis with Cholangitis

- Acute bile duct obstruction presents early on with **increased aminotransferases**(>than alkaline phosphatase)
- Acute cholangitis should be suspected with the presence of RUQ pain, fever, chills, and leukocytosis
- Acute cholangitis with evidence of obstruction or stone is an indication for **urgent ERCP**
- Removal of obstruction leads to rapid clinical and biochemical improvement

Chronic Hepatocellular Injury


Most common	Also consider
<ul style="list-style-type: none"> ▪ Steatohepatitis <ul style="list-style-type: none"> ▪ Non-alcoholic and alcoholic ▪ Viral hepatitis ▪ Drug-induced 	<ul style="list-style-type: none"> ▪ Autoimmune hepatitis ▪ Wilson's disease ▪ α-1 antitrypsin deficiency

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Does My Patient Have Cirrhosis

- Jaundice
- Temporal and proximal muscle wasting
- Palmar erythema
- Spider angiomas
- Palpable left lobe of liver
- Splenomegaly
- Ascites
- Any alteration of mental status
- Asterixis



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Laboratory and Imaging Evidence of Cirrhosis

Laboratory	Imaging/Other
<ul style="list-style-type: none"> ▪ Low platelet count ▪ Low albumin ▪ Prolonged PT/INR ▪ Increased bilirubin ▪ Increased globulin levels ▪ In patients with viral hepatitis a change from ALT > AST to AST > ALT 	<ul style="list-style-type: none"> ▪ Nodular liver ▪ Splenomegaly ▪ Collaterals ▪ Stiff liver by transient elastography (Fibroscan®) or other method

Case 5

- 45 year old Asian man
- Married; army officer
- Mother died of jaundice and liver cancer
- Noted on routine physical exam to have mildly elevated AST and ALT
- Denies any history of known liver disease, jaundice or ascites
- No medications except for daily multivitamin

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Labs and Imaging

- ALT **65**; AST **60**
- Repeat liver enzymes 1 month later confirm ALT **59** and AST **55**
- Anti-HCV negative, **HBSAg positive**
- Normal platelet count
- Total bilirubin, INR, and albumin normal
- HBeAb negative, **HBeAg positive**, **HBcAb positive**

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- Ultrasound-normal liver echotexture, not nodular
- Alpha fetoprotein(AFP) normal
- Livers enzymes over the next 6 months elevated

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Treatment and Outcome

- HBV DNA level is persistently >1,000,000 IU/mL
- Patient is started on tenofovir with normalization of aminotransferases
- HBV DNA 6 months after initiation of tenofovir is undetectable
- Patient is maintained on long term antiviral treatment
- He is followed for many years and is stable

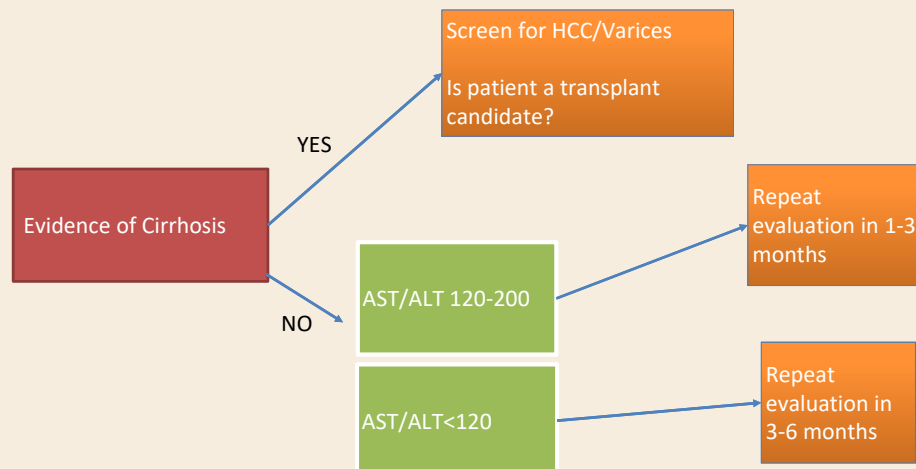
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Important Points

- In a patient with chronic abnormalities in AST/ALT, chronic hepatitis B could have been suspected because of:
 - Asian ethnicity
 - Mother died with liver cancer
- Diagnosis of chronic HBV established by positive HBsAg and HBV DNA
- No evidence of cirrhosis; normal liver synthetic function, liver on imaging without nodularity
- Early treatment with viral suppression will greatly reduce the risk for cirrhosis and liver cancer

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Management of Chronic Hepatocellular Injury



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Case 7

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- 43 year old Caucasian woman presents with vague RUQ discomfort with no other associated gastrointestinal symptoms
- Patient works long hours and admits to a “poor diet”
- Relatively sedentary desk job
- Mother has adult onset diabetes
- She reports a history of gestational diabetes with her pregnancies

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- PMHx...Overweight with BMI 28, diet controlled diabetes, gestational diabetes
- Medications ... none
- Social History ... Rare alcohol consumption

