Medical Liver

Steatosis/Steatohepatitis

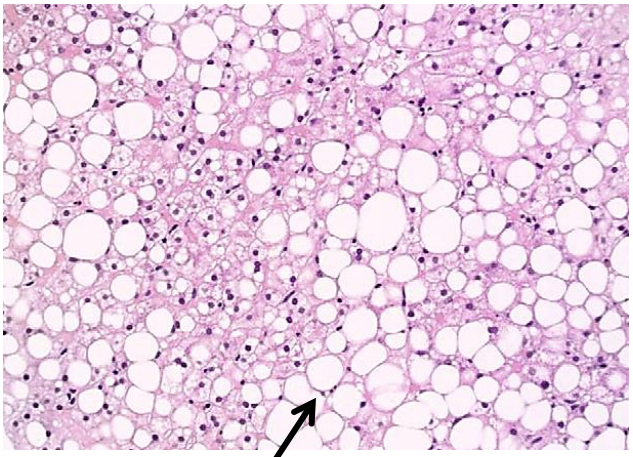
Steatosis = Abnormal accumulation of fat within hepatocytes

Steato<u>hepatitis</u> = Fat + inflammation, acidophil bodies, and/or ballooning (<u>active lobular injury</u>)

These are part of the <u>same disease process</u>, and <u>both</u> lead to fibrosis, but steatohepatitis leads to fibrosis ***<u>faster</u>*** (essentially a difference in grading activity).

Portal infiltrates may be present, but are usually mild. If they are severe, consider additional Dx's.

Ballooned hepatocytes: <u>Enlarged</u> (such that they "stand out") with no fat and thin, wispy cytoplasm. Most often Zone 3.



<u>Macro</u>vesicular
Represents a change in <u>lipid metabolism</u>
Predominant pattern = Nucleus pushed to the side by usually a single medium to <u>large sized droplet</u>
Ok to have smaller droplets mixed in also

<u>Micro</u>vesicular
Usually represents <u>mitochondrial injury</u>
Nucleus remains central with <u>innumerable, fine fat droplets</u>
Only use this term if it is a **diffuse** change (not focal, or in a mostly macrovesicular case)

Quantifying Fat

Estimate the % of cells with macrovesicular steatosis
Average over the entire specimen
Report rounded to the nearest 10%

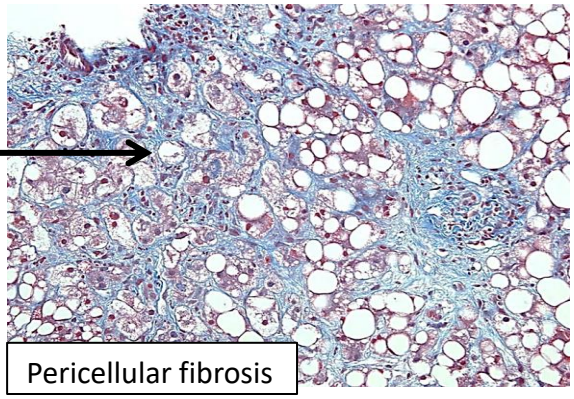
Often found in zone 3 first.

Amount of Fat	Grade
<5%	Normal
5-33%	Mild
34-66%	Moderate
>67%	Severe

Fibrosis

Fatty liver disease causes **<u>pericellular</u>**, **<u>pericentral</u>** fibrosis first (where the most fat is)
→ Progresses to portal and pericentral fibrosis
→ Bridging fibrosis
→ Cirrhosis

Once cirrhotic, there may be relatively <u>little</u> fat!



Pericellular fibrosis

Alcoholic Hepatitis

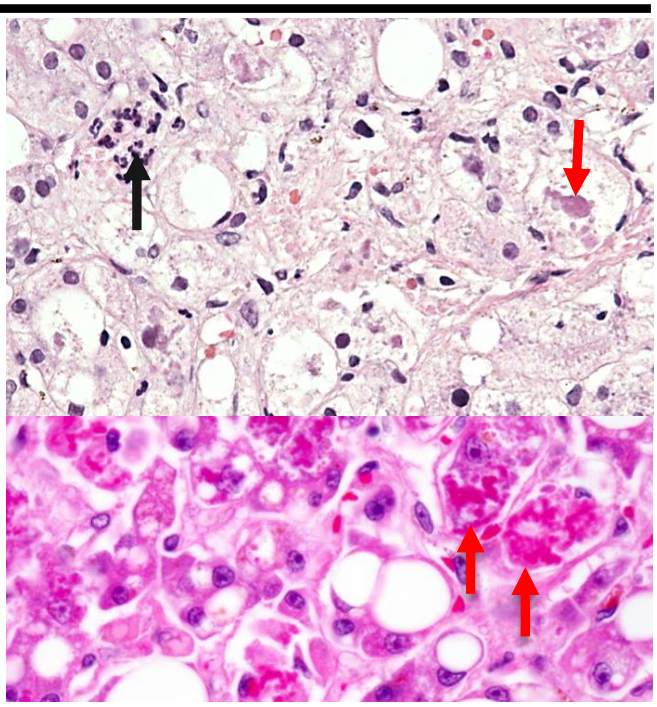
Hepatocyte injury and inflammation resulting from chronic alcohol consumption

AST/ALT ratio typically >2

Micro: Macrovesicular Steatosis.
Findings that Favor EtOH (over NASH): *More* hepatocyte ballooning, *more* neutrophilic lobular inflammation (→), *More* Mallory-Denk bodies (→), lobular cholestasis, and *more, diffuse* pericellular fibrosis

Mallory-Denk Bodies = pink, ropey cytoplasmic inclusions = ubiquitinated cytokeratins. Cells also loose expression of CK8/18.

But Histology ***can*** be identical to NASH!



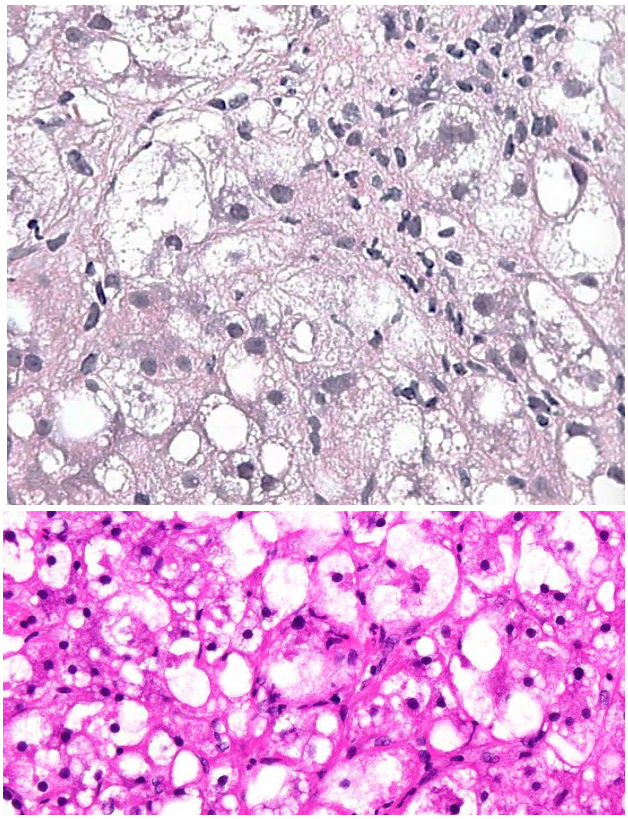
Non-Alcoholic Steatohepattis (NASH)

Associated with metabolic syndrome, including obesity, type 2 diabetes, dyslipidemia, hypertension

Micro: Macrovesicular Steatosis, Ballooning, Lobular lymphs and Neuts (exception in pediatric patients, where inflammation is more portal), acidophil bodies, and Pericellular fibrosis. Sometimes adults have mild portal inflammation, mostly lymphs.

Grade/Stage usually using **NASH-CRN system:**

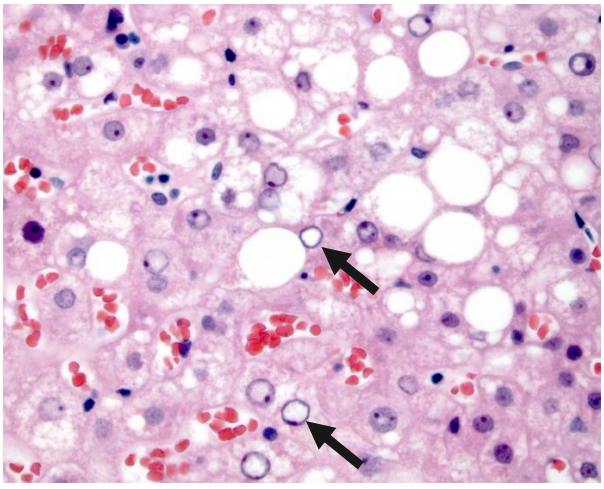
Fibrosis	
0	None
1a	Mild zone 3 sinusoidal fibrosis
1b	Moderate zone 3 sinusoidal fibrosis
1c	Portal fibrosis only
2	Zone 3 sinusoidal fibrosis and portal fibrosis
3	Bridging fibrosis
4	Cirrhosis



