Chapter 5. Intra-Hepatic Cholestasis

5.1 Cholestatic Liver Disease

Causes

- **Immune**
  - **Primary Biliary Cholangitis (PBC)** *[see Chapter 5.2]*
  - **Primary Sclerosing Cholangitis (PSC)** *[see Chapter 5.2]*
  - **Acute or chronic cellular rejection** of liver transplant allograft *[see Chapter 15]*
  - **Graft Versus Host Disease (GVHD)** in bone marrow transplant recipients
- **Inflammatory**
  - **Alcohol hepatitis** *[see Chapter 7.1]*
  - **Drug induced liver injury (DILI)** *[see Chapter 9.2]*
  - **Sarcoidosis** – is an inflammatory disease which causes granulomas in the lungs and liver and is associated with lymphadenopathy, skin rashes, and arthritis
- **Infection**
  - **Viral hepatitis** *[see Chapter 6]*
    - Can have a cholestatic phase during resolution of an acute hepatitis (e.g. HAV)
    - Some viruses like cytomegalovirus (CMV) tend to cause more cholestasis
  - **Sepsis**
    - **The most common cause of cholestasis in hospitalized patients**
    - Severe systemic infections may lead to cholestasis, with or without jaundice, as inflammatory cytokines interfere with bile excretion

    - Liver biopsy (not usually required) shows **cholangitis lenta**

- **Infiltrative**
    - **Amyloidosis** – is related to the deposition of insoluble protein in organs (kidney, heart, liver, GI tract, etc.) and can be primary or secondary
    - **Malignancy** – the liver can be diffusely infiltrated by lymphoma or metastatic disease
    - **Granulomatous hepatitis** – is a pathologic diagnosis (granulomas on liver biopsy) which can be related to infections, drugs, immune conditions, malignancy or idiopathic (see below)
- **Congenital**
    - **Progressive Familial Intrahepatic Cholestasis (PFIC)** are rare genetic causes of cholestasis related abnormalities of bile transporters *[see Chapter 1.6]*
    - **PFIC-1** is from a mutation in FIC-1 (protein responsible for phospholipid translocation) and mutations in this gene also cause **benign recurrent intrahepatic cholestasis (BRIC)**
    - **PFIC-2** is from a mutation in the bile salt export pump (BSEP)
    - **PFIC-3** is from a mutation in MDR3 (multi-drug resistance protein 3) which is the phosphatidylcholine translocator
- **Pregnancy**
    - **Intrahepatic cholestasis of pregnancy (ICP)**
        - Occur in up to 1.5% of pregnancies (more common with twins)
        - Presents with intense pruritus, ALT > ALP and ↑ serum bile acids, in the 3rd trimester
        - Mutations in MRD3 can be seen 15%

- ↑ risk of premature labour and ↑ risk of stillbirths
- Moms should receive ursodeoxycholic acid (UDCA) and cholestyramine
- Vitamin K is given before delivery to reduce bleeding complications
- It recurs in >50% of subsequent pregnancies

Diagnosis

- Patients presenting with cholestasis need an abdominal ultrasound to rule out extra-hepatic obstruction of the bile duct or infiltration of the liver
- Alcohol and medications (including OTC drugs and herbals) should be excluded by history
- **Anti-mitochondrial antibody (AMA)** should be done to rule out PBC *[see Chapter 5.2]*
- An **MRCP** can be done to rule out PSC *[see Chapter 5.3]*, and is especially important if patient has a history of colitis
- If these tests are negative, the patient may need a **liver biopsy** for diagnosis
  - **Liver biopsy** may show features of cholestasis
    - Feathery degeneration of hepatocytes
    - Accumulation of bile with hepatocytes
    - Bile plugs in bile ducts
    - There may be granulomas present

