Resident Lecture 2022

ROHIT NATHAN, DO

ROHIT.NATHAN@BANNERHEALTH.COM

- A 44 yo female presents to your clinic as a hospital follow up. She has history of celiac disease and adheres to GFD. She does not drink alcohol, use illicit drugs, or have high risk behaviors. Family history includes sister with Hashimoto thyroiditis. She is generally asymptomatic at this vist.
- She had a recent hospitalization for new onset jaundice and progressive fatigue. Lab evaluation at the time was significant for Tbili 6.5, AST 1700, ALT 1300, ALP 225, INR 1.6, IgG 2200, IgM 60. She had no prior history of liver disease or abnormal LFT.
- After workup, which included imaging, liver biopsy and serologies, she was started on a medication and asked to follow up with her PCP and hepatology.

- A 44 yo female presents to your clinic as a hospital follow up. She has history of **celiac** disease and adheres to GFD. She does not drink alcohol, use illicit drugs, or have high risk behaviors. Family history includes **sister with Hashimoto** thyroiditis. She is generally asymptomatic at this visit.
- She had a recent hospitalization for new onset jaundice and progressive fatigue. Lab evaluation at the time was significant for **Tbili 6.5**, **AST 1700**, **ALT 1300**, ALP 225, INR 1.6, **IgG 2200**, IgM 60. She had **no prior history** of liver disease or abnormal LFT.
- After workup, which included imaging, liver biopsy and serologies, she was started on a medication and asked to follow up with her PCP and hepatology.

- Which of the following medications was she most likely started on prior to discharge:
  - Tenofovir
  - Ursodiol
  - Prednisone
  - Sofosbuvir/Velpatasvir

Autoimmune Hepatitis

Autoimmune Hepatitis

- Immune-mediated inflammatory liver disease
- Can affect all ages, genders, and ethnicities
  - More common in middle age and women
- May have concurrent autoimmune disease (thyroid, celiac)
- Challenging diagnosis to make

Clinical Manifestations

- Variable clinical presentation
  - Asymptomatic (25-34%)
  - Symptomatic/acute severe hepatitis
    - Jaundice; INR 1.5-2
  - Cirrhosis (25-33%)
  - Acute Liver Failure (<5%)

- Non-specific symptoms – **fatigue,** malaise, arthralgias

Diagnostic Testing

- Hepatic function panel: AST/ALT elevated of varying degree, mild to marked
- Increased serum IgG, positive serologic markers
- Exclude other etiologies (viral hepatitis, metabolic, etc)
- Liver biopsy