Steatosis	Lobular Inflammation	Hepatocellular Ballooning
0: <5%	0: None	0: None
1: 5-33%	1: <2 foci/20x field	1: Mild, few
2: 34-66%	2: 2-4 foci/20x field	2: Moderate-marked, many
3: >66%	3: >4 foci/20x field	

Sum the individual components for a total grade (maximum of 8)

Wilson's Disease



Mutations of **copper transport** protein (*ATP7B* gene) results in inability to excrete copper in bile → accumulate copper in liver and other tissues

Variable presentation: Acute or chronic liver disease, neurologic/psychiatric findings, hemolytic anemia, ± Kayser-Fleischer rings

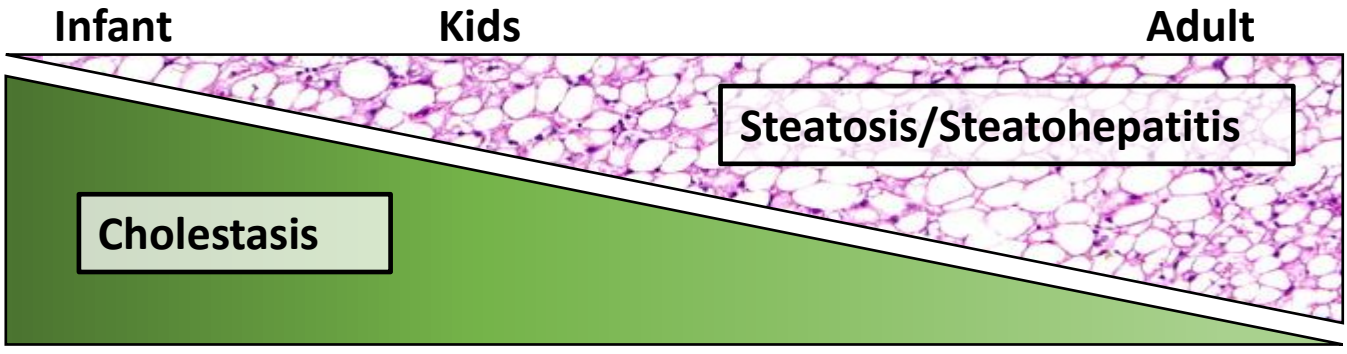
Labs: Low ceruloplasmin, Increased urine copper, AST/ALT ratio >2.2, Alk phos/T. Bili <4

Micro: Variable! Steatohepatitis, possible Malory-Denk bodies and glycogenated nuclei (→; common, non-specific); Later chronic hepatitis

When considering diagnosis→ send block for copper quantification

Total Parental Nutrition

Variable steatohepatitis or cholestasis depending on age



Other causes of Macrovesicular steatosis

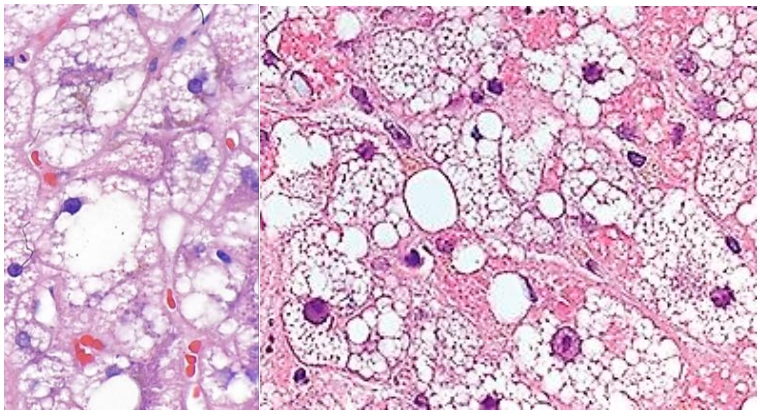
Drugs including: Amiodarone, Glucocorticoids, methotrexate, tamoxifen, and certain chemotherapeutic agents

Other conditions, including: **Malnutrition** (marasmus or kwashiorkor), **hormone alterations** (e.g., hypothyroidism, elevated cortisol, growth hormone deficiency), **cystic fibrosis**, and lipodystrophies.

Microvesicular steatosis

Finely divided fat cells accumulate in cytoplasm as a result of **Mitochondrial damage**, which is often serious

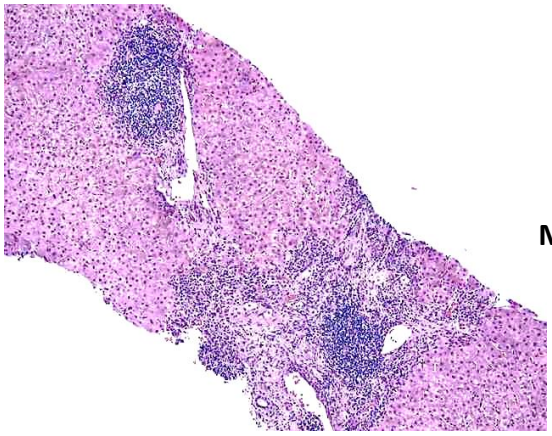
DDX: Reye's syndrome, inborn errors of metabolism, Drugs, Toxins, Acute fatty liver of pregnancy



Portal Tract Chronic Inflammation

Basic DDX: viral, autoimmune, drug

Chronic Viral Hepatitis C



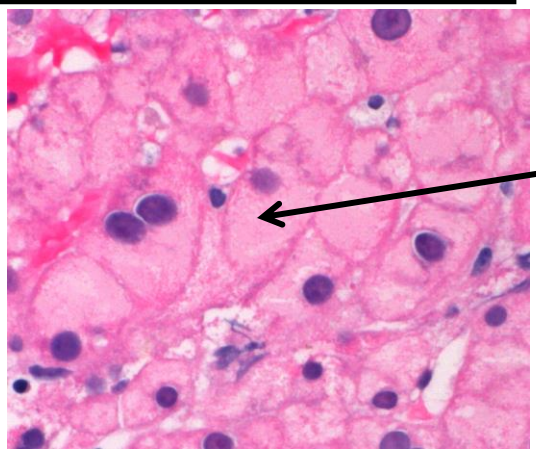
~90% Develop chronic infection; Bloodborne
Antibodies (anti-HCV) indicate exposure
Detection of HCV RNA indicates virus persistence

Newer Meds: Ledipasvir/sofosbuvir (Harvoni) → highly effective
Slow, silent, progressive disease (over decades)
→cirrhosis (risk of HCC)

Micro: Variably dense portal lymphocytic infiltrates
Periportal interface activity
Scattered lobular collections of inflammatory cells
± acidophil bodies
Portal lymphoid aggregates
Rare plasma cells allowed.

Viral Hepatitis: Distinguishing Acute vs Chronic:
Often use clinical definition = elevated liver enzymes for ≥6 months.
Fibrosis also indicates chronic damage. Diffuse moderate lobulitis means acute or acute-on-chronic.
Stage viral hepatitis using Batts-Ludwig, Ishak, Sheuer, or METAVR systems (fairly similar)

Chronic Viral Hepatitis B



~10% Develop chronic disease; Bloodborne

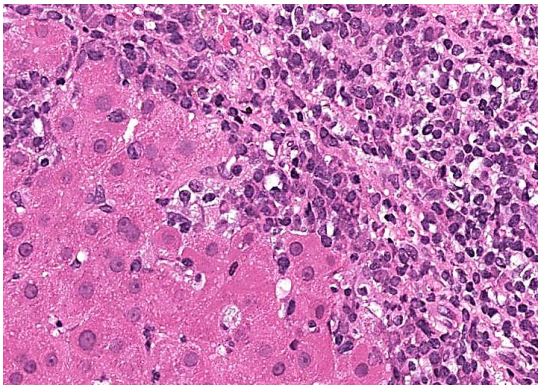
Micro: Portal chronic inflammatory infiltrates
Interface activity, Lobular hepatitis
Ground glass inclusions
Sanded nuclei

IHC: HBsAg = infected, HBcAg = actively replicating

Fibrosing Cholestatic Hep B: Variant with more progressive/worse disease. Usu. Immunosuppressed state (e.g., post-transplant). Extensive cholestasis, bile ductular reaction, hepatocyte swelling, and fibrosis

Hepatitis D: Requires Hep B → acute-on-chronic hepatitis

Autoimmune Hepatitis



Strong Female Predominance

Elevated AST/ALT (often marked)

Serology: + anti-Smooth Muscle Antibody, ANA, LKM-1, Elevated IgG

Micro: Dense portal infiltrates with marked interface activity → Lymphs & Plasma Cells
Lobular injury→ Scattered acidophil bodies
Regenerative rosette formation

Can have "Overlap" with PBC

See Scoring Rubric on next page.