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Labs

- AST...45
- ALT...60
- HgbA1c...6.3%
- Triglycerides ...2.68
- HDL...0.7
- LDL...3.6
- HBsAg...negative
- HCV...negative

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Ultrasound

- Echogenic
- No nodularity or splenomegaly

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Treatment and Outcomes

- Comprehensive evaluation for autoimmune hepatitis, hemochromatosis, Wilson's disease, celiac disease, and A1AT deficiency were unrevealing
- Patient is counselled on lifestyle modification with routine exercise and a low calorie, lower carbohydrate diet
- She is effective at gradual weight loss(10%) of body weight over 12 months
- Follow up AST decreased 24 and ALT to 22
- She is referred to a nutritionist and is able to maintain weight loss
- A follow up U/S shows a normal liver

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NAFLD

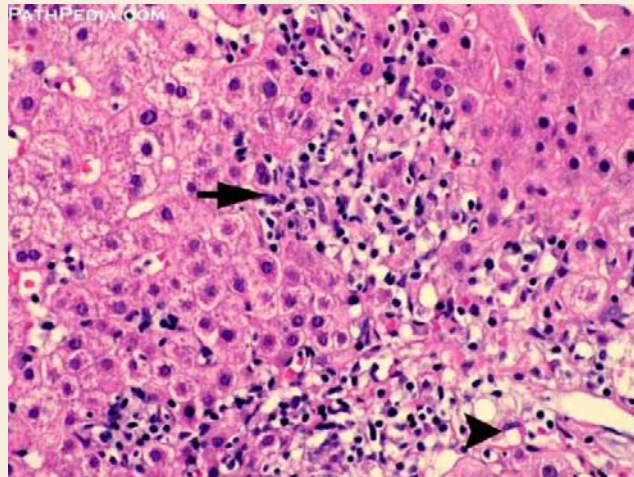
- Non-Alcoholic Steatohepatitis(NASH) vs Non-Alcoholics Fatty Liver(NAFL)
- NASH is strongly associated with obesity, western diet(fructose), sedentary lifestyle and metabolic syndrome
- Patients with a family history or personal history of prediabetes or diabetes are at increased risk of NASH
- NASH is a diagnosis of exclusion
- First line treatment is weight loss

Other causes of Chronic Hepatocellular Injury

- Young woman with a history of hypothyroidism
- AST 560 and ALT 650; fluctuating for the last 6 months
- Normal liver function
- High IgG 35
- Positive anti-smooth muscle antibody
- Positive Anti-nuclear antibody

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Autoimmune Hepatitis



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AIH

- Can present acutely as well
- Associated autoimmune disease- hypothyroidism, graves, SLE, celiac, rheumatoid arthritis
- Treatment consists of steroids(prednisone) and usually azathioprine

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- 58 year old Caucasian man
- Complains of joint pain in hands
- Recently diagnosed with diabetes

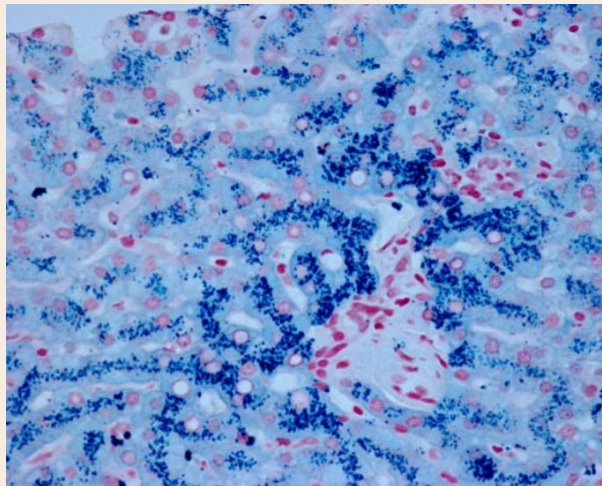


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- Iron % saturation 75
- Ferritin 2500
- HFE gene test - Homozygous for C282Y

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Hereditary Hemochromatosis



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- Cirrhosis
- Hepatomegaly
- Asymptotic
- HCC
- Bronze Diabetes
- Pituitary dysfunction (loss of libido and testicular atrophy)
- Arthropathy(chondrocalcinosis)
- Cardiomyopathy and dysrhythmias
- Porphyria cutanea tarda

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HH Treatment

- Phlebotomy for goal ferritin 50-100

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- 23 year old man with history of bipolar
- Referred for fatty liver
- Not obese and no metabolic risk factors
- Mildly elevated AST 60 and ALT 85



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Wilson's Disease

- Low ceruloplasmin
- High 24h urine copper
- Kayser Fleisher Rings
- ATP7B mutation
- Non-immune hemolytic anemia
- Neuropsychiatric symptoms

