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AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES

# Metabolic and Genetic Diseases

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## Metabolic and Genetic Diseases

| **Pretransplant** | **45%** of Exam |
|---|---|
| ~~Biliary atresia (pediatrics only)~~ | ~~2%~~ |
| **Genetic liver disease** | 4% |
| ~~Cholestatic syndromes (including progressive familial intrahepatic cholestasis [PFICs])~~ | |
| Hereditary hemorrhagic telangiectasia (internal medicine only) | |
| Wilson disease | |
| Alpha-1-antitrypsin deficiency | |
| Iron overload syndromes | |
| Mitochondrial defect | |
| ~~Urea cycle defect (pediatrics only)~~ | |
| Cystic fibrosis | |
| Fibrocystic diseases (including Caroli disease and choledochal cysts) | |
| Familial amyloid polyneuropathy (FAP) | |
| Other genetic liver diseases (including EPP) | |

**<4% of 240 questions**
**9 questions**





## Hereditary Hemorrhagic Telengiectasia

- Rendu-Osler-Weber syndrome; rare, 1-2 cases/10,000, AD inheritance
- Widespread cutaneous, mucosal and visceral AVMs (skin, mucous membranes, lung, brain, GI tract, liver)
- Mutation in TGF-beta signaling pathway genes: endoglin (ENG, type 1), activin receptor-like kinase type 1 (ALK-1 or ACVRL-1, type 2)
- Diagnosis (3 of 4): epistaxis, cutaneous or mucosal telengiectases, visceral involvement (lung, CNS, GI tract, or liver), family history of HHT
- Liver involvement results in shunting: arteriovenous, portovenous, arterioportal
- Most common initial presentation: high-output heart failure, followed by portal hypertension and biliary ischemia
- Most common biochemical abnormalities: elevated alk phos and GGT
- Liver synthetic function normal, platelet count normal, do not develop cirrhosis

## Hereditary Hemorrhagic Telengiectasia

- Portal hypertension from arterioportal shunting or NRH
- “Hepatic disintegration”: bile duct and liver necrosis from biliary ischemia
- NRH and FNH (100x general population) frequently associated with liver involvement by HHT
- “Pseudocirrhosis”: liver may appear nodular (NRH)
- FNH can be mistaken for HCC
- RUQ thrill/bruit may suggest liver involvement
- Gold standard is angiography but Doppler US or multiphase CT also useful
- Avoid liver biopsy (bleeding)
- Treat biliary ischemia with UCDA, antibiotics, avoid ERCP
- LT only curative treatment for portal hypertension, high-output heart failure, acute biliary necrosis
- Non-standard MELD exception for heart failure or severe diffuse bilobar hepatic necrosis




## Wilson Disease

- Inherited disorder of excessive copper accumulation
- ATP7B gene (>300 mutations identified): transmembrane transport of copper within hepatocytes
- Absent/reduced function causes decreased hepatocellular excretion into bile→hepatic copper accumulation and injury→copper release into bloodstream→organ deposition (brain, kidneys, cornea)
- Failure to incorporate copper into ceruloplasmin
- Disease spectrum: asymptomatic with only biochemical manifestations, brief clinical illness like acute viral hepatitis or autoimmune hepatitis, ALF, predominantly neurologic presentation
- Classic presentation: cirrhosis, neurological manifestations, KF rings (half of patients presenting with liver disease do not possess 2 of these 3 criteria)
- Usually <40 years old but age alone should not exclude the diagnosis

## Wilson Disease

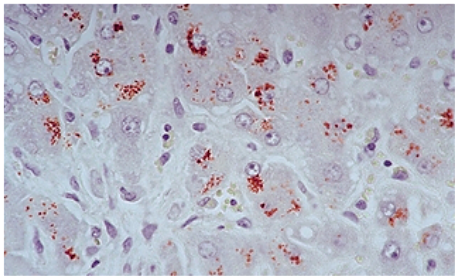
- Kaiser-Fleischer Rings
  - Copper deposits in cornea
  - Not specific for WD; found in other chronic cholestatic diseases and neonatal cholestasis
  - 44-62% of pts w/mainly hepatic disease
  - Absence does not exclude WD
  - KF rings and sunflower cataracts (copper deposits in lens) found by slit-lamp examination
  - Disappear with effective medical treatment or after LT