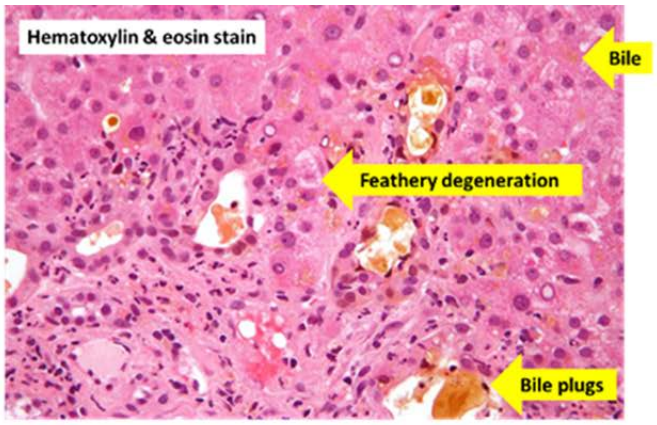
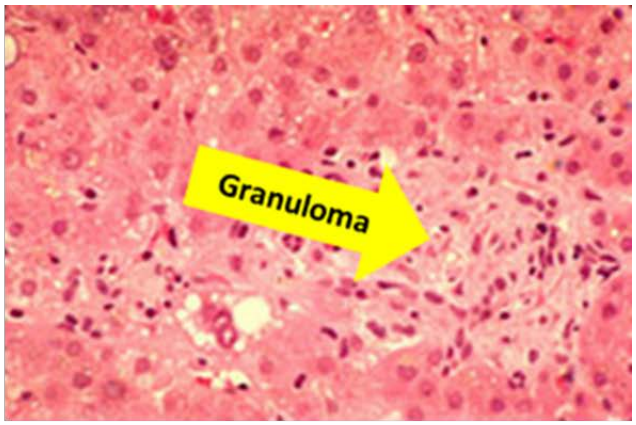


Image Source: http://en.wikipedia.org/wiki/Elevated_alkaline_phosphatase



- **Granulomatous Hepatitis** has many causes
  - Infections – TB, coccidiomycosis, schistosomiasis, cytomegalovirus, Q fever, syphilis
  - Drugs – sulfonamides, allopurinol, etc.
  - Immune – PBC, sarcoidosis
  - Malignancy – Hodgkin's lymphoma
  - Idiopathic

Symptoms & Management

- **Symptoms of Cholestasis** (some are seen with chronic cholestasis*)
  - Pruritus (itchiness), fatigue*, dark urine, pale stools, RUQ pain, fever, weight loss
- **Signs of Cholestasis**
  - Excoriations, hyperpigmentation*, xanthoma* (cholesterol deposits in skin), xantholasma* (cholesterol deposits on eyelids)

- **Fat soluble vitamin deficiencies** can develop (replace with ADEK vitamins)
  - **A** → night blindness
  - **D** → metabolic bone disease, immune dysfunction
  - **E** → neurologic symptoms
  - **K** → bleeding & bruising, ↑ INR
- **Metabolic bone disease** can develop even in the absence of vitamin D deficiency
  - Osteopenia (thin bones), osteoporosis (brittle bones with bone density < 2.5 standard deviations below median for healthy controls), osteomalacia (soft bones)
  - Managed with calcium, vitamin D supplementation and bisphosphonates (bone building medications) or parathyroid hormone
- **Pruritus** management
  - Pruritus can be one of the most troubling symptoms
  - First line agents include **sedating antihistamines** (take at bedtime as they cause drowsiness) and **cholestyramine** which binds the pruritogen (component of bile that causes itching) so that it is passed in the stool instead of undergoing enterohepatic circulation
  - Second line agents include **rifampin** (antibiotic which upregulate enzymes in the liver that metabolize the pruritogen), **naloxone or naltrexone** (narcotic reversal agents which blocks the increased opioid tone associated with chronic cholestasis), **sertraline** (Zoloft® an anti-depressant which is a selective serotonin reuptake inhibitor)
  - Third line therapies include **plasmapheresis** and ultimately **liver transplantation**

- **Fatigue** management
  - Can be severe (similar to patients with multiple sclerosis) and treatment is difficult
  - Must rule out depression, sleep disturbance and hypothyroidism
  - Regular exercise helps
  - You can use low doses of anti-depressants even in the absence of depression