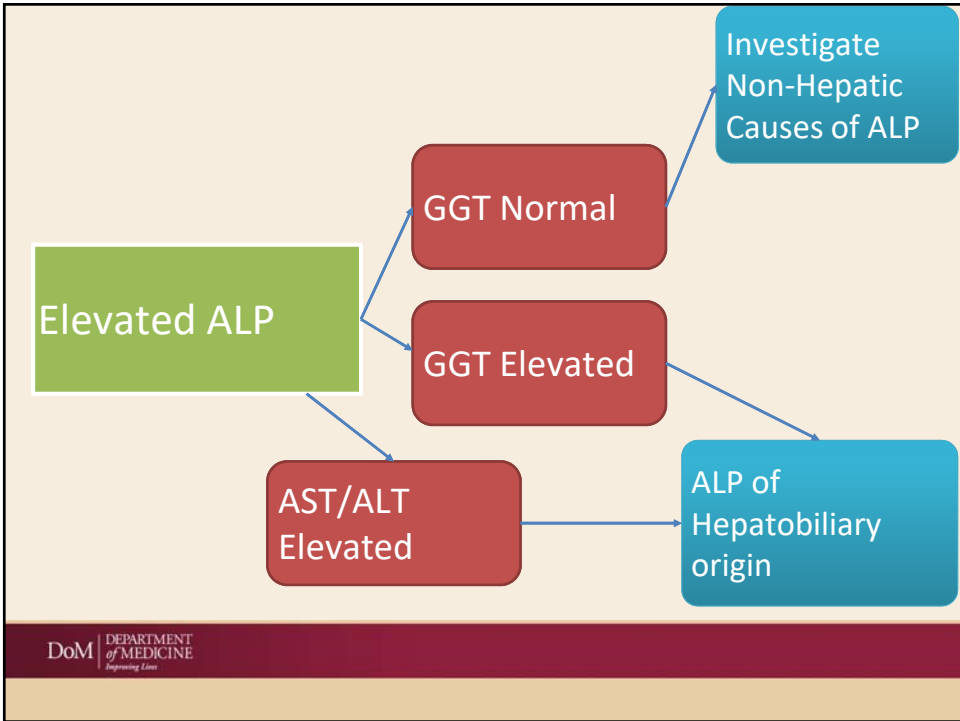
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Chronic Cholestatic Liver Injury

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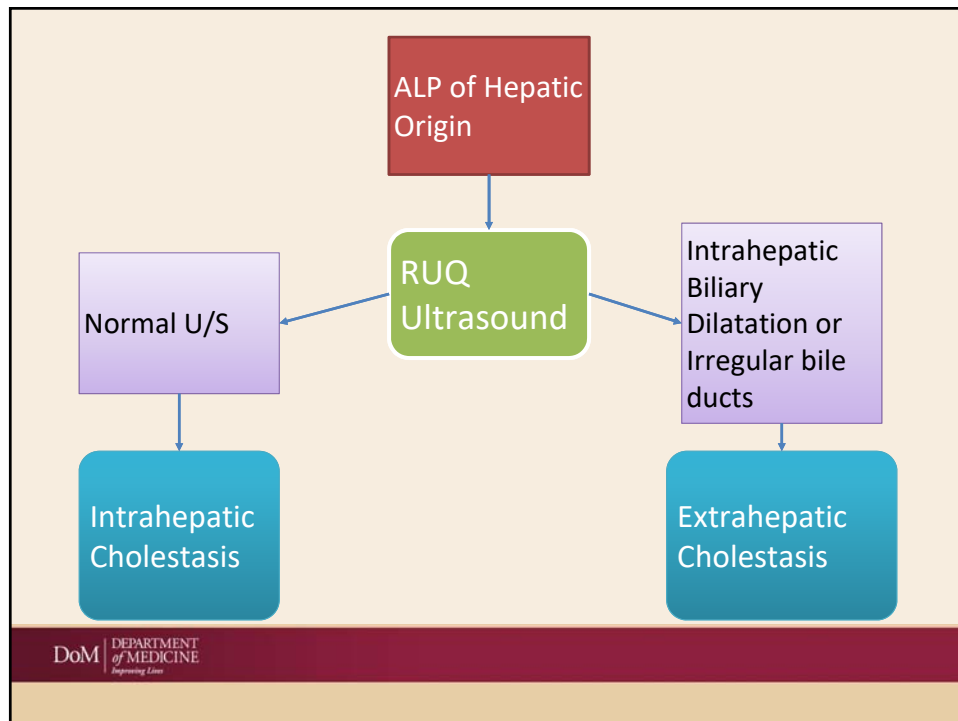


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ALP of Hepatobiliary Origin

- Next best step is Liver Ultrasound
- Differentiates Intrahepatic from Extrahepatic Cholestasis