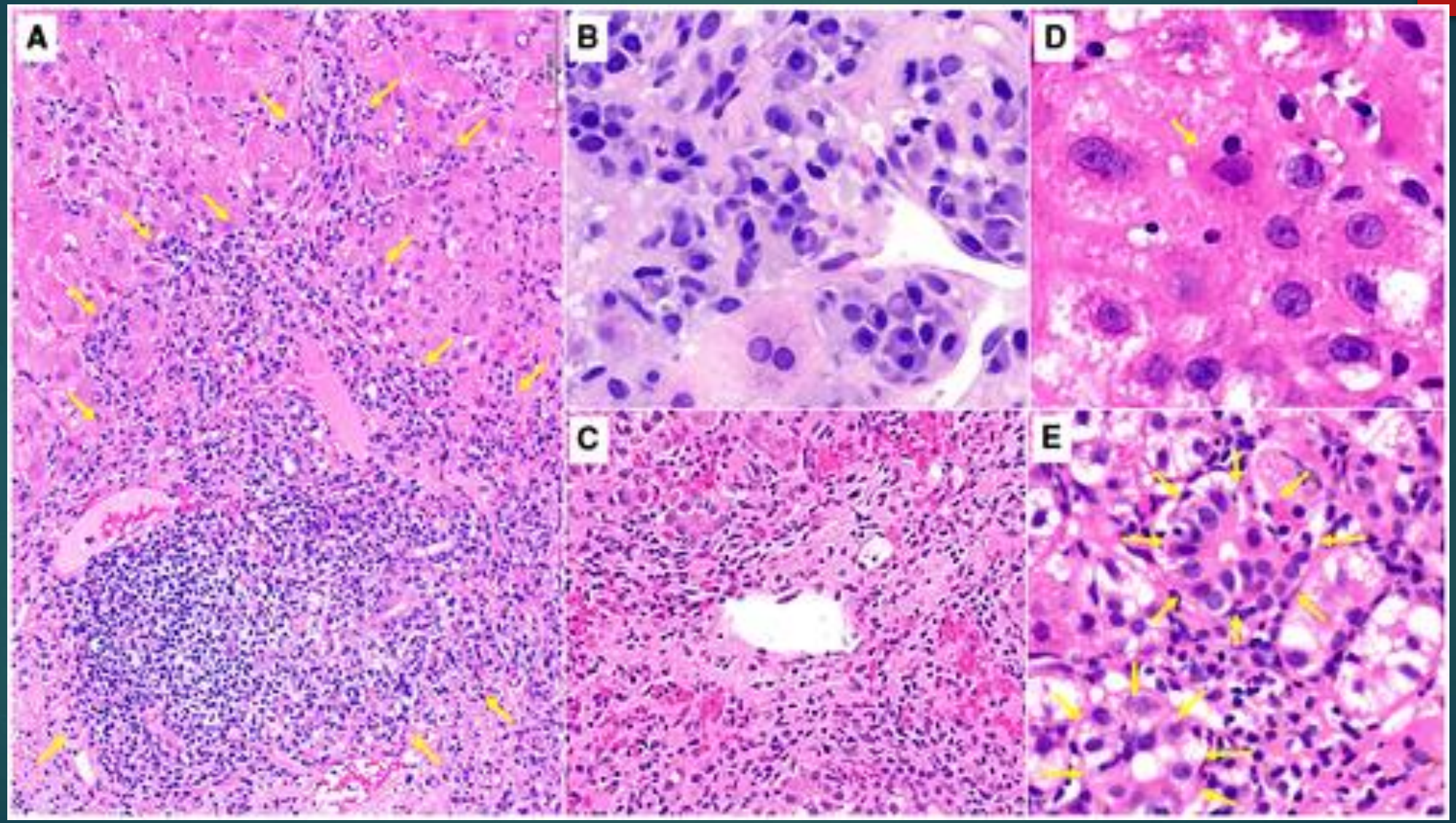
- Which of the following auto-antibodies is most associated with autoimmune hepatitis?
  - Anti-mitochondrial antibody
  - Anti smooth-muscle antibody
  - Anti-centromere antibody
  - Anti tissue transglutaminase antibody