5.2 Primary Biliary Cholangitis (formerly called primary biliary cirrhosis)

Epidemiology & Pathophysiology

- **Epidemiology**
  - Incidence = 30 per million
  - Prevalence = 227 per million in Calgary Health Region
  - Disease of predominately middle aged women
    - 9:1 female to male ratio
    - Median onset of age 50-60 years
- **Pathophysiology**
  - Cause is unknown
  - Autoimmune condition in which a genetically susceptible host has a dysregulated immune response to an unknown environmental trigger (? virus)

Diagnosis & Natural History

- **Diagnosis**
  - Cholestasis (increased ALP) with no significant alcohol, drug history or other chronic liver disease and normal bile ducts on ultrasound

- **Anti-mitochondrial antibody (AMA)** is positive in 95% and is diagnostic
  - Immunoblot for pyruvate dehydrogenase complex (PDC) subunits are more specific and can be ordered when you suspect PBC but the AMA is negative
- May have non-specific elevation of immunoglobulin M (IgM) and high cholesterol as part of chronic cholestasis (**NOTE:** not at increased risk of cardiovascular disease)

- **Liver biopsy**
  - Is <u>not</u> needed to make diagnosis if AMA is positive
  - A liver biopsy should be done if AMA is negative or if there are features of overlap with autoimmune hepatitis (AIH), such high ALT, increased IgG, positive anti-nuclear and/or anti-smooth muscle antibodies (ANA, ASMA)
  - Classic finding on biopsy is a **florid duct lesion** with granulomatous destruction of the bile ducts (BD)
  - Stages 1 – 4 (**REMEMBER** not all patients have cirrhosis)

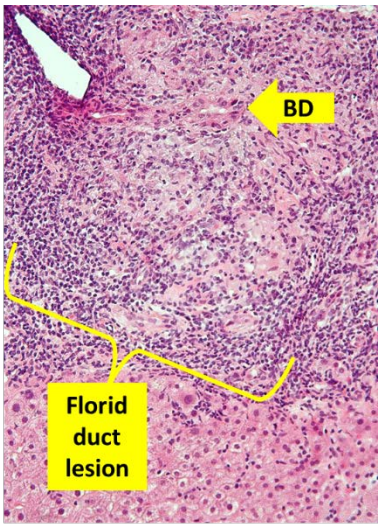


Image Source: en.wikipedia.org

- **Clinical features**
  - Can be asymptomatic
  - Frequently have other autoimmune conditions
  - Fatigue and pruritus are common
  - Sicca syndrome = dry eyes and dry mouth
  - Metabolic bone disease is common (screen with DEXA to assess bone mineral density)
  - If cirrhotic can progress to liver failure and may develop hepatocellular carcinoma (HCC)

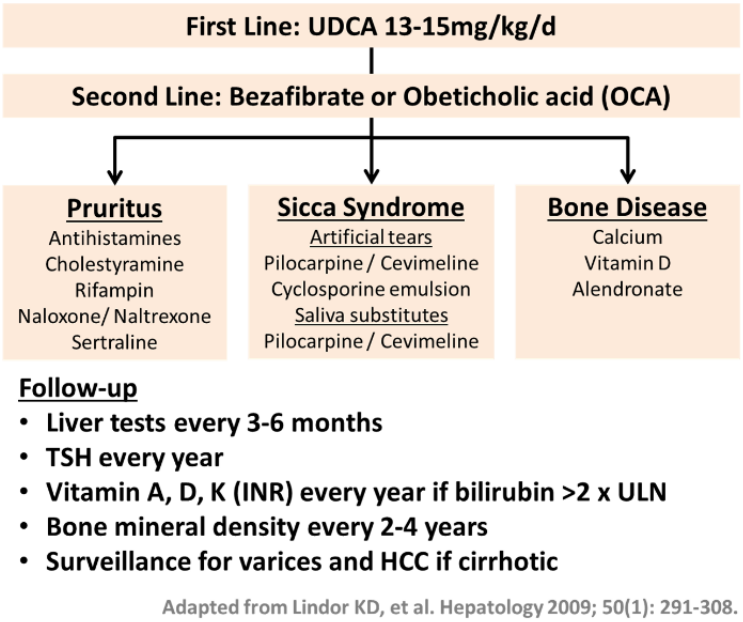
- Portal hypertension and bleeding from varices can develop early