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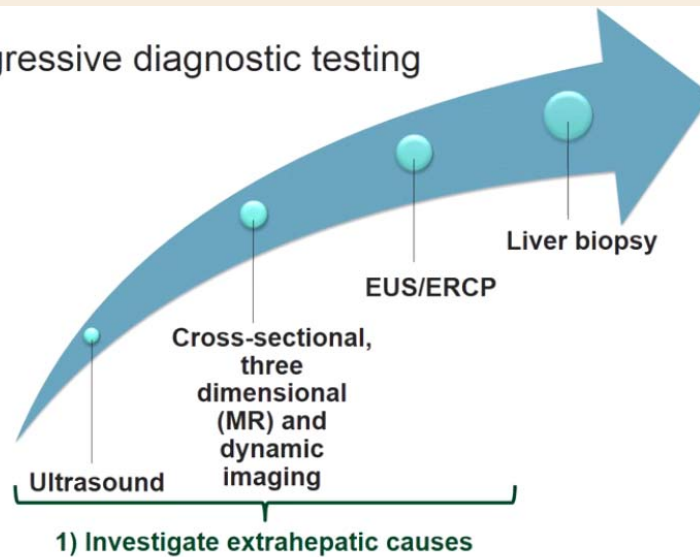
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Chronic Extrahepatic Cholestasis

Most common	Also consider
<ul style="list-style-type: none"> ▪ Primary sclerosing cholangitis ▪ Secondary sclerosing cholangitis <ul style="list-style-type: none"> ▪ IgG4 ▪ Ischemic cholangiopathy ▪ Chronic pancreatitis ▪ Complication from manipulation of biliary tree 	<ul style="list-style-type: none"> ▪ Cholangiocarcinoma and other malignant obstruction <i>(liver/gallbladder/pancreas/ampulla)</i> ▪ Anastomotic strictures ▪ Infections <ul style="list-style-type: none"> ▪ Ascaris ▪ Liver flukes ▪ AIDS cholangiopathy

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▪ Progressive diagnostic testing



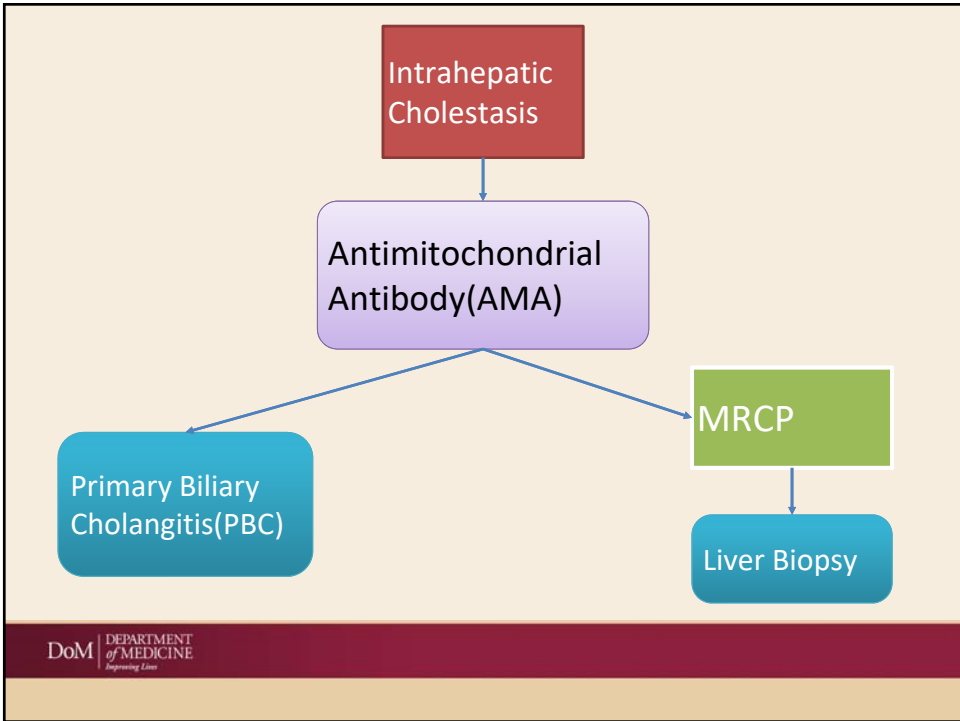
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Chronic Intrahepatic Cholestasis

Most common	Also consider
<ul style="list-style-type: none"> ▪ Drug-induced liver injury ▪ Primary biliary cholangitis* ▪ Primary sclerosing cholangitis 	<ul style="list-style-type: none"> ▪ Infiltrative liver disease (sarcoidosis, tuberculosis, amyloidosis, lymphoma, hepatic abscess) ▪ Total parenteral nutrition ▪ Steatohepatitis ▪ Ischemic cholangiopathy ▪ Sickle cell disease ▪ Allograft rejection ▪ Metastatic disease

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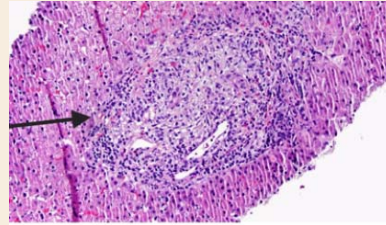
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Liver Biopsy is Helpful