Simplified Diagnostic Criteria for AIH

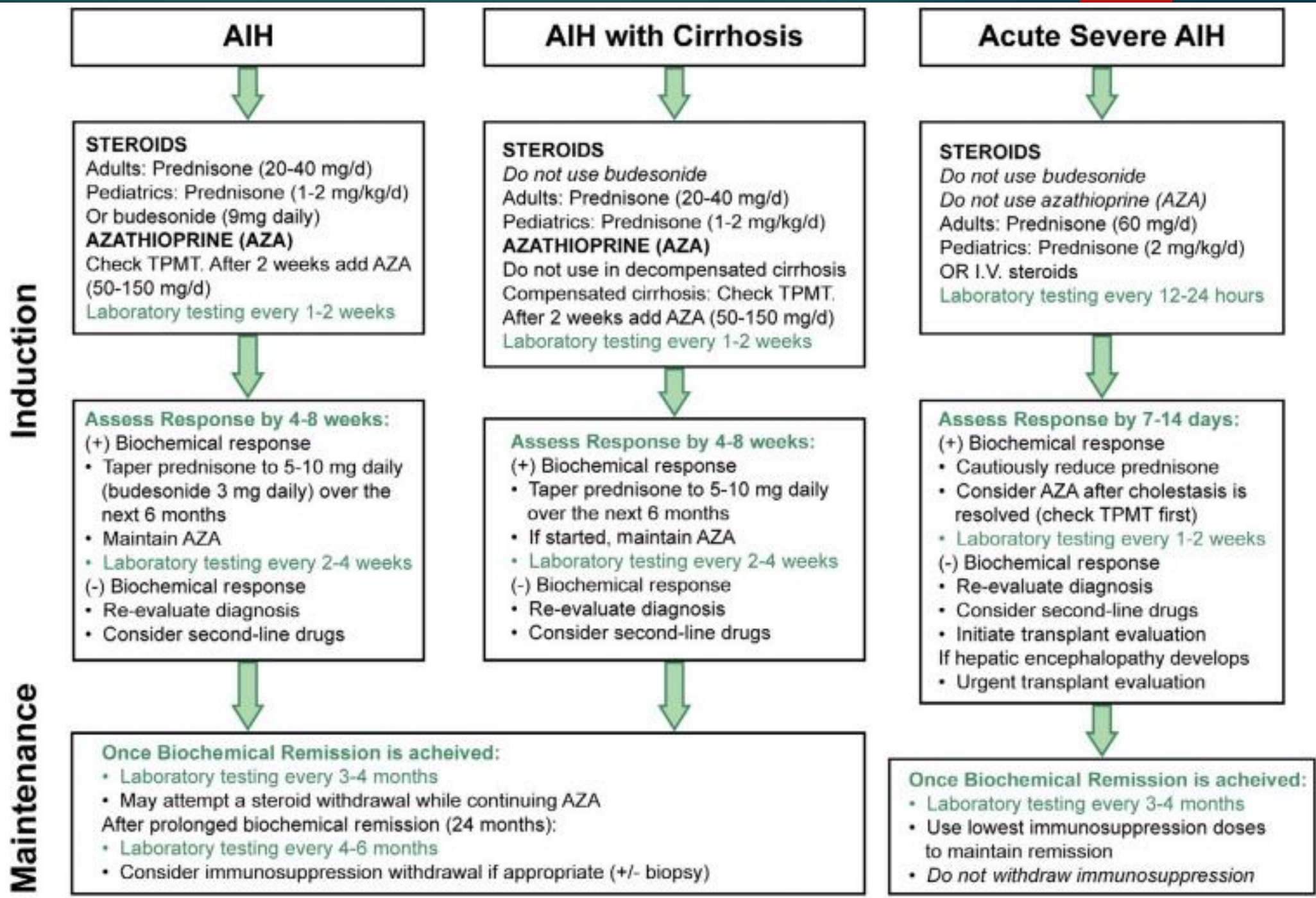
- Good guideline
- Patient doesn't always fit perfectly
  - ~20% seronegative
  - +antibodies in other conditions
- Liver biopsy for definitive dx
  - "interface hepatitis"
  - "plasma cell infiltrate"
- Assess response to treatment

Variable	Cut-off	Points
ANA or SMA	≥1:40	1
ANA or SMA	≥1:80	2[a]
Or anti-LKM-1	≥1:40	
Or SLA	Positive	
IgG	>Upper limit of normal	1
	>1.10 times upper limit of normal	2
Liver histology	Compatible with AIH	1
	Typical of AIH	2
Absence of viral hepatitis	Yes	2

Adapted from Hennes EM, Zeniya M et al. Hepatology 2008;48:169–176.
Score ≥6: probable AIH; ≥7: definite AIH.
ANA, anti-nuclear antibody; SMA, anti-smooth muscle antibody; anti-LKM-1, anti-liver kidney microsomal antibody type 1; SLA, soluble liver antigen; IgG, immunoglobulin G; AIH, autoimmune hepatitis.
[a] Addition of points achieved for all autoantibodies cannot exceed a maximum of 2 points.


A
B
D
C
E

AIH Tx



Mack et al
AASLD Practice Guidelines

Second line treatments

- Mycophenolate Mofetil (contraindicated during pregnancy)
- Calcineurin Inhibitors (tacrolimus, cyclosporine)

AIH and pregnancy

- Ideally, biochemical remission 1 yr prior to conception
- Continue maintenance therapy (AZA and/or prednisone. No MMF!
- Increased risk of flare during pregnancy (5-15%) and post-partum (20-40%)

AIH Potpourri

- Azathioprine can cause bone marrow suppression and hepatotoxicity
  - Can check thiopurine metabolites
- Do not use budesonide in cirrhosis/portal hypertension.
- AIH overlap with other autoimmune liver dz: PBC, PSC
- Check hepatitis B status
- Can be inactive in cirrhosis = no treatment needed
- Can recur after OLT