- **Natural History**
  - Shorter survival than controls with a 10 year survival of 50-70%
  - Median survival 5-8 years if symptomatic
  - Poor predictors include older age at diagnosis, ↑ fibrosis stage, ↑ bilirubin, presence of symptoms and lack of response to ursodeoxycholic acid (UDCA)
  - Models have been developed to predict survival (e.g. Mayo Risk Score based on age, bilirubin, albumin, INR, edema and need for diuretics)

Treatment

- **Ursodeoxycholic acid (UDCA)** at a dose of 13-15 mg/kg once daily has been shown to slow histologic progression, reduces formation of varices and improves survival free of liver transplant (LT)
  - 40% normalize ALP and these patients have the same natural history as controls
  - Well tolerated but can cause diarrhea and weight gain
  - Important to separate from cholestyramine by >2 hours as this will bind UDCA
  - Unfortunately, has minimal impact on symptoms such as fatigue or pruritus
- **Second line therapy** (UDCA non-responders)
  - **Obeticholic acid (OCA)** = FXR agonist which influences bile acid synthesis and secretion, shown to improve ALP, but can induce pruritus
  - Fibrates (**bezafibrate**) can normalize ALP in many not responding to UDCA
  - Budesonide = corticosteroid with high first pass metabolism, but still can have steroid related side effects (e.g. worsen bone density)

- Also manage pruritus, sicca syndrome and metabolic bone disease (see below)



5.3 Primary Sclerosing Cholangitis

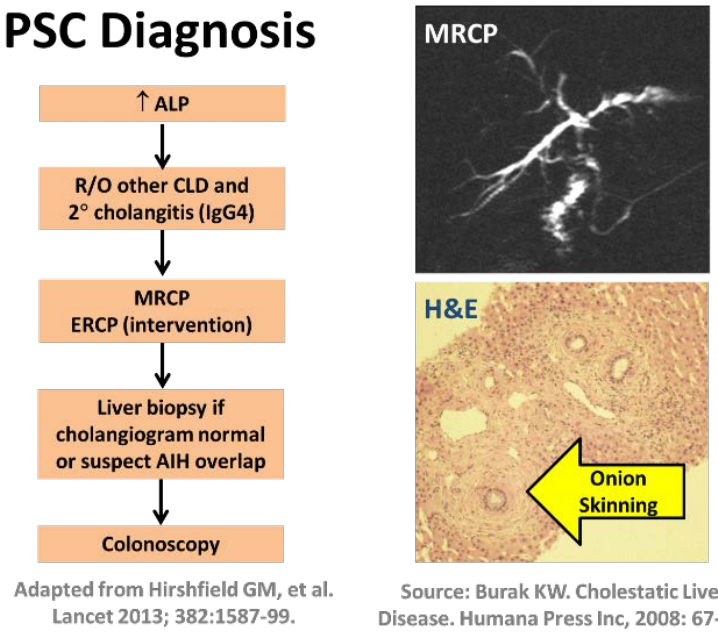
Epidemiology & Pathophysiology

- **Epidemiology**
  - Incidence = 10-20 per million
  - Prevalence = 160 per million
  - Disease seen in association with inflammatory bowel disease (IBD) of the colon
  - 60-80% have Ulcerative Colitis (UC) or Crohn's Disease (CD) in the colon
  - Complicates <5% of UC patients
  - Male to female ratio 2:1
  - Median onset of age 40-50 years

- **Pathophysiology**[3]
  - Cause is unknown
  - **Genetically susceptible host** = half of identified genes are also associated with IBD and half are associated with other autoimmune diseases
  - **Environmental factors** = association with colitis, toxic bile acids, recurrent infections, ischemia to bile ducts
  - **Dysregulated immune system** = T cells from the inflamed colon expressing α4β7 integrin track to the liver where MADCAM1 is expressed on endothelium

Diagnosis & Natural History

- **Diagnosis**
  - Suspect if elevated ALP, especially in the presence of IBD
  - Rule out other chronic liver disease, AMA should be negative, and exclude secondary causes of cholangitis (IgG4 disease)
  - Autoantibodies are frequently present but are not specific (pANCA most common)
  - **MRCP** shows strictures and areas of dilatation or **"chain of lakes"** appearance
  - **Liver biopsy** is performed if MRCP is normal (to look for small duct PSC) or if suspicious for overlap with autoimmune hepatitis (AIH-PSC overlap frequent in children)
    - Classic finding is **"onion-skin fibrosis"** around the bile duct (see below), which is pathognomonic but is only present in one-third of biopsies



Adapted from Hirshfield GM, et al. Lancet 2013; 382:1587-99.