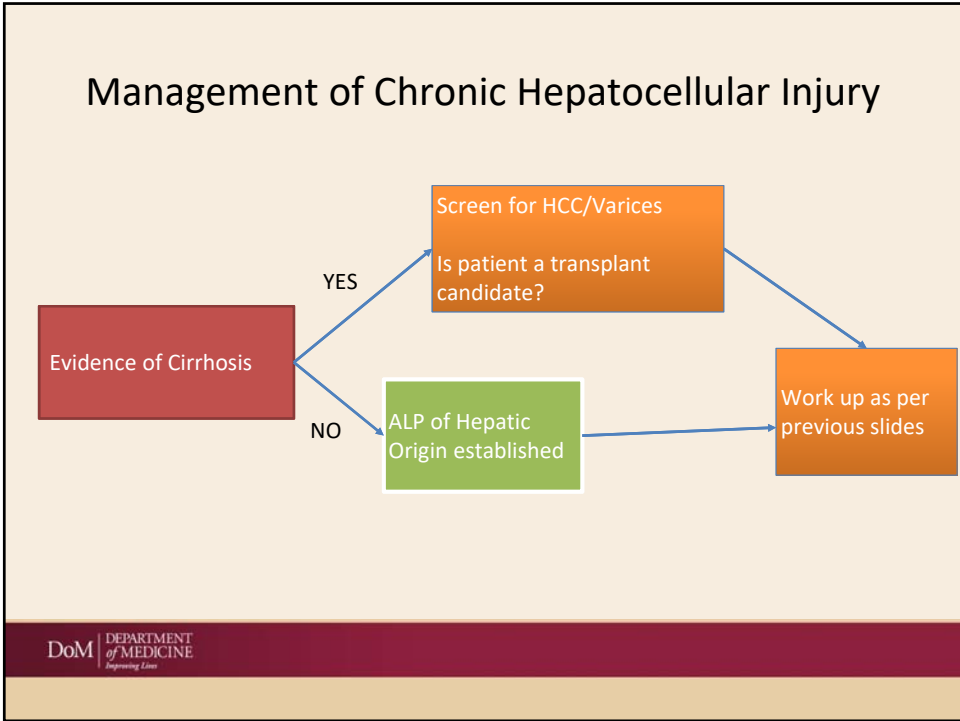
- AMA-negative PBC
- Granulomatous disease
- Infiltrative disease
- Small duct PSC
- Drug induced liver injury
- Overlap
 - AIH-PBC, AIH-PSC, PBC-NASH etc



Drug Induced Chronic Cholestasis

Intrahepatic cholestasis	Extrahepatic bile duct strictures
Amoxicillin-clavulanate	Intra-arterial floxuridine
Ampicillin	
Azathioprine	
Azithromycin	
Barbiturates	
Carbamazepine	
Chlorpromazine*	
Cimetidine	
Clindamycin	
Erythromycin*	
Estradiol	
Flucloxacillin*	
NSAIDs	

* ≈ 1% of these cases may progress to vanishing bile duct syndrome



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Case 8

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- A 54 year old woman saw her primary care physician for an annual visit
- She complains of mild itching and fatigue
- Patient never had any surgeries and her only medications are calcium and vitamin D
- Her exam is unremarkable apart from below



Labs

January 2017

- Alk Phos **426**
- AST **40**
- ALT **54**
- Total bilirubin 17

January 2018

- Alk Phos **398**
- AST **39**
- ALT **58**
- Total bilirubin 19

Ultrasound

- Normal liver, gallbladder and spleen

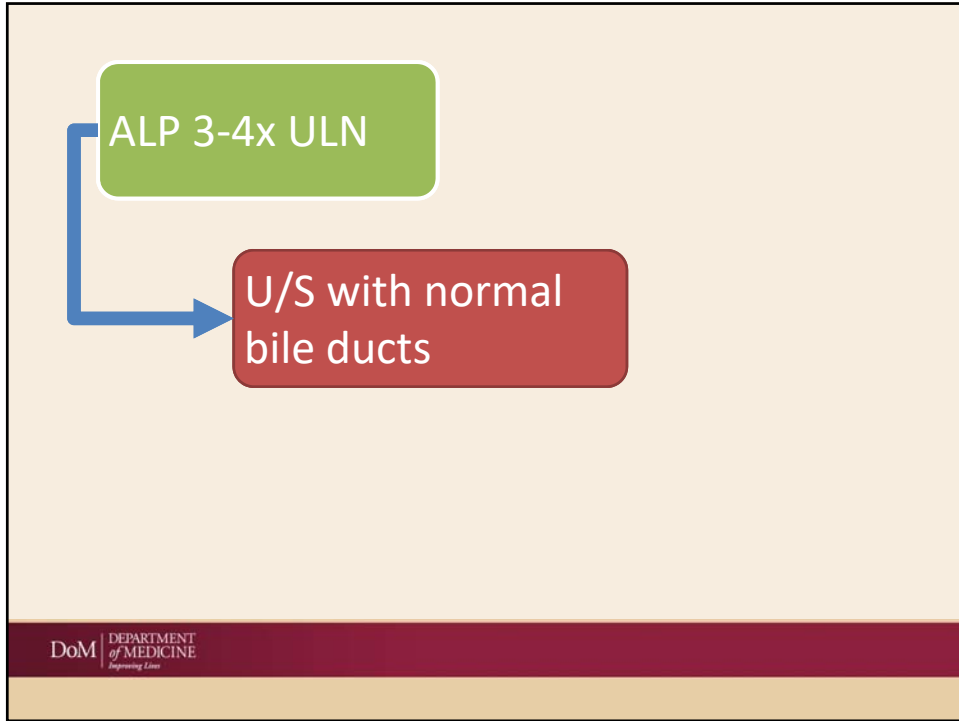
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Work-Up