- Ceruloplasmin
  - Major copper carrier in blood
  - Usually decreased in WD
  - Can be low in renal or enteric protein loss or severe ESLD
  - <20 mg/dL consistent with WD, diagnostic if associated with KF rings
  - Modestly low levels need further eval
  - Normal levels do not exclude WD (acute phase reactant)
- Serum/urine copper
  - Serum copper usually decreased
  - Exception is ALF: marked increase
  - 24-hr urine copper typically >100 ug; >40 ug requires further evaluation




## Wilson Disease – Liver Biopsy

- Hepatic copper content >250 ug/g dry weight is highly suggestive of WD
- <50 ug/g dry weight excludes WD (in untreated patients)
- 70-250 ug/g dry weight requires further eval
- Mild steatosis, glycogenated hepatocyte nuclei, focal hepatocellular necrosis, fibrosis
- Cirrhosis by second decade of life
- May mimic autoimmune hepatitis or NAFLD/NASH
- Hepatocyte apoptosis in WD-ALF
- Absence of copper on liver biopsy does not exclude WD



## Wilson Disease – Acute Liver Failure

- Coombs-negative hemolytic anemia, acute intravascular hemolysis
- Coagulopathy unresponsive to IV vitamin K
- Rapid progression to renal failure
- Modest increase in aminotransferases (<2000 U/L)
- AST>ALT (mitochondrial damage?)
- Normal of very low alkaline phosphatase (<40 U/L)
- Alkaline phosphatase:total bilirubin ratio <2
- Ceruloplasmin usually low
- Very high serum and 24-hour urine copper
- KF rings may be absent in 50% of patients
- F:M = 2:1
- Cirrhosis typically present even if ALF is first presentation of WD
- Requires urgent LT (status 1A)

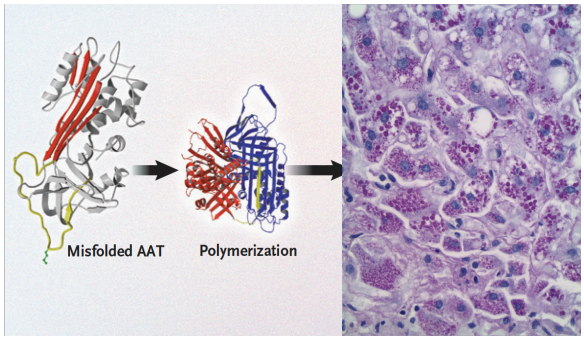



## Wilson Disease – Treatment

- D-penicillamine
  - Promotes urinary excretion of copper
  - Numerous side effects: sensitivity/allergic reaction, nephrotoxicity, lupus-like syndrome, thrombocytopenia/total aplasia, dermatologic toxicity, myasthenia gravis, polymyositis, loss of taste, retinitis
- Trientine
  - Promotes copper excretion by kidneys
  - Few side effects: gastric irritation
- Zinc
  - Induces enterocyte metallothionein, endogenous chelator of metals
  - Can remove stored copper (unlike penicillamine and trientine)
  - Generally reserved for maintenance treatment or first-line treatment in asymptomatic/presymptomatic patients
- Treatment monitored by 24-hour urinary copper
  - Penicillamine/trientine: 200-500 ug/day (<200 ug/day indicates nonadherence or overtreatment)
  - Zinc: <75 ug/day

## Alpha-1-Antitrypsin (AAT) Deficiency

- Liver is primary site of AAT protein synthesis
- Primary role is to inhibit neutrophil elastase, protect lung tissue
- M: wild-type allele of SERPINA1 (**ser**ine **p**rotease **in**hibitor A1)
- Z, S: point mutations/severe deficiency alleles
  - Do not affect synthesis
  - Cause degradation or formation of ordered polymers (some secreted)
  - Polymers persist in ER, positive on periodic acid-Schiff staining and resistant to diastase (PAS-D), toxic – cause liver disease