Source: Burak KW. Cholestatic Liver Disease. Humana Press Inc, 2008: 67-83.

- **Clinical features**
  - Can be asymptomatic
  - Fatigue, pruritus and metabolic bone disease are common
  - Can progress to cirrhosis with liver failure
  - PSC patients often have a specific phenotype of IBD
    - Extensive colitis with predominately right-sided activity, rectal sparing, and backwash ileitis
    - Mild or quiescent course
    - ↑ risk of colorectal neoplasia
    - ↑ risk of pouchitis if ileo-pouch anal anastomosis (IPAA)
    - ↑ risk of peristomal varices after ileostomy if cirrhotic
  - They have a higher risk of malignancies
    - 50% risk of **colorectal neoplasia** at 25 years (versus 10% if colitis without PSC)

- 10% lifetime risk of **cholangiocarcinoma (CCA)** *[see Chapter 13.2]*
- Higher risk of **gallbladder cancer,** so patients should have yearly ultrasounds, and if GB polyps found they should undergo cholecystectomy

- **Natural History**
  - Asymptomatic patients have decreased survival compared to healthy controls
  - If symptomatic, median survival (without liver transplant) is approximately 8 - 10 years
  - Prognosis of cholangiocarcinoma is very poor

Treatment

- There is **no effective medical therapy** for PSC and **liver transplant** is the only lifesaving therapy[4]
  - Many immunosuppressive agents have been shown not to be effective
  - Vancomycin (oral antibiotic) has been shown to lower ALP but impact on clinical outcomes are unknown
  - UDCA is controversial as low doses (13-15mg/kg/d) reduces the ALP but does NOT improve survival and high doses (25-30mg/kg/d) also lower ALP but actually increased the chance of death or need for transplant in placebo-controlled trials
    - One approach is to start low dose UDCA and if ALP normalizes then it can be continued, but if ALP remains high it could be stopped and clinical trials should be explored
- **Cholangitis (ascending cholangitis)**
  - Patient presents with fever, RUQ pain and jaundice

- Infection in the obstructed biliary system typically with gram negative bacteria, enterococcus, bacteroides or clostridia
- Treatment is with ciprofloxacin or piperacillin / tazobactam
- It is important to look for dominant strictures (which can be treated by balloon dilation or short-term stenting) and rule out cholangiocarcinoma by doing brushings or biopsy[5]
- If recurrent bouts of cholangitis you should give long-term prophylaxis with rotating oral antibiotics using ciprofloxacin, amoxicillin-clavulanic acid or trimethoprim/sulfamethoxazole (TMP-SMX)

Abbreviations

Anti-TNF – anti-tumour necrosis factor

BRIC – benign recurrent intrahepatic cholestasis

CD – Crohn's disease

CLD – chronic liver disease

DEXA – dual energy X-ray absorptiometry

FXR – farnesoid X receptor

GVHD – graft versus host disease

HCC – hepatocellular carcinoma

HT – hypertension

ICP – intrahepatic cholestasis of pregnancy

IgM – immunoglobulin M

IPAA – ileo-pouch anal anastomosis

LT – liver transplant

NRH – nodular regenerative hyperplasia

OCA – obeticholic acid

pANCA – perinuclear anti-neutrophil cytoplasmic antibodies

PFIC – progressive familial intrahepatic cholestasis

TMP-SMX –trimethoprim/sulfamethoxazole

UC – ulcerative colitis

Figure Citations

Liver Pathology (Cholestasis). Elevated alkaline phosphatase. Retrieved July 20, 2017 from Wikipedia. https://en.wikipedia.org/wiki/Elevated_alkaline_phosphatase

Liver Pathology (Granuloma). Slide courtesy of Dr. Stefan Urbanski.

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