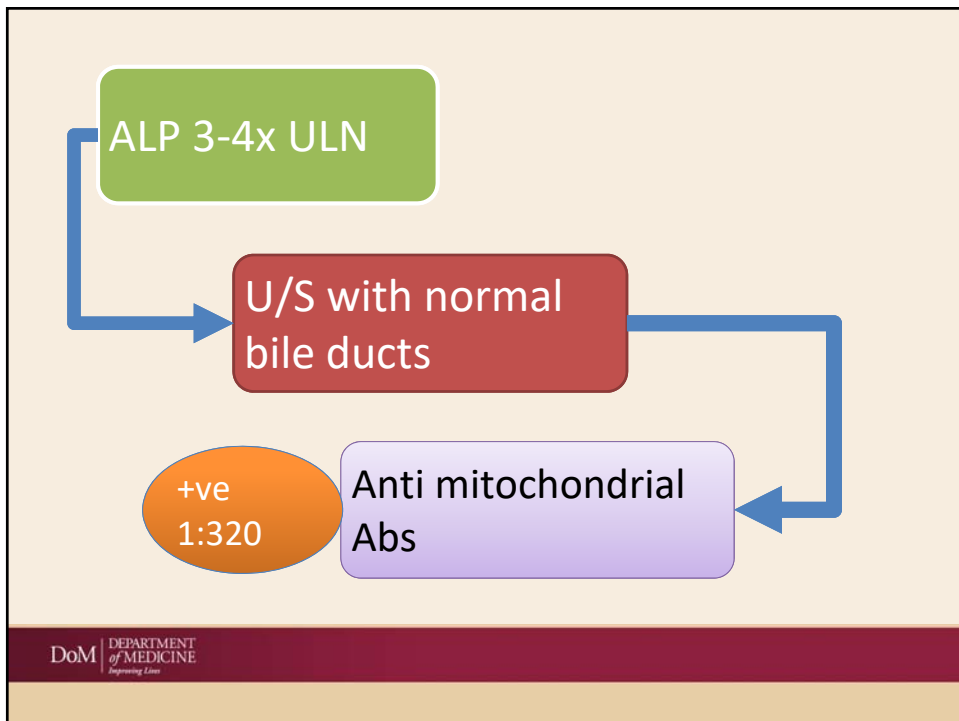
ALP 3-4x ULN

- Chronic middle aged woman
- Pruritis and fatigue
- AST/ALT elevated(ALP Hepatic origin)

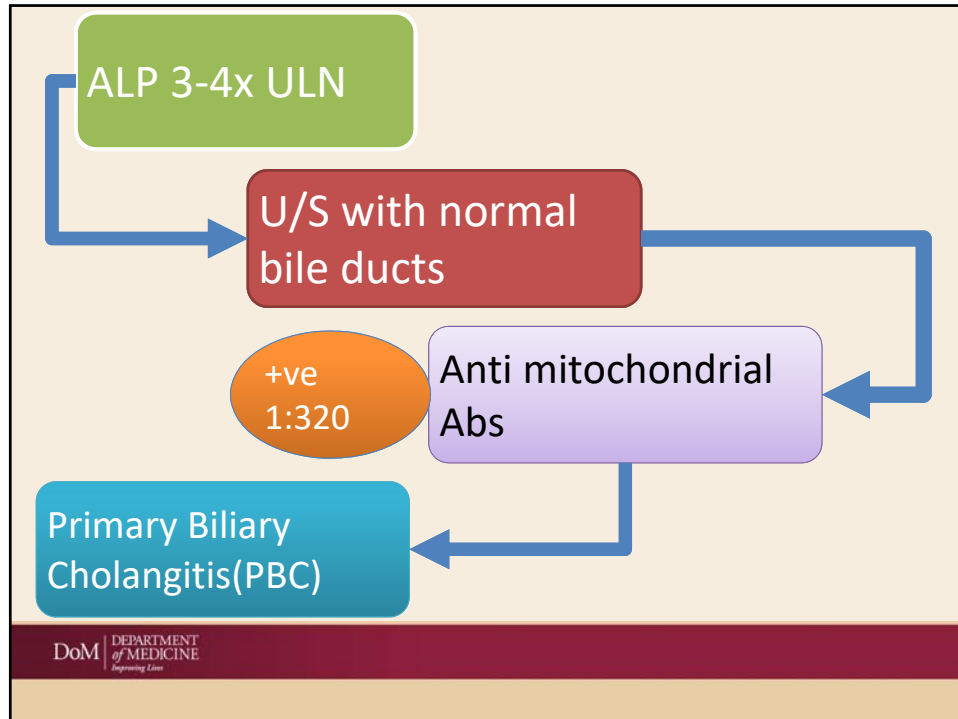
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PBC