## AAT Deficiency – Clinical Presentation

- Liver and/or lung disease
- Chronic hepatitis, cirrhosis, HCC, rarely ALF
- Liver and lung disease risks are independent and different ages of peak incidence – same patient can have both
- Neonatal hepatitis syndrome
  - Typical presentation in neonatal period (10% of infants with PI ZZ)
  - Cholestatic jaundice, pruritis, poor feeding, poor weight gain, hepatosplenomegaly
  - Indistinguishable from extrahepatic biliary atresia, CF
- Rarely present with vitamin K-deficient coagulopathic hemorrhage
- Emphysema not observed in children – takes decades

## AAT Deficiency – Deficiency Alleles

- PI ZZ
  - Risk of cirrhosis associated with advancing age
  - Smoking contributes to earlier/more severe lung disease
- PI MZ
  - Usually asymptomatic
  - Modifies risk of other liver diseases
  - Over-represented in CLD (NAFLD, alcohol, cryptogenic cirrhosis)
- PI SZ
  - Children rarely have clinically relevant liver disease
  - May develop liver disease identical to PI ZZ
- Null homozygotes
  - No circulating AAT
  - More severe lung disease
  - No increased risk of liver disease




## AAT Deficiency – Diagnosis & Treatment

- Diagnosis
  - Measure serum AAT level, then phenotype/genotype
  - Recall that AAT is an acute phase reactant
  - Assess for advanced liver disease
  - HCC surveillance in patients with cirrhosis
- Treatment
  - Refer to pulmonologist
  - Augmentation therapy may reduce pulmonary disease but has no effect on liver disease
  - Avoid NSAIDs: increase AAT synthesis and hepatic accumulation
  - Smoking cessation
  - Liver transplantation

## Iron Overload Syndromes

- Hereditary hemochromatosis
  - Inherited iron overload disorder caused by excessive iron absorption due to hepcidin deficiency
  - Hepcidin: expressed predominantly in hepatocytes, binds to ferroportin (macrophages and enterocytes), induced by excess iron or inflammation, decreased by iron deficiency, ineffective erythropoiesis, hypoxia
  - Northern European ancestry (Nordic/Celtic): prevalence 1/250
  - Cirrhosis, HCC, diabetes, cardiomyopathy, hypogonadism, arthropathy, skin pigmentation
  - C282Y homozygotes account for 80-90% of typical HH
  - Low penetrance: 70% of C2828Y homozygotes have phenotypic expression, 10% develop severe iron overload and organ damage
- Secondary iron overload




## Iron Overload Syndromes

- Type 1 HH (HFE)
  - HFE mutations (C2828Y, H63D, S65C)
  - Grade 4 stainable iron in hepatocytes with periportal distribution
  - Lack of stainable iron in Kupffer cells
- Type 2 HH (juvenile hemochromatosis)
  - Mutations in hemojuvelin (HJV) or hepcidin (HAMP)
  - Early onset (<30 years old)
  - Cardiomyopathy, hypogonadism prevalent
  - Same biopsy findings as type 1
- Type 3 HH:
  - TfR2 mutations
  - Same biopsy findings of type 1
- Type 4 HH (ferroportin disease)
  - Only AD form of HH
  - Mutations in FPN1 gene (SLC40A1)
  - Spleen is most affected organ (high FPN1 activity in macrophages)
  - Iron preferentially in Kupffer cells
  - MRI can distinguish from HFE-HH

## Iron Overload Syndromes – Clinical Features

- Fatigue and arthralgias (2nd and 3rd MCP joints) are most common early symptoms
- Additional symptoms: RUQ pain, chondrocalcinosis, impotence, decreased libido, heart failure, diabetes
- Signs: hepatomegaly, testicular atrophy, skin pigmentation, changes of PCT
- Women present ~10 years later (menstrual blood loss, maternal iron loss during pregnancy)
- Alcohol is main modifier associated with HH-related cirrhosis