Criteria for Autoimmune Hepatitis:

Finding	Cutoff	Points
Autoantibodies	*(maximum 2 points!)*	
ANA or SMA	≥ 1:40	1
ANA or SMA	≥ 1:80	2
LKM	≥ 1:40	2
SLA	Positive	2
Serum IgG		
	> Upper limit of normal	1
	> 1.10 times the upper limit of normal	2
Histology		
	No evidence of hepatitis	Disqualifying *(Not AIH!)*
	Atypical for AIH	0
	Compatible with AIH	1
	Typical of AIH	2
Absence of viral hepatitis		
Viral serology all negative		2

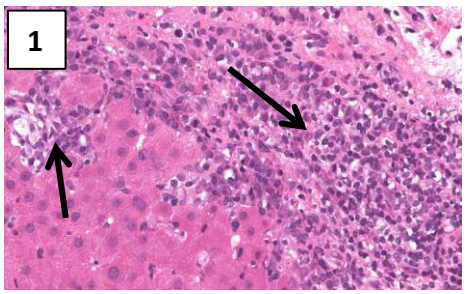
Histology:

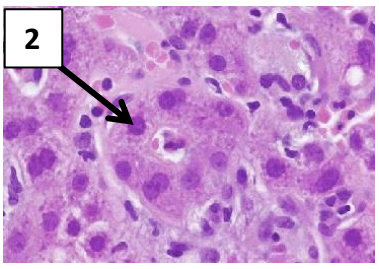
Typical: 1) Lymphoplasmacytic interface hepatitis extending into the lobule, 2) Regenerative rosette formation, 3) Emperipolesis

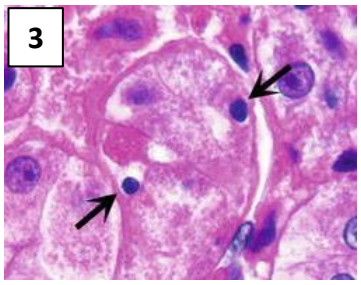
Compatible: Chronic hepatitis with lymphocytic infiltration without all the features considered typical

Atypical: Signs of another diagnosis, such as steatohepatitis

Scoring:
≥6: Probable AIH
≥7: Definite AIH

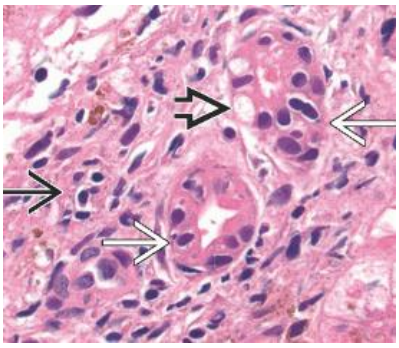






Modified from: Hennes EM et al. Simplified criteria for the diagnosis of autoimmune hepatitis. Hepatology. 2008 Jul;48(1):169-76.

Graft-vs-host Disease (GVHD)



Usually post-stem cell transplant (transplanted immunocompetent T-cells attack new host)

Involves skin, liver, GI tract → rash, ↑LFTs, diarrhea, and vomiting

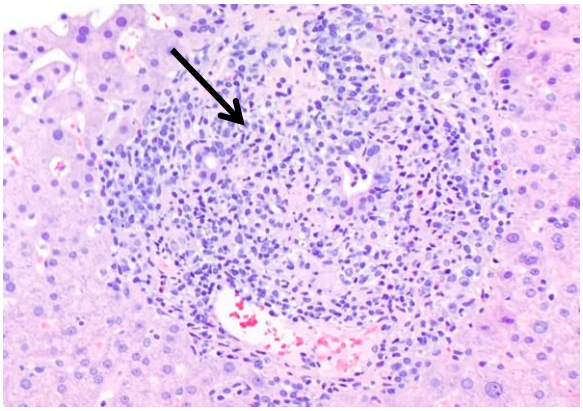
Micro: Bile duct epithelial injury (lymphocytic inflammation, withering, drop out)
Mild portal inflammation; Possible endothelitis

Allograft Rejection

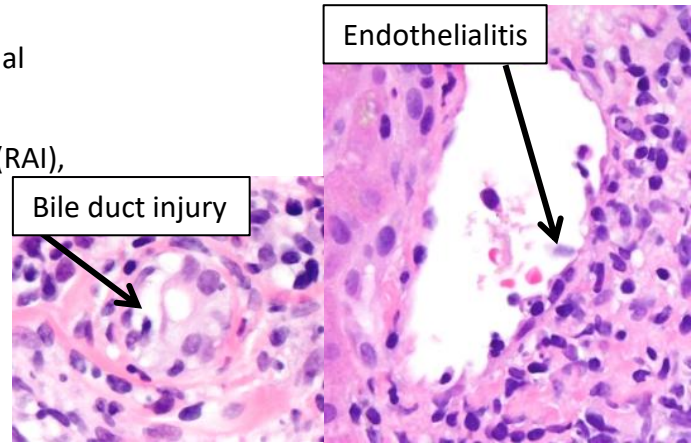
Immune-mediated inflammation/damage in transplanted liver.

T cell-mediated rejection

Formerly: *Acute Cellular Rejection*



Micro: 1) Mixed portal tract inflammation – mostly lymphs, including activated lymphs, with Eos, rare PMNs, etc..
2) Bile duct damage/inflammation – intraepithelial lymphocytes in bile duct epithelium with injury such as apoptosis, disorder, vacuolization, and increased N:C ratio.
3) Endothelialitis – activated endothelial cells with lymphocytes adjacent and underneath, lifting the endothelial cells from the basement membrane or lymphocytes within the lumen, adherent to endothelial cells. Can be central (perivenular) or portal.



Can grade globally (below) or give quantitative score (RAI), but not usually required/done in daily practice.

Most common in months immediately after transplantation, but can happen years later. Present with sudden increase in LFTs.

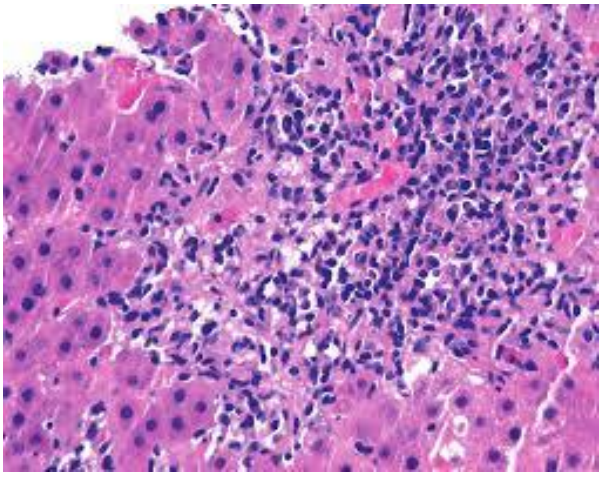
Late onset→ more mild, "muted" findings

T cell–mediated rejection Global assessment:

Grade	Findings
Indeterminate	Portal and/or perivenular inflammatory infiltrate that is related to an alloreaction, but shows insufficient tissue damage to meet criteria for a diagnosis of mild acute rejection
Mild	Rejection-type infiltrate in a minority of the triads or perivenular areas, that is generally mild, and mostly confined within the portal spaces for portal-based rejection and an absence of confluent necrosis/hepatocyte dropout for those presenting with isolated perivenular infiltrates.
Moderate	Rejection-type infiltrate, expanding most or all of portal tracts and/or perivenular areas with confluent necrosis/hepatocyte dropout limited to a minority of perivenular areas.
Severe	As above for moderate, with spillover into periportal areas and/or moderate-to-severe perivenular inflammation that extends into the hepatic parenchyma and is associated with perivenular hepatocyte necrosis involving a majority of perivenular areas

Adapted from: Demetris et al. Am J Transplant. 2016 Oct;16(10):2816-2835. PMID 27273869

Plasma cell-rich rejection



Formerly: *de novo* autoimmune hepatitis

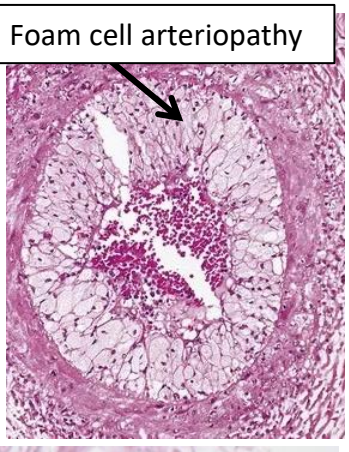
Uncommon, late presenting.

Micro: Portal and/or central plasma cell-rich (>30%) infiltrates with easily recognizable periportal/interface and/or perivenular necro-inflammatory activity usually involving a majority of portal tracts and/or central veins
Lymphocytic cholangitis (desired criteria, but not required)

Note: Original disease <u>MUST</u> <u>not</u> be autoimmune hepatitis (otherwise, classify as recurrent autoimmune hepatitis likely)

Chronic rejection

From recurrent/persistent T cell mediated rejection.

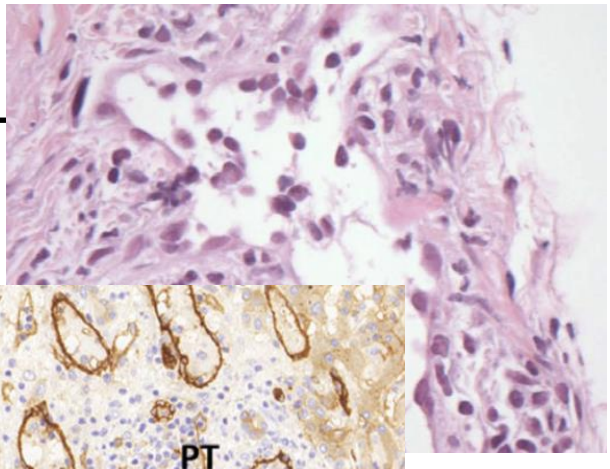


Micro:
Chronic Bile duct injury→ eventual loss/paucity of bile ducts with bile ducts present in <50% of tracts (and degenerative changes in remaining).
CK7 or CK19 can help highlight bid ducts for identification/quantification.
Often not much of a bile ductular reaction.