- Autoimmune cholestatic liver disease affecting intrahepatic biliary ducts
- F>M
- Treatment with 13-15mg/kg/d of **ursodeoxycholic acid**
- If no/partial response after 6-12 months add **obeticholic acid**

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Case 9

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- A 34 year old African Canadian male comes in for follow up. He had been complaining of chronic diarrhea with blood and associated abdominal cramps, on/off for past year.
- Referred to gastroenterologist who performed colonoscopy which led to diagnosis of pan **ulcerative colitis**
- He was started on mesalamine 4 months ago and reports resolution of his symptoms

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Labs

- AST 80
- ALT 101
- ALP 580
- Total bilirubin 23
- Hgb 118
- Platelets 213
- Comparing to your previous notes, there has been a mild worsening over the past 4-6 months. His ALP was previously 398 and bili 7

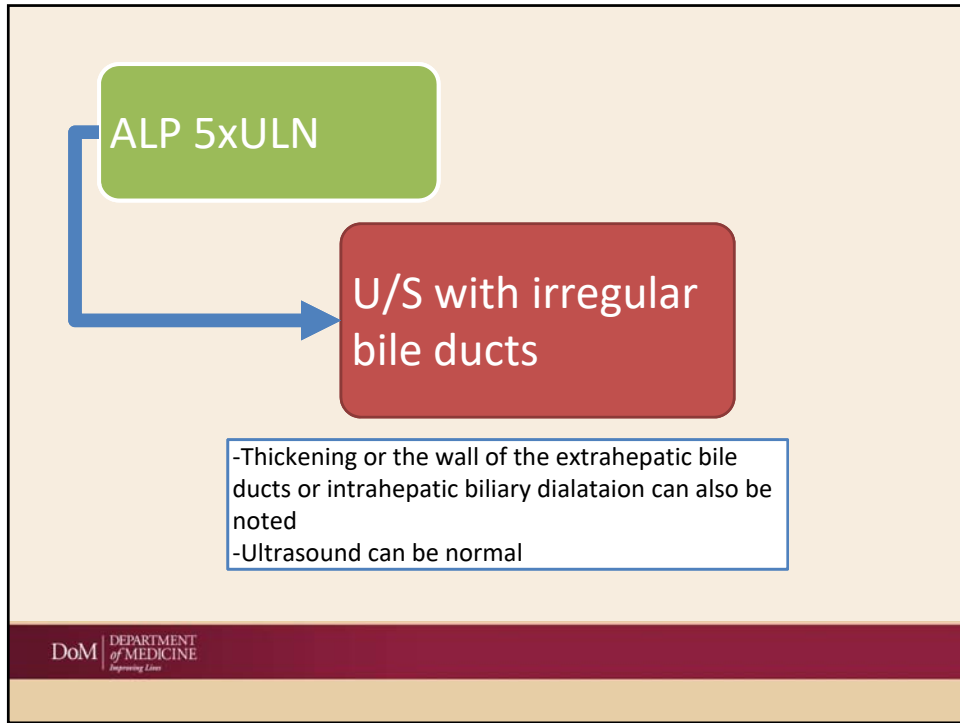
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Work-Up