## Iron Overload Syndromes – Diagnosis

- Elevated ferritin levels + C282Y homozygosity or C282Y/H63D compound heterozygosity
- Normal ferritin (<200 ug/L in premenopausal women, <300 ug/L in men/postmenopausal women) + transferrin saturation <45% has 97% NPV for excluding iron overload
- Ferritin can be elevated in absence of increased iron stores: alcoholic liver disease, chronic HBV/HCV, NAFLD, lymphomas, chronic inflammatory conditions
- Ferritin <1000 ug/L predicts absence of fibrosis, no need for liver biopsy unless concomitant excessive alcohol use or elevated liver biochemistries
- Liver biopsy: HIC >71 mmol/g dry weight, HII >1.9 (HII = HIC/age)

## Iron Overload Syndromes – Treatment

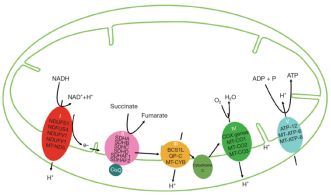
- Phlebotomy weekly as tolerated until target ferritin 50-100 ug/L
- Improved with phlebotomy: fatigue, skin pigmentation, insulin requirements for diabetics, abdominal pain, cardiomyopathy, liver fibrosis (13%-50%)
- Irreversible despite phlebotomy: arthropathy, hypogonadism, advanced cirrhosis, insulin-dependent diabetes
- Normal life expectancy when patients are treated before onset of cirrhosis or diabetes
- Continue HCC surveillance in patients with cirrhosis following phlebotomy
- Liver transplantation




## Iron Overload Syndromes – Secondary

- Causes
  - Ineffective erythropoiesis (e.g., thalassemia, sickle cell anemia), parenteral iron overload, liver disease, malignancy, chronic inflammatory states
- Consider liver biopsy in patients with iron overload who are not C282Y homozygotes or compound heterozygotes
  - Pattern of iron distribution similar to type 4 HH (primarily in Kupffer cells rather than periportal hepatocytes)
- MRI can also show splenic iron deposition (absent in HFE-HH)
- Phlebotomy useful in some forms of secondary iron overload and in patients with PCT
- No evidence that phlebotomy is beneficial in alcoholic liver disease
- Iron chelation is treatment of choice for iron overload from ineffective erythropoiesis
  - Deferoxamine (IV/SC), deferiprone (oral), deferasirox (Exjade, oral)

## Mitochondrial Defect




- Clinically heterogeneous (single organ or multisystem)
- Heterogeneous presentation: neonatal acute liver failure, lactic acidosis, cholestasis, chronic liver failure
- Suspect mitochondrial disorder when:
  - Neuromuscular symptoms + liver dysfunction
  - Multisystem involvement in patient with acute or chronic liver disease
  - Rapidly progressive course of liver disease
  - Presence of lactic acidosis (not present in all disorders), hepatic steatosis, or ketonemia
- Abnormal liver biopsy: micro/macrovesicular steatosis, cholestasis, hepatocellular degeneration/swelling, lobular inflammation, portal fibrosis, cirrhosis
- LT survival <50%; unrecognized neurologic involvement pre-LT may progress rapidly post-LT
- Significant neuromuscular or cardiovascular involvement are absolute contraindications to LT




## Cystic Fibrosis

- Most common AR systemic disease of newborns in US
- Mutations in CF transmembrane conductance regulator (CFTR) protein
- CFTR located on apical surface of cholangiocytes, not on hepatocytes
- CFTR mutations cause: viscous bile, decreased bile flow and alkalinity, biliary mucus plugging, periductal inflammation, cholangiocyte damage, bile duct proliferation, periductal fibrosis, hepatic steatosis
- CF liver disase (CFLD) is umbrella term for:
  - elevated liver enzymes
  - hepatic steatosis
  - neonatal cholestasis
  - focal biliary cirrhosis
  - multilobular cirrhosis
  - cholangiopathy
- Clinically important CFLD includes biliary cirrhosis and portal hypertension