Drug-Induced AIH

- Usually acute onset with temporal relationship with drug
  - Onset: 1-8 weeks to 3-12 months (nitrofurantoin and minocycline)
- Biopsy looks similar to AIH except may lack fibrosis/cirrhosis
- Treatment:
  - Stop offending agent
  - Start steroids (20-40 mg qd) and taper 3-6 months
- No recurrence after discontinuation of steroids
  - If recurs → suggestive of classic AIH

Bjornnson, Talwalkar et al. Hepatology

Checkpoint Inhibitor Liver Injury

- Immune-related adverse event
- Common culprits: Ipilimumab, Pembrolizumab, Nivolumab
- Lack typical laboratory or histological features of AIH
- Usually improve with steroid therapy

AIH Pearls

- Various presentations: asymptomatic/symptomatic; cirrhosis to ALF
- Antibodies do NOT definitively make dx. Biopsy recommended.
- Initial treatment: Prednisone then AZA (TPMT permitting)
- Gradual withdrawal of pred w/goal of biochemical remission on AZA
- High recurrence rate off IS
- Drug-induced AIH/Checkpoint inhibitor not chronic
  - Resolve with shorter course of steroids without recurrence

- A 44 yo female presents to your clinic as a follow up from recent lab testing. She has history of celiac disease and adheres to GFD. She does not drink alcohol, use illicit drugs, or have high risk behaviors. Family history includes sister with Hashimoto thyroiditis.
- She had presented 2 weeks ago with worsening pruritus over a 6 month span without any rash or initiation of new medications. Topical lotions have not helped.
- Lab testing show TBili 1.3, AST 57, ALT 48, ALP 275, IgG 1400, IgM 250, ANA neg, ASMA neg, AMA positive at 1:640
- RUQ u/s showed an 'echogenic' non cirrhotic appearing liver.

- A 44 yo female presents to your clinic as a follow up from recent lab testing. She has **history of celiac** disease and adheres to GFD. She does not drink alcohol, use illicit drugs, or have high risk behaviors. Family history includes **sister with Hashimoto** thyroiditis.
- She had presented 2 weeks ago with **worsening pruritus** over a 6 month span without any rash or initiation of new medications. Topical lotions have not helped.
- Lab testing show TBili 1.3, AST 57, ALT 48, ALP 275, IgG 1400, **IgM 250,** ANA neg, ASMA neg, **AMA positive at 1:640**
- RUQ u/s showed an 'echogenic' non cirrhotic appearing liver.

- Which of the following other conditions does the patient need to be screened for?
  - Vitamin D Deficiency
  - Coronary artery disease
  - SLE
  - Polymyositis