Chronic vascular damage
Lose hepatic arterioles (usually in a minority of portal tracts)
Intimal damage with inflammation, foam cell arteriopathy, and luminal narrowing
Can cause ischemic pericentral necrosis.

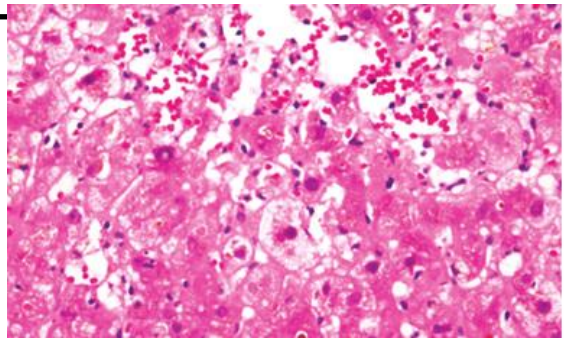
Fibrosis

Antibody-mediated rejection



Diagnosis of "probable" AMR requires:
1) Compatible histology: Portal vascular dilation, endothelial hypertrophy, and microvasculitis,
Often edematous portal tract and cholestasis.
2) C4d IHC showing >50% staining of vein and capillaries;
3) Recent **positive Serum Donor-specific Antibody** (DSA)
4) Exclusion of other etiologies

Ischemia Reperfusion Injury



Caused by ischemia during transplantation process
Usually resolves in a few days.

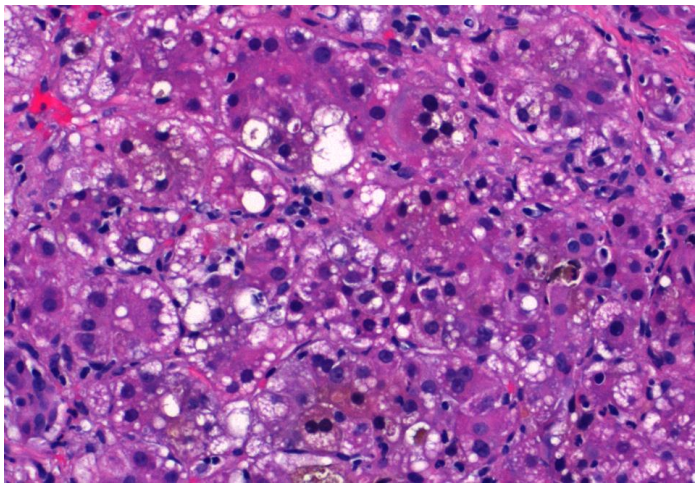
Micro: Ballooning, small droplet steatosis. Pale appearance.
Necrosis (esp. zone 3) and acidophil bodies. Variable PMNs.
Cholestasis with possible bile ductular reaction.

Lobular Injury

Indicates an **acute process** (too injurious to be chronic!)
Often very high transaminases.

Lobular disarray (normal plate structure disrupted→ chaotic architecture)
Lobulitis (lymphs attacking hepatocytes in lobule)
Acidophil bodies (apoptotic pink hepatocytes)

Acute Viral Hepatitis



Usu. due to Hep. A or B

(Hep A and E are spread by fecal-oral; "the vowels hit the bowels")

Diagnosis confirmed with serology or serum PCR.

Micro: Lobular damage and disarray
Diffuse lobular inflammation
Hepatocyte ballooning/swelling
Hepatocyte necrosis and regeneration
May see mild portal and periportal inflammation
NO fibrosis

Drug reaction

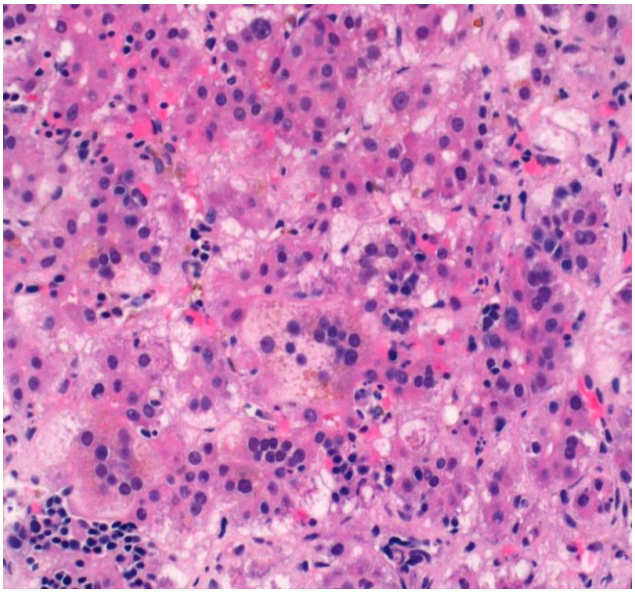
2 chief mechanisms: ***Intrinsic*** (predictable, dose-dependent, less inflammation, more necrosis) vs. ***Idiosyncratic*** (majority of cases, not dose-dependent, more inflammation)

Herbal and botanical drugs are important but often overlooked cause of hepatotoxicity

Very Diverse findings. Can mimic many other disorders (e.g., Autoimmune hepatitis)

A very helpful website to consult when you're wondering about a particular drug:
https://livertox.nih.gov/

Idiopathic Neonatal Hepatitis



aka Neonatal giant cell hepatitis

Neonatal jaundice with hepatomegaly, elevated T. Bili and Conj. Bili, variable AST/ALT

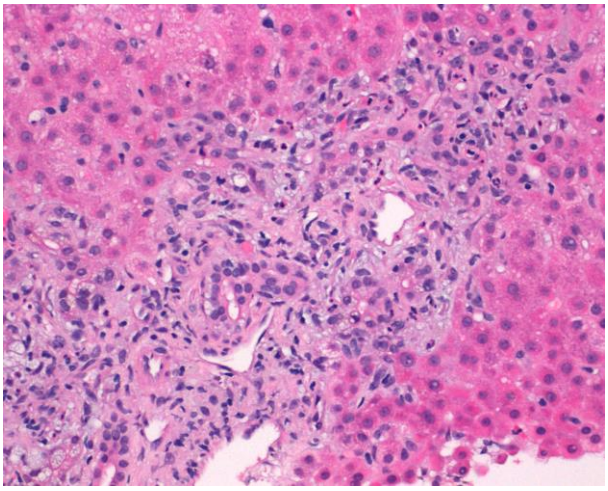
Diagnosis of exclusion (must exclude biliary atresia)
Loose association with hypopituitarism

Micro: Lobular disarray with prominent giant cell transformation
Absent to mild lobular inflammation (despite name)
Canalicular and hepatocellular cholestasis
Minimal portal tract changes and preserved bile ducts

Cholestasis/Biliary

Labs: Elevated Alkaline phosphatase, GGT, and serum bilirubin. Can highlight bile ducts with CK7 and CK19. Often see increased copper deposition in periportal hepatocytes with cholestasis.

Large Duct Obstruction



Mechanical blockage of bile ducts (by gallstones, stricture, or tumor)→ usually diagnosed clinically

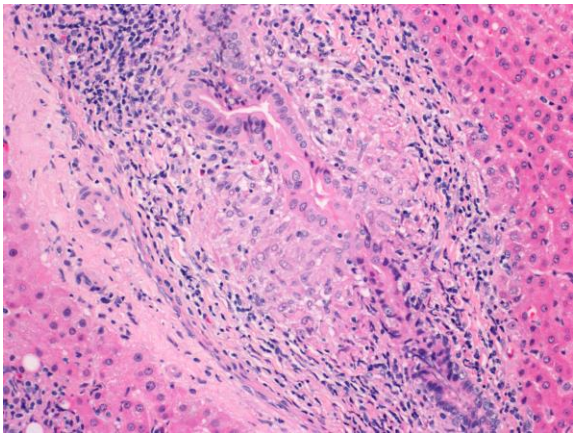
Micro: Portal tract edema, mixed inflammation with prominent neutrophils, and bile ductular reaction
Canalicular and/or ductular cholestasis

Additional considerations:
Lots PMNs in duct epithelium or lumen→ consider **ascending cholangitis**

Can see prominent bile ductular reaction with extensive **necrosis/hepatitis** as part of liver regeneration (so look for lobular injury!)

Primary Biliary Cholangitis

aka "PBC" ***old name: "Primary Biliary Cirrhosis"***



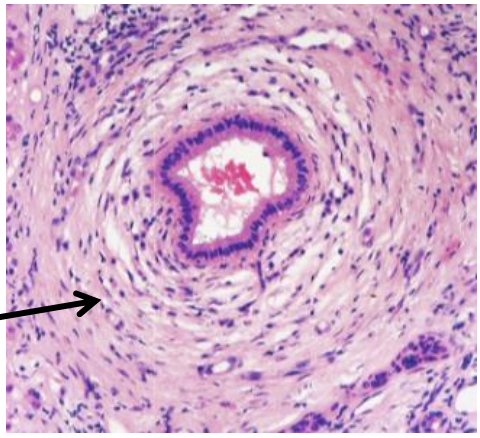
Autoimmune disease with destruction of intrahepatic bile ducts

Usu. Older women with +AMA serology (M2 subtype)

Micro: Moderate portal chronic inflammation.
"Florid duct lesion"→ lymphocytic cholangitis with bile duct injury, +/- Granulomas
Often causes bile ductular reaction and bile duct paucity

Primary Sclerosing Cholangitis

aka "PSC"



Progressive fibrosis and stricturing of bile ducts—predominantly seen extrahepatic, but also intrahepatic
Often diagnosed by cholangiography (multiple strictures)
→ Increased risk of cholangiocarcinoma

Frequently young to middle-age men; Strong association with UC

Micro: Classically, Concentric fibrosis of ducts—"Onion Skin"
(but not often seen on bx)
Biliary obstruction pattern (edema, PMNs, ductular reaction)
Eventual bile duct obliteration by fibrosis with ductopenia

Biliary Atresia

Idiopathic prenatal destruction/fibrosis of extrahepatic bile ducts—Most common cause of pathologic infant jaundice. Usually present in first few weeks of life with jaundice and failure to thrive.
Hepatobiliary (HIDA) scan demonstrates failure of excretion of radiotracer into duodenum.
Surgical intervention with Kasai procedure and/or liver transplantation required.

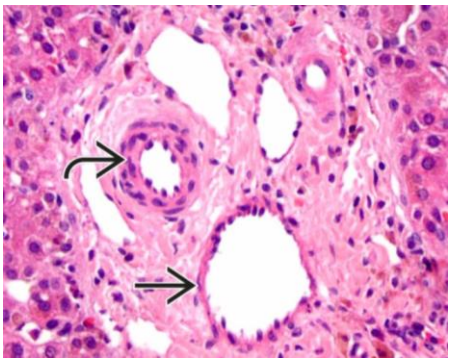
Micro: Large bile duct obstruction findings—(non-specific, requires clinical/radiographic correlation)

Also consider in pediatric cholestatic liver disease: Bile salt deficiency diseases (formerly, Progressive Familial Intrahepatic Cholestasis, or, PFIC), and inherited defects in bilirubin metabolism (mostly tested for with send-out testing).

Neonatal Paucity of Intrahepatic Bile Ducts

Can by Non-syndromic or Syndromic (Alagille syndrome—JAG1 mutations; associated with other abnormalities such as cardiac and skeletal)

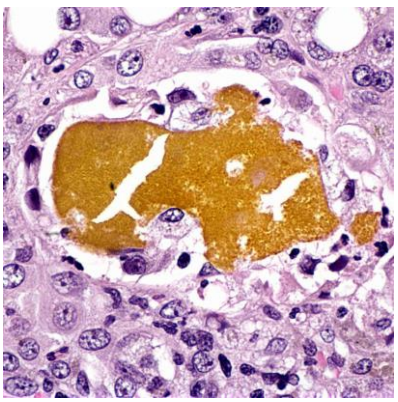
Micro: Interlobular bile ducts absent in > 50% of portal tracts. Can highlight with CK7.
Ductular reaction may be present



Sepsis

Patients systemically ill, often with sepsis and/or bacteremia
Often jaundiced

Micro: *Classically,* Ductular cholestasis ("cholangitis lenta")
However, this is challenged by some as this seems to be common in any condition with cholestasis (including during the hepatic dysfunction seen with sepsis)
Ductular reaction with inspissated bile and flattened, atrophic epithelium.



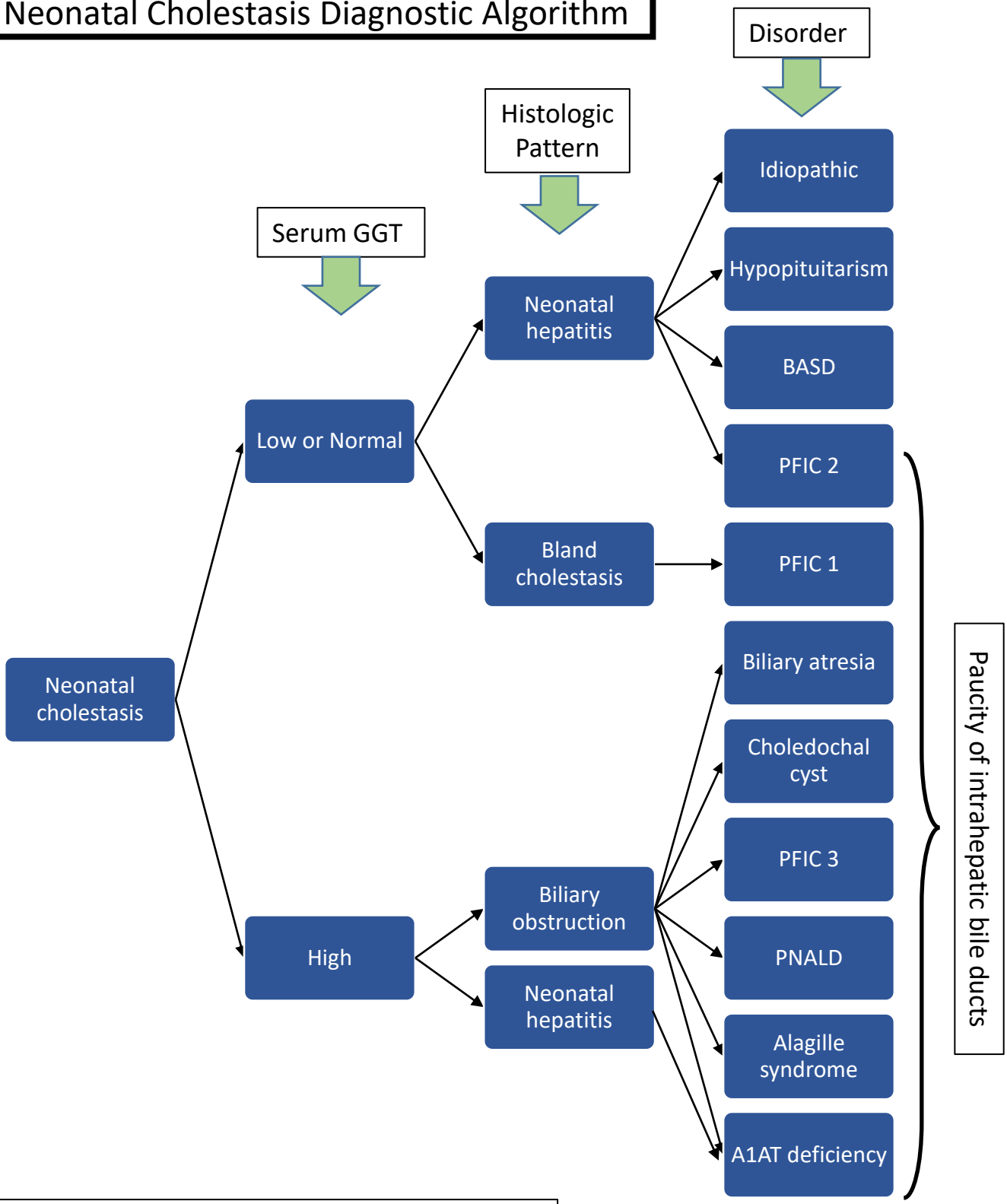
Drug Reaction

Most common histologic pattern of drug-induced liver injury is cholestasis

Can have several patterns:
Bland/Pure cholestasis: Cholestasis with minimal inflammation (also see with systemic illness and pregnancy)
Cholestatic hepatitis: Cholestasis with inflammation and hepatocellular damage
Prolonged cholestasis/ductopenia: > 3 months,
Sclerosing duct injury: Fibrosis affecting large bile ducts (similar to PSC)

https://livertox.nih.gov/

Neonatal Cholestasis Diagnostic Algorithm

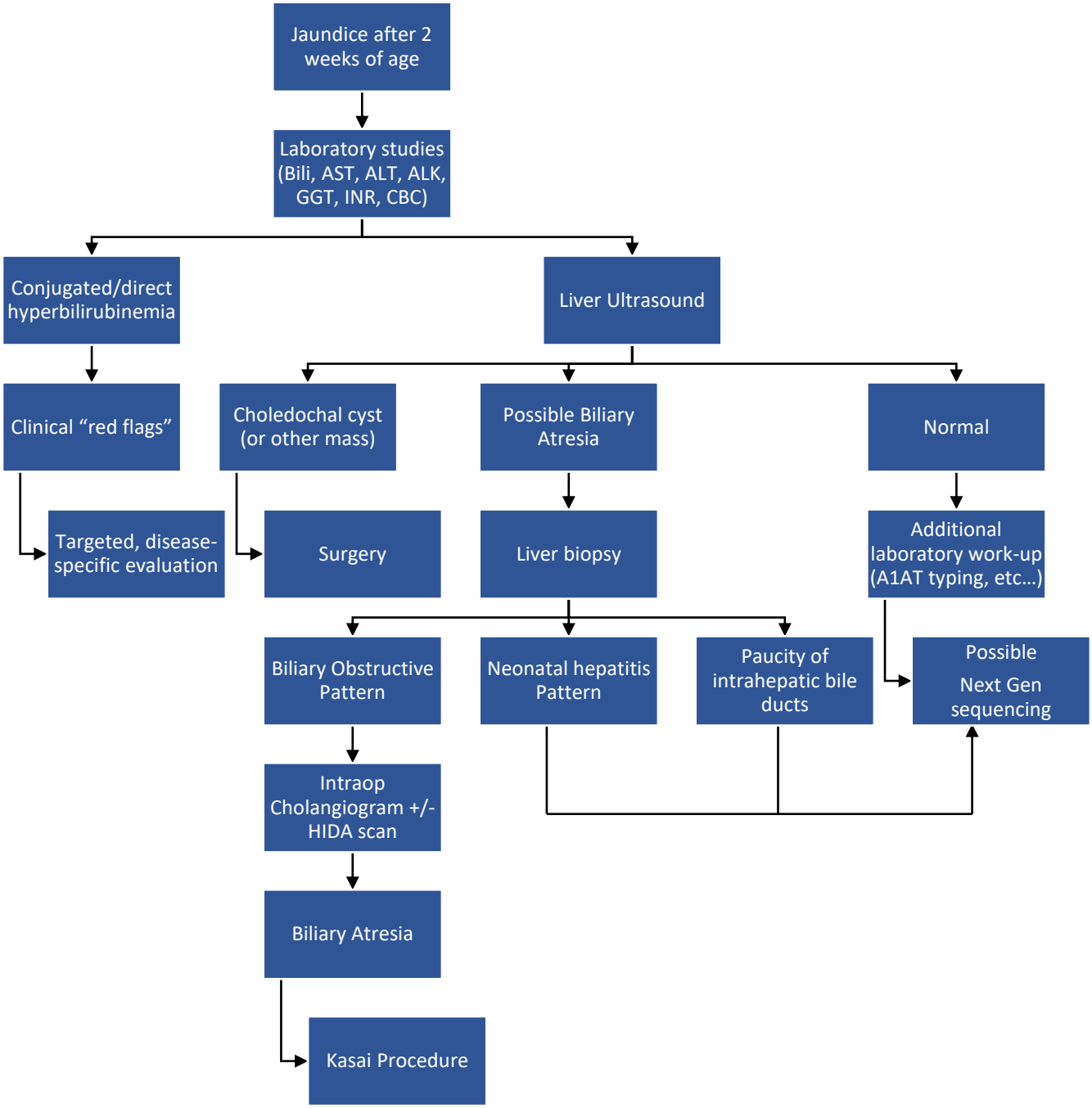


Most common causes of Neonatal Cholestasis:

1) Biliary atresia (BA)
2) Idiopathic Neonatal Hepatitis (INH)

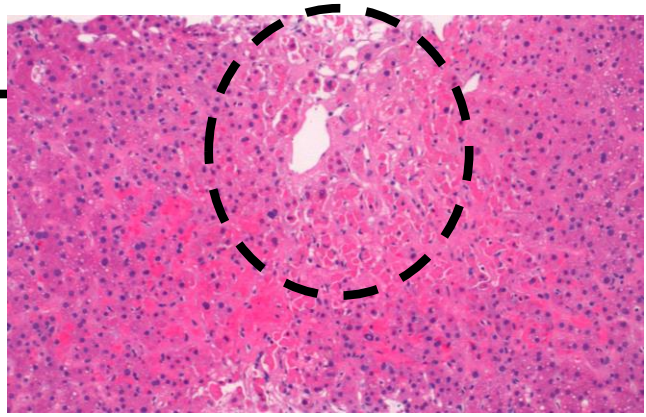
Modified from a presentation from Grace Kim MD at USCAP March 2020

Clinical Neonatal Cholestasis Algorithm



Modified from a presentation from Grace Kim MD at USCAP March 2020

Altered Blood Flow



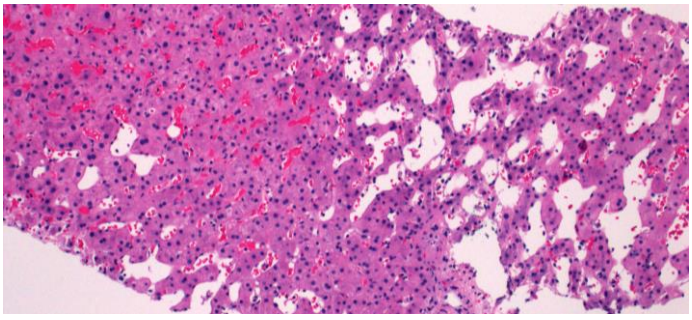
"Shock Liver"

Liver hypoperfusion of any cause
Massive elevation in AST & ALT (thousands)

Micro: Central coagulative necrosis (zone 3)
Collapse of reticulin plates. No inflammation.

Other causes of bland Central Necrosis:
Acetaminophen toxicity (indistinguishable histologically)

Congestive Hepatopathy



Caused by hepatic venous outflow obstruction
Can be due to RHF, Budd-Chiari, etc…
Grossly: Nutmeg liver

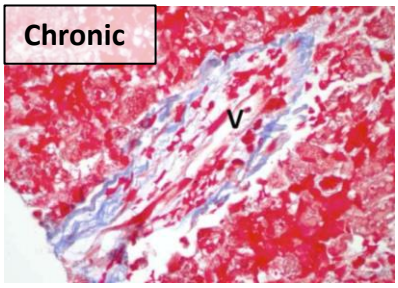
Micro: Central zone sinusoidal dilatation, congestion, hepatic plate atrophy, and necrosis
Chronic cases can lead to central vein and sinusoidal fibrosis → Cirrhosis

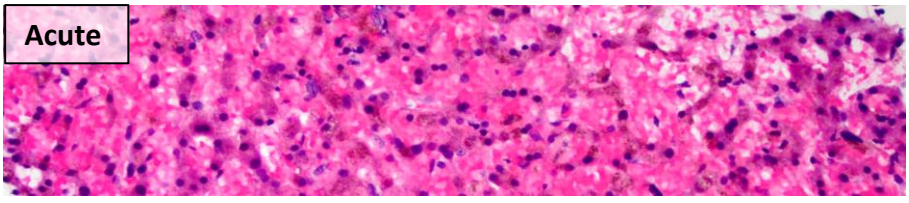
Sinusoidal Obstruction Syndrome

aka Veno-Occlusive Disease

Sinusoidal endothelial injury
Often due to chemotherapy or Stem Cell Transplantation

Micro: *Acute:* Sinusoidal dilation/congestion; Sinusoidal endothelial edema. Chronic: Central vein obliteration (best seen on trichrome) →

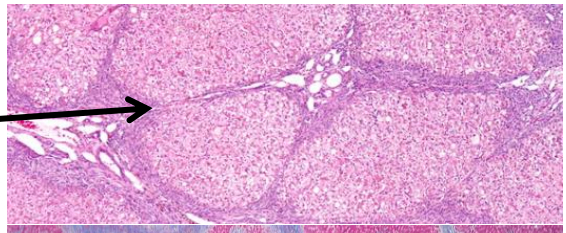




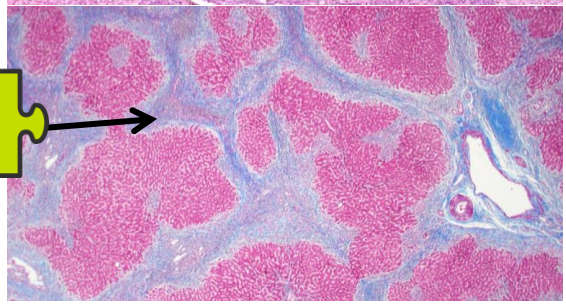
Cirrhosis

Common End-Stage for many liver disorders

Regenerative nodules surrounded by fibrosis (want to see both for Dx)



Special type: "Biliary Cirrhosis" seen with long-standing cholestasis
Cholate stasis (ballooning, feathery degeneration at edges of nodules), "jigsaw" pattern of cirrhosis (instead of round nodules, biliary cirrhosis is classically irregular), copper deposition in zone 1, ductopenia, periductal fibrosis, bile infarcts.

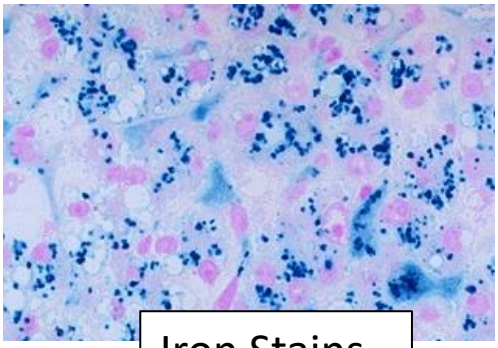


Miscellaneous

Iron Overload *aka Hemosiderosis*

With excessive transfusions or iron supplementation

Iron accumulates in Kupffer cells (sinusoidal macrophages) first. When those are saturated, then it is deposited in hepatocytes

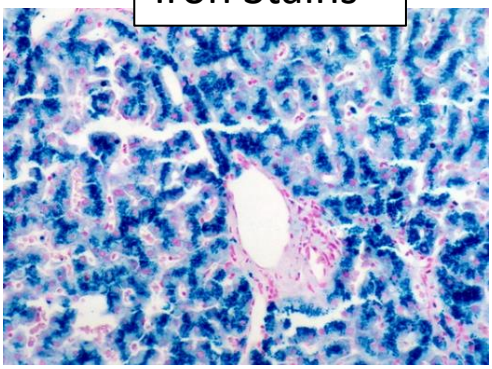


Iron Stains

Hereditary Hemochromatosis

Inherited disorder of iron metabolism
HFE gene mutations cause increased iron absorption & storage

Iron accumulates first in periportal hepatocytes
→progressively involves all zones & bile duct epithelium
Less Kupffer cell involvement (relatively)

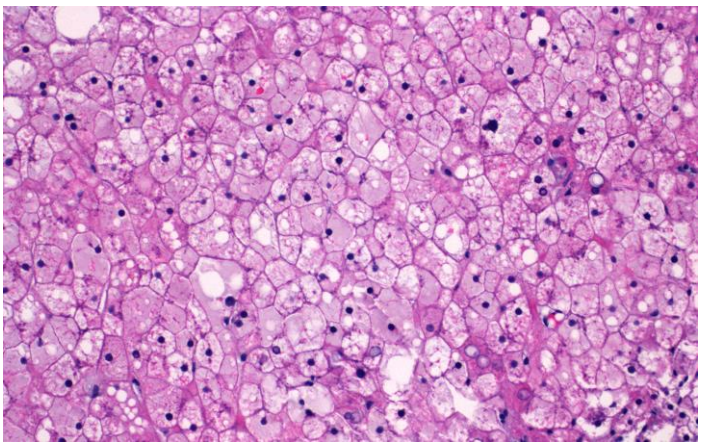


Glycogenic Hepatopathy

Poorly-controlled diabetes→ abundant glycogen stores → Hepatomegaly and elevated LFTs

A component of Mauriac Syndrome (with delayed puberty and Cushingoid features)

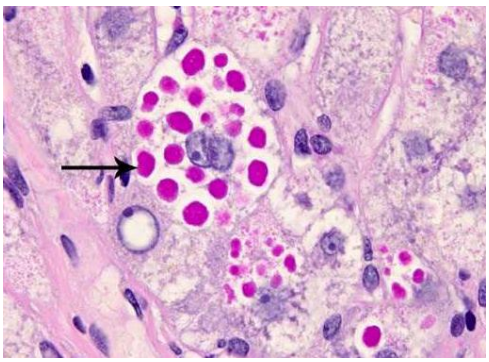
Micro: Diffuse glycogenation of hepatocytes
Demonstrated by PAS stain (Diastase sensitive)
Absence of inflammation



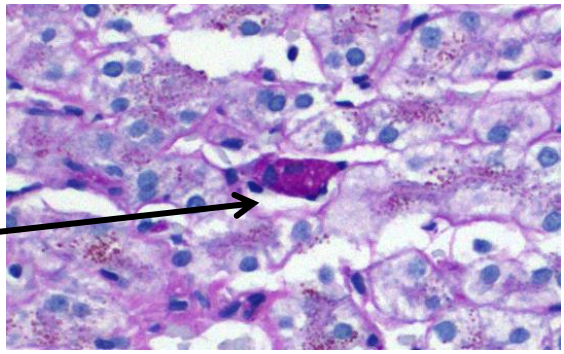
α1-Antitrypsin Deficiency

Genetic disorder characterized by abnormal α-1-antitrypsin protein synthesis (SERPINA1 gene mutation, autosomal recessive)
PiZZ phenotype accounts for most cases
→ Chronic liver disease and emphysema

Micro: Eosinophilic, PAS-D (+) globules within periportal hepatocytes are characteristic
Neonatal hepatitis features cholestasis and hepatocyte injury (too early for globule formation)
In endoplasmic reticulum by electron microscopy



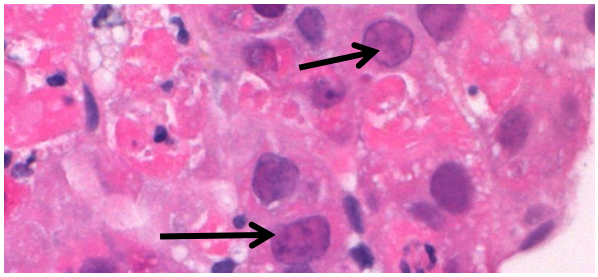
"Resolving Hepatitis"



Can look "**almost normal**"
Minimal/no lobulitis or portal inflammation

Mild lobular disarray (somewhat disorganized plates)
Kupfer cell hypertrophy (cleaning up debris)
Highlighted with a PASd stain
Most common causes: acute self-limited viral infection or idiosyncratic drug reaction

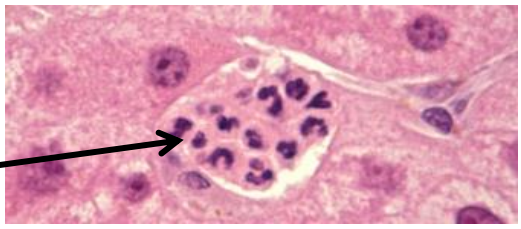
Adenovirus/Herpes Hepatitis



Massive, bland azonal necrosis with characteristic viral **inclusions** at edge of necrosis.

Usu. Immunocompromised/transplanted. Poor prognosis.

CMV Hepatitis

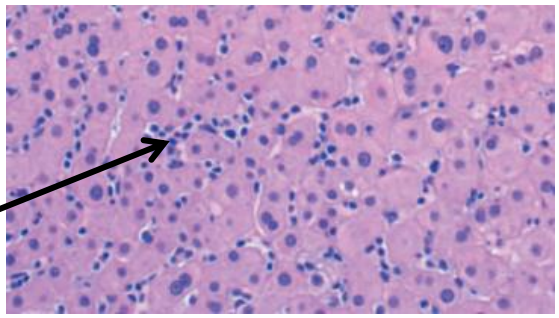


Almost exclusively in immunocompromised individuals.

Inclusions can be subtle (so use stain liberally).

Classically: Neutrophilic microabscesses.

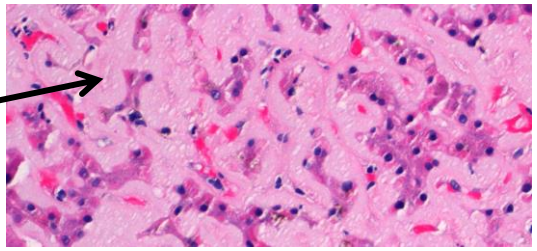
EBV Hepatitis



Often looks like a nondescript hepatitis with mild to moderate portal and lobular inflammation (so often keep in DDX, esp. if young or immunocompromised!)

Classically: Lots of activated lymphocytes in sinuses (T cells)
EBER highlights *rare* infected B cells

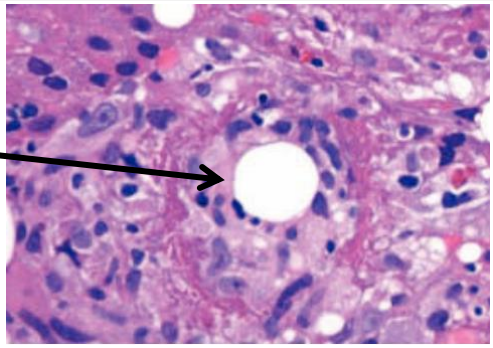
Amyloid



Part of systemic illness, often plasma cell dyscrasias.
Abundant amyloid deposited in sinuses.

Required: Apple-green birefringence on Congo Red stain

Q Fever



Rickettsial disease that usually manifests as pneumonitis or carditis

Classic finding: **Fibrin Ring granulomas** (epithelioid granuloma with central lipid droplet surrounded by an eosinophilic fibrin ring that is trichrome positive)

Note: These granulomas can also be seen with other infections and drugs (not super specific, just classic)!

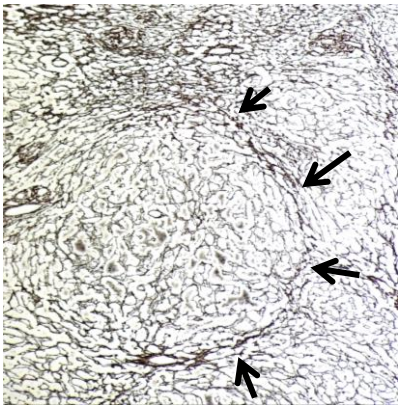
Nodular Regenerative Hyperplasia

Think: "Cirrhosis-like nodules, but <u>without</u> the fibrosis"

Multiple <u>hyperplastic parenchymal nodules</u> (with normal to enlarged hepatocytes) with intervening compressed/atrophied parenchyma

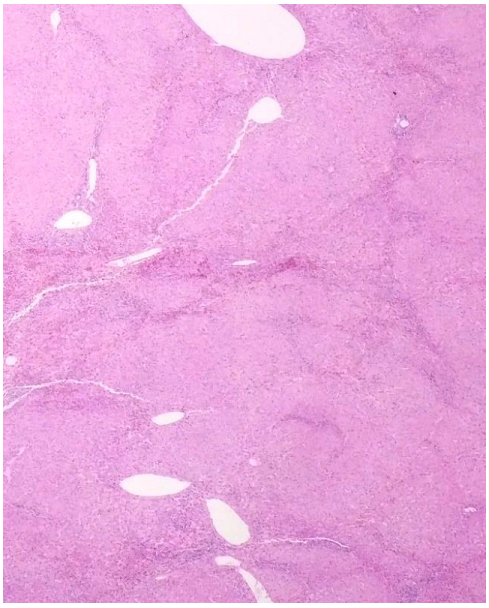
<u>No</u> significant fibrosis

Best seen on reticulin stain →



Results from <u>changes in hepatic blood flow</u> from obliteration of small portal veins → leads to localized atrophy → other areas grow to compensate.

Can cause portal hypertension.

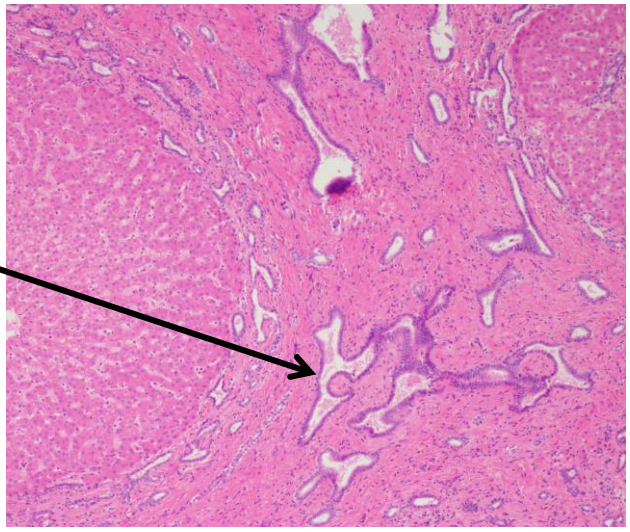


Congenital Hepatic Fibrosis

<u>Embryologic</u> ductal plate malformation that leads to bridging fibrosis (<u>cirrhosis</u>) with <u>prominent malformed ducts.</u>

Ducts ectatic, anastomosing, and irregularly shaped. <u>No significant inflammation</u>.

Few/abnormal portal veins → Leads to portal hypertension.

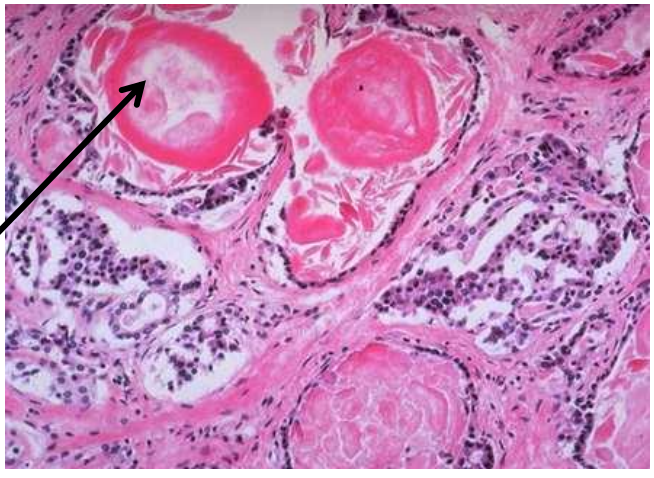


Cystic Fibrosis

CFTR (Chloride ion channel) mutations result in <u>exocrine gland malfunction</u>.
Autosomal recessive. Usually presents with respiratory problems, meconium ileus, or pancreatic insufficiency.

In liver, **<u>thick abnormal secretions</u>** are present **in bile ducts** (similar to in lungs and pancreas) → biliary obstruction → epithelial atrophy, bile ductular proliferation, inflammation → fibrosis → biliary **cirrhosis**. Also often **steatohepatitis**.

Secretions stain with **PAS-D**



Laboratory Correlation

Acute Hepatitis

Marked Transaminitis (AST & ALT >5x normal)

Non-Hepatotropic Virus (CMV, EBV, Adeno)

HAV & HEV: Fecal oral transmission; only acute

HBV: Ground Glass inclusions

AIH: Plasma cells

Adverse drug reaction

Massive altered hepatic blood flow (e.g., Shock)

Chronic Hepatitis

Mild Transaminitis (AST & ALT <5x normal)

HBV: 5% develop chronic hepatitis

AIH: + ANA, ASMA, Elevated IgG; Interface necroinflammatory lymphoplasmacytic infiltrate

HCV: 80% develop chronic hepatitis; nodular aggregates of lymphocytes

Hereditary Hemochromatosis: + HFE genetic mutation
Elevated Transferrin saturation and serum ferritin

Wilson's: Increased liver copper quantification; + *ATP7B* gene; AST/ALT ratio >2.2, Alk. Phos./T. Bili <4

A1AT Deficiency: PiZZ phenotype, Hyaline globules in hepatocytes stain with PAS with diastase stain

Alcoholic: Clinical history of alcohol, AST:ALT > 2, more likely to show neutrophils and Mallory's hyaline

NASH: Diabetes or metabolic syndrome, Obesity

Drug reaction

Cholestatic Hepatitis

Elevated Alk Phos. & GGT; +/- Bili
Jaundice

Large duct obstruction

PBC: Female, + AMA, IgM, lymphocytic cholangitis and florid duct lesion

PSC: Male, IBD, diagnosed with cholangiography, concentric fibrosis around bile ducts, risk of cholangiocarcinoma

Drug reaction

Cirrhosis/Liver Failure

Synthetic Dysfunction (Elevated INR, Low Albumin, Low platelets)

Based on a presentation from Max Smith M.D., Mayo Clinic

(more) Differential Diagnoses

Acute Liver Failure

Histologically, typically lobulitis or necrosis patterns (as they are too injurious to be chronic)

- Acetaminophen toxicity (40 – 50%)
- Drug reaction (10 – 20%)
- Acute viral hepatitis (10 – 20%)
- Idiopathic (20 – 30%)
- Rare causes: Wilson's disease, Autoimmune hepatitis, Budd-Chiari syndrome, Non-hepatotropic viruses

Almost Normal Liver

With Elevated LFTs

- Systemic autoimmune conditions
- Vascular outflow obstruction
- Intermittent ischemia
- Metabolic syndrome (even if fat-free)
- Medication

With Portal hypertension and/or ascites

- Hepatoportal sclerosis
- Portal venopathy
- Peritoneal serositis (no liver disease)

Fatty Liver

- Metabolic syndrome (NASH)
- Alcohol use
- Drug effect
- Wilson's disease (and other genetic disorders)
- Cystic fibrosis
- Elevated cortisol

Bland Lobular Necrosis

Necrosis with NO (or little) associated inflammation
Due to direct injury/toxicity (not secondary immune damage)

Zone 1	Zone 2	Zone 3	Azonal
Iron Toxicity Phosphorous Toxicity Hepatitis A Some industrial chemicals	Poisons Beryllium Yellow fever	Acetaminophen Ischemia Some toxins	Herpes Adenovirus Varicella

Based on: Atlas of Liver Pathology: A Pattern-based Approach, by Dr. Michael Torbenson

Granulomas

- Primary biliary cholangitis
- Sarcoidosis
- Drug effect
- Infection (Mycobacteria, fungal, Q fever, etc…)
- CVID and other systemic granulomatous diseases
- Paraneoplastic

Bland Lobular Cholestasis

- Drug effect
- Severe systemic illness/sepsis
- Paraneoplastic syndrome

Ductopenia *(adult)*

- Chronic obstruction
- Primary biliary cholangitis
- Chronic rejection
- GVHD
- Drug effect
- Idiopathic

Chronic Hepatitis Pattern

- Viral Hepatitis
- Autoimmune hepatitis
- Drug effect

Microvesicular Steatosis

- Medication (e.g., Reye's syndrome)
- Toxin (e.g., arsenic)
- Acute fatty liver of pregnancy
- Alcohol foamy degeneration
- Genetic diseases (e.g., Alper's syndrome)
- Infection (e.g., HDV + HBV)

Pediatric Cholestatic Disease

- Biliary atresia (extrahepatic)
- Paucity of intrahepatic bile ducts
    - Non-syndromic vs Syndromic
- Neonatal giant cell hepatitis
- Sepsis
- TPN
- Bile salt deficiency (PFIC's)
- Genetic diseases (e.g., alpha-1 antitrypsin, Niemann-Pick, etc…)

Cystic Biliary Malformations

- Congenital hepatic fibrosis
- Caroli syndrome/disease
- Autosomal recessive polycystic kidney disease
- Autosomal dominant polycystic kidney disease

Based on: Atlas of Liver Pathology: A Pattern-based Approach, by Dr. Michael Torbenson

Portal Hypertension

Pre-hepatic

- Portal vein thrombosis
- Portal vein stricture

Hepatic

- Cirrhosis
- Schistosomiasis
- Sarcoidosis
- Nodular regenerative hyperplasia
- Hepatoportal sclerosis
- Peliosis hepatitis
- Veno-occlusive disease

Post-Hepatic

- Hepatic vein thrombosis
- Heart failure

Sinusoidal Obstruction Syndrome

- Bone marrow transplantation
- Chemotherapy medications
- Radiation therapy
- Herbal teas/remedies

Congestive Hepatopathy

- Budd-Chiari syndrome
- Right-sided heart failure
- Compression of hepatic veins or IVC
- Medications (e.g., estrogen)
- Veno-occlusive disease
- Sickle cell anemia
- Hemophagocytosis syndrome
- Autoimmune diseases
- Paraneoplastic syndromes

Things that are easy to overlook

- Glycogenopathy
- Alpha-1-antitrypsin deficiency
- Nodular regenerative hyperplasia
- Hepatoportal sclerosis
- Early bile duct loss
- Amyloid
- Stellate cell hyperplasia

Based on: Atlas of Liver Pathology: A Pattern-based Approach, by Dr. Michael Torbenson