## Cystic Fibrosis

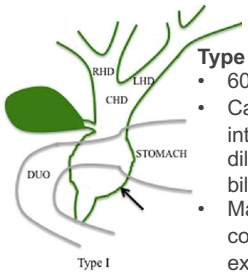
- 25% of CF patients with portal hypertension have cirrhosis, rest have non-cirrhotic portal hypertension (pre-sinusoidal from obliterative venopathy)
- Endoscopy complicated by increased risk of anesthesia
- Variceal band ligation preferred to NSBB because of bronchoconstriction
- UDCA most commonly used drug for CFLD despite controversy/limited data
- LT alone contraindicated in:
  - active pulmonary infection
  - FEV1 <50%
  - extensive pulmonary fibrosis
  - pulmonary hypertension (>35 mmHg)
- Standardized MELD/PELD exception for LT:
  - Diagnosis confirmed by genetic analysis and FEV1 <40% predicted
  - ≥18 years: MMaT-3
  - 12-17 years: MMaT
  - <18 years: MPaT




## Fibrocystic Diseases – Choledochal Cysts

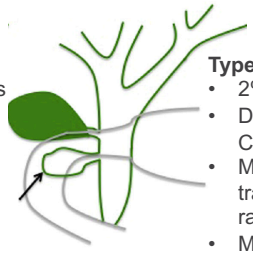
- Choledochal cysts are rare congenital cystic dilations of biliary tract
- Complications: malignant transformation, cholangitis, pancreatitis, cholelithiasis
- Incidence: 1/100,000-1/150,000 in Western countries, 1/13,000 in Japan
- 80% diagnosed in infants/young children, F:M = 4:1
- Anomalous pancreaticobiliary duct union (APBDU) in 30%-70%
- Congenital cardiac abnormalities in 31% of pediatric patients
- 10-30% incidence of cancer
  - Rare in children
  - Dismal prognosis
  - Most common in types I and IV, rare in II, III, V
- MRCP is diagnostic modality of choice for infants/children
  - Direct communication between biliary tree and cystic duct

## Fibrocystic Diseases – Choledochal Cysts

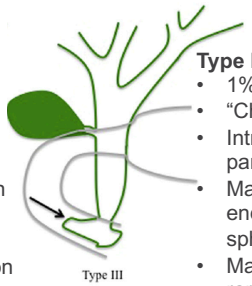


Type I

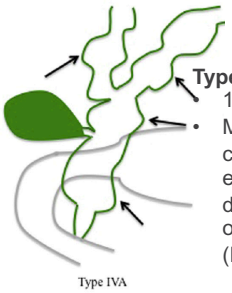
**Type I**
- 60%-80% of CCs
- Can include mild intrahepatic dilatation from biliary stasis
- Managed with complete extrahepatic bile duct excision + R-en-Y HJ


Type II

**Type II**
- 2% of CCs
- Diverticula of CBD
- Malignant transformation rare
- Managed by simple excision or diverticu-lectomy

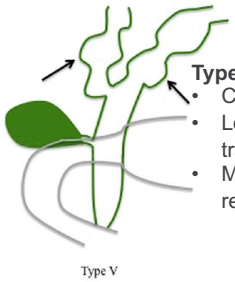

Type III

**Type III**
- 1%-4% of CCs
- "Choledochocele"
- Intraduodenal at pancreaticobiliary jcn
- Managed primarily endoscopically (e.g., sphincterotomy)
- Malignant transformation rare