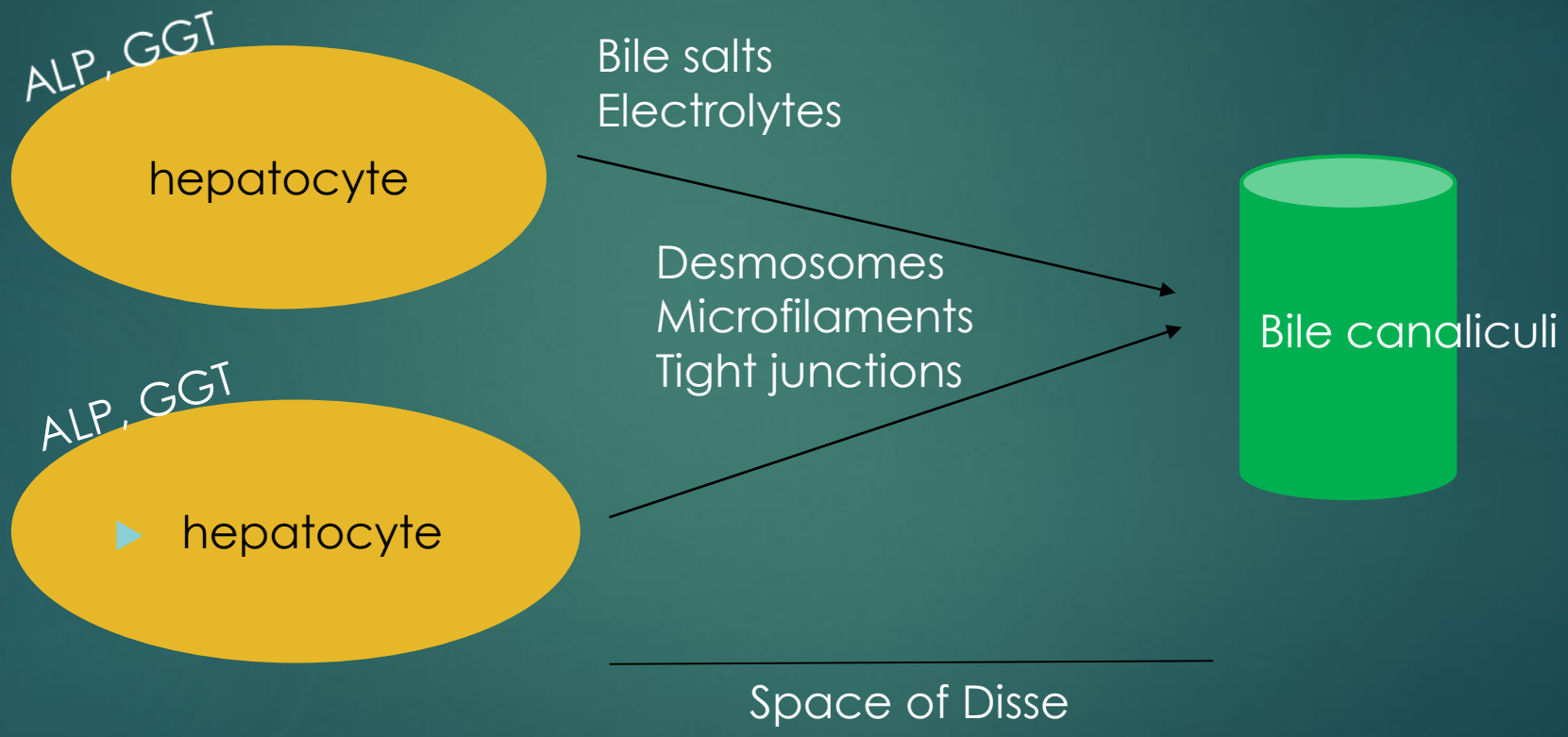
Cholestatic Liver Diseases

Basics

- Impaired bile synthesis
- Impaired bile flow
- Obstructed bile flow

- Intrahepatic
- Extrahepatic

Pathophysiology



Cholestatic liver diseases

- Many
  - Intrahepatic
    - Immune mediated
    - Infectious
    - Malignancy
    - Miscellaneous
  - Extrahepatic
    - structural/anatomic

PBC

- Autoimmune, chronic cholestatic disease
- 95% AMA positive
- Female predominance, ~4:1
- Ethnic predominance, Mediterranean/Hispanic descent
  - 0.5% of Italians AMA positive
- Familial predominance
  - Female FDRs 10-20%

Diagnosis

- Need 2 of 3
  - Elevated ALP
  - Positive AMA
    - ~5% AMA negative (other autoantibodies {sp100, gp120} not checked typically)
  - Histologic findings
- Correlative symptoms
  - Fatigue (50-70%)
  - Pruritus (20-70%, less in UDCA era)
  - RUQ pain (15-20%, nonspecific)

Workup

- Fibrosis assessment
  - Typically LBx initially for confirmation and staging.
  - Elastography
- Concomitant diagnoses?
  - AIH
  - Other autoimmune conditions
  - NAFL/DM2
  - HLD
  - Fat sol Vit deficiency
  - BMD

All PBC pts screen for:
Lipid panel
TSH
Vit D
DEXA
Celiac

PBC, pre vs post UDCA

- UDCA ~1990
- Disease progression was faster pre UDCA
  - Difficult to estimate, many asymptomatic pts found later in disease course.
  - Median survival 16 yrs (asymptomatic) vs 7 yrs (symptomatic)
  - Fibrosis stages progressed on average every 1.5 in paired biopsy studies
- Post UDCA
  - Progression to cirrhosis 13% vs 49% in early longitudinal studies