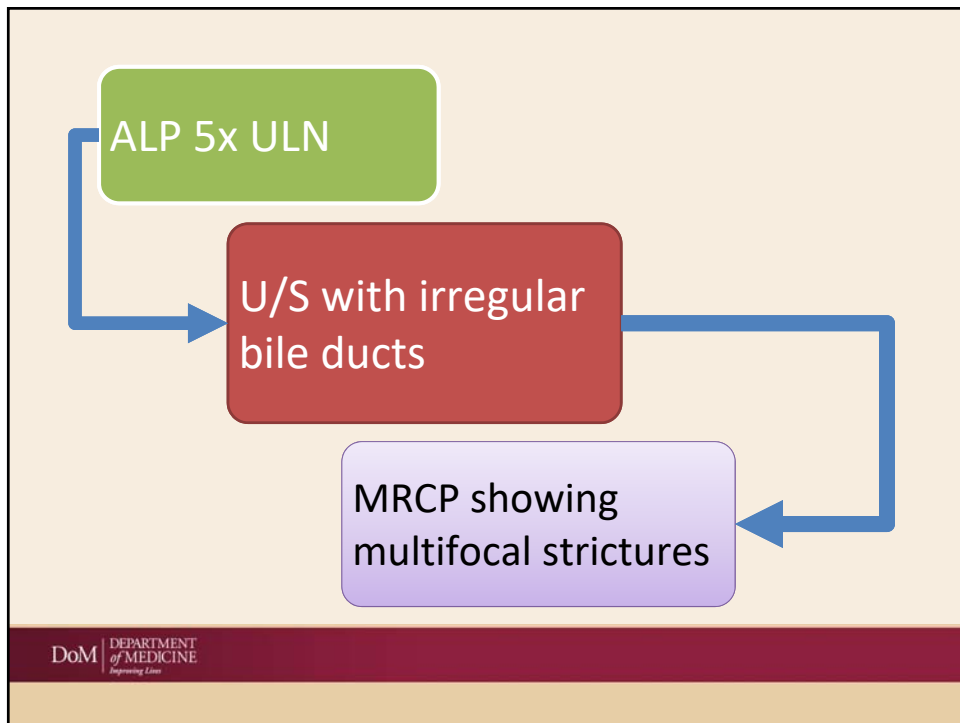
ALP 5x ULN

-Young male with IBD
-chronic Cholestasis and prurite

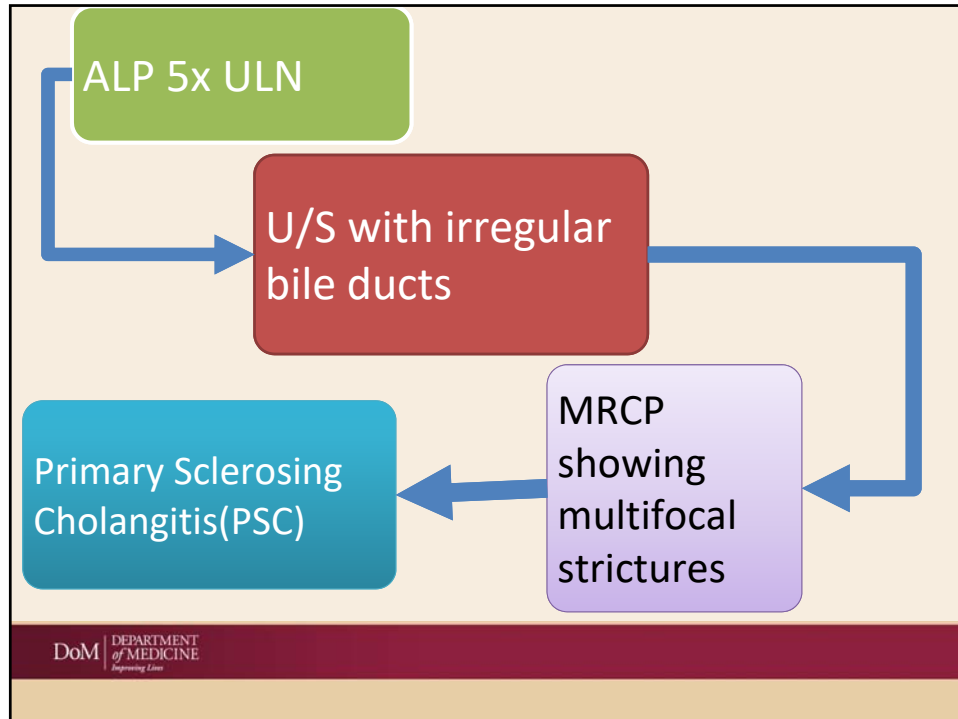
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PSC

- No available medical therapy. Role of UDCA is unclear.
- Watch for acute cholangitis
- Treat symptomatically
- Recommend annual colonoscopy with biopsies
- Recommend annual cross sectional imaging of liver to survey for cholangiocarcinoma and gallbladder polyps/cancer

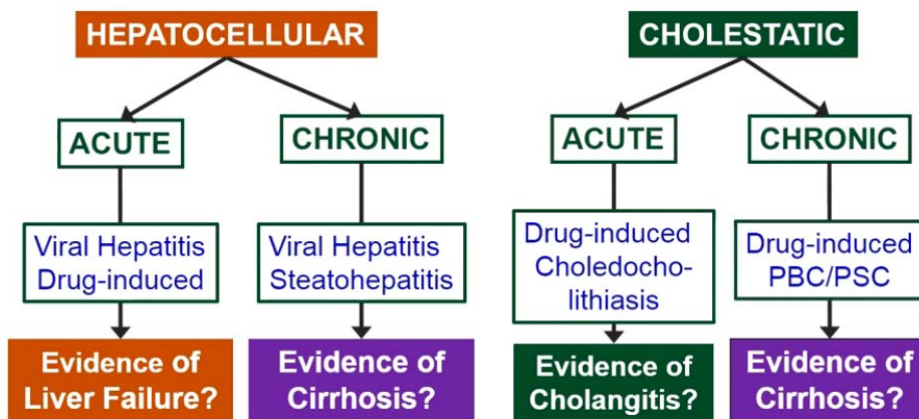
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- 4% of all patients with IBD develop PSC. Most have UC but can have CD or indeterminate colitis. Conversely 80% of patients with PSC have IBD
- 2/3rds of patients with PSC are male

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Summary



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Questions?

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