Type IVA

**Type IV**
- 15%-20% of CCs
- Managed with complete extrahepatic bile duct excision (IVB) or hepatectomy (IVA)


Type IVB


Type V

**Type V**
- Caroli's Disease
- Low risk of malignant transformation (7%)
- Managed by liver resection or LT



## Fibrocystic Diseases – Caroli's Disease

- Due to ductal pate malformation, associated with polycystic kidney disease
- 1/1,000,000, F:M = 1:1, >80% before age 30, can be asymptomatic up to 20
- Main presentation: recurrent acute cholangitis
- Classic triad (rare, usually children): abdominal pain, jaundice, RUQ mass
- Also: liver abscesses, intra/extrahepatic stones, acute/chronic pancreatitis, cholangiocarcinoma, portal hypertension, cirrhosis
- Differential: PSC, recurrent pyogenic cholangitis, polycystic liver disease
- Caroli Syndrome = type V CCs + congenital hepatic fibrosis
- "Central dot sign": portal vein enhancement surrounded by dilated intrahepatic bile ducts on MRCP or contrast CT
- Surgical management or LT indicated because of cholangitis or liver disease rather than malignant potential

## Familial Amyloid Polyneuropathy (FAP)

- Multisystem condition due to mutations in transthyretin (TTR) gene (formerly prealbumin), now called hereditary transthyretin amyloidosis (hATTR)
- Over 120 TTR variants, Val30Met most common
- Involves sensory-motor and autonomic nervous system, heart, kidney, ocular vitreous, death within 10 years of clinical presentation
- Diagnosis: tissue biopsy w/Congo red staining, IHC or MS to confirm TTR
- Treatment includes LT (>90% of circulating TTR produced in the liver)
- Liver is otherwise structurally/functionally normal
- FAP is most common source of domino livers
- Iatrogenic FAP in domino liver recipient, often at accelerated pace (7-9 yrs)
- Standardized MELD exception (all of the following):
  - Waitlisted for heart transplant or echo with EF >40%, can walk without assistance, confirmed TTR gene mutation, biopsy-proven amyloid




## Erythryopoietic Protoporphyria (EPP)

- Cutaneous porphyria, overproduction of protoporphyrin by bone marrow
- Complex inheritance, M:F = 1:1, 2 types:
  - Ferrochelatase deficiency (“classical” EPP)
  - Delta aminolevulinic acid synthase 2 hyperactivity (X-linked protoporphyria)
- Symptoms start in early infancy: painful photosensitivity without blisters
  - Stinging, burning, itching on sun-exposed skin, mild swelling/erythema, hyperkeratosis/ lichenification with repeated injury, urine color is normal
- Biliary system exposed to high concentrations of protoporphyrin, highly toxic
  - Cholelithiasis (pigment gallstones) before age 30 (20% of patients)
  - Biliary obstruction, inflammation, fibrosis, cirrhosis, liver failure
- Diagnosis: fluorescent erythrocytes (flurocytes), measure total blood porphyrin (high free protoporphyrin), increased fecal protoporphyrin
- Treatment: Avoid sunlight, oral beta-carotene, activated charcoal/cholestyramine, afamelanotide (alpha-melanocyte-stimulating hormone analogue), LT + BMT

# References


### Hereditary Hemorrhagic Telengiectasia

- DeLeve LD et al. Vascular disorders of the liver (AASLD Practice Guideline). Hepatology 2009;49:1729-64 https://aasldpubs.onlinelibrary.wiley.com/doi/epdf/10.1002/hep.22772
- Garcia-Tsao G. Liver involvement in hereditary hemorrhagic telangiectasia (HHT). J Hepatol 2007;46:499-507 https://www.journal-of-hepatology.eu/action/showPdf?pii=S0168-8278%2806%2900687-8
- EASL clinical practice guidelines: Vascular diseases of the liver. J Hepatol 2015;64:179-202 https://www.clinicalkey.com/service/content/pdf/watermarked/1-s2.0-S0168827815005474.pdf?locale=en_US&searchIndex=

### Wilson Disease

- Robert EA and Schilsky ML. Diagnosis and treatment of Wilson's Disease: an update (AASLD Practice Guideline). Hepatology 2008;47:2089-2111 https://www.aasld.org/sites/default/files/2019-06/Wilson-Disease2009.pdf

### Alpha-1-Antitrypsin Deficiency

- Strnad P et al. Alpha-1-antitrypsin deficiency. N Engl J Med 2020;382:1443-1455 https://www.nejm.org/doi/pdf/10.1056/NEJMra1910234
- Patel D and Teckman JH. Alpha-1-antitrypsin deficiency liver disease. Clin Liv Dis 2018;22:643-655 https://www.clinicalkey.com/service/content/pdf/watermarked/1-s2.0-S1089326118300618.pdf
- Nelson DR et al. Diagnosis and management of patients with alpha-1-antitrypsin (A1AT) deficiency. Clin Gastroenterol Hepatol 2012;10:575-580 https://www.clinicalkey.com/service/content/pdf/watermarked/1-s2.0-S1542356511013899.pdf

### Iron Overload Syndromes

- Bacon BR et al. Diagnosis and management of hemochromatosis: 2011 practice guideline by the American Association for the Study of Liver Diseases. Hepatology 2011;54:328-343 https://aasldpubs.onlinelibrary.wiley.com/doi/pdf/10.1002/hep.24330
- Kowdley KV et al. ACG clinical guideline: hereditary hemochromatosis. Am J Gastroenterol 2019;1202-1218 https://journals.lww.com/ajg/pages/articleviewer.aspx?year=2019&issue=08000&article=00011&type=Fulltext
- Pietrangelo A. Hereditary hemochromatosis: pathogenesis, diagnosis, and treatment. Gastroenterol 2010;139:393-408 https://www.gastrojournal.org/action/showPdf?pii=S0016-5085%2810%2900872-3






# References


### Mitochondrial Defect

- Lee WS and Sokol RJ. Liver disease in mitochondrial disorders. Semin Liv Dis 2007;27:259-273 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3888320/pdf/nihms-516081.pdf

### Cystic Fibrosis

- Kamal N et al. Liver disease in patients with cystic fibrosis. Curr Opin Gastroenterol 2018;34:146-151 https://journals.lww.com/co-gastroenterology/Abstract/2018/05000/Liver_disease_in_patients_with_cystic_fibrosis.6.aspx
- Sakiani S. Hepatic manifestation of cystic fibrosis. Clin Liv Dis 2019;23:263-277 https://www.clinicalkey.com/service/content/pdf/watermarked/1-s2.0-S1089326118301120.pdf?locale=en_US&searchIndex=

### Fibrocystic diseases

- Soares KC et al. Choledochal cysts: presentation, clinical differentiation, and management. J Am Coll Surg 2014;219:1167-1180 https://www.journalacs.org/action/showPdf?pii=S1072-7515%2814%2900504-3
- Ronnekleiv-Kelly SM et al. Management of choledochal cysts. Curr Opin Gastroenterol 2016;32:225-231 https://journals.lww.com/co-gastroenterology/Fulltext/2016/05000/Management_of_choledochal_cysts.14.aspx
- Yonem O and Bayraktar Y. Clinical characteristics of Caroli's disease. World J Gastroenterol 2007;13:1930-1933 https://www.wjgnet.com/1007-9327/full/v13/i13/1934.htm

### Familial Amyloid Polyneuropathy

- Luigetti M et al. Diagnosis and treatment of hereditary transthyretin amyloidosis (hATTR) polyneuropathy: current perspectives on improving patient care. Ther Clin Risk Manag 2020;16:109-123 https://www.dovepress.com/front_end/cr_data/cache/pdf/download_1593983412_5f0241b46780f/tcrm-219979-diagnosis-and-treatment-of-hereditary-transthyretin-amyloido.pdf
- Kitchens WH. Domino liver transplantation: indications, techniques, and outcomes. Transplant Rev 2011;25:167-177 https://www.clinicalkey.com/service/content/pdf/watermarked/1-s2.0-S0955470X11000553.pdf?locale=en_US&searchIndex=

### Erythropoietic Protoporphyria (EPP)

- Bissell DM et al. Porphyria. N Engl J Med 2017;377:862-872 https://www.nejm.org/doi/pdf/10.1056/NEJMra1608634
- Lecha M et al. Erythropoietic protoporphyria. Orphanet J Rare Dis 2009;4:19 https://ojrd.biomedcentral.com/track/pdf/10.1186/1750-1172-4-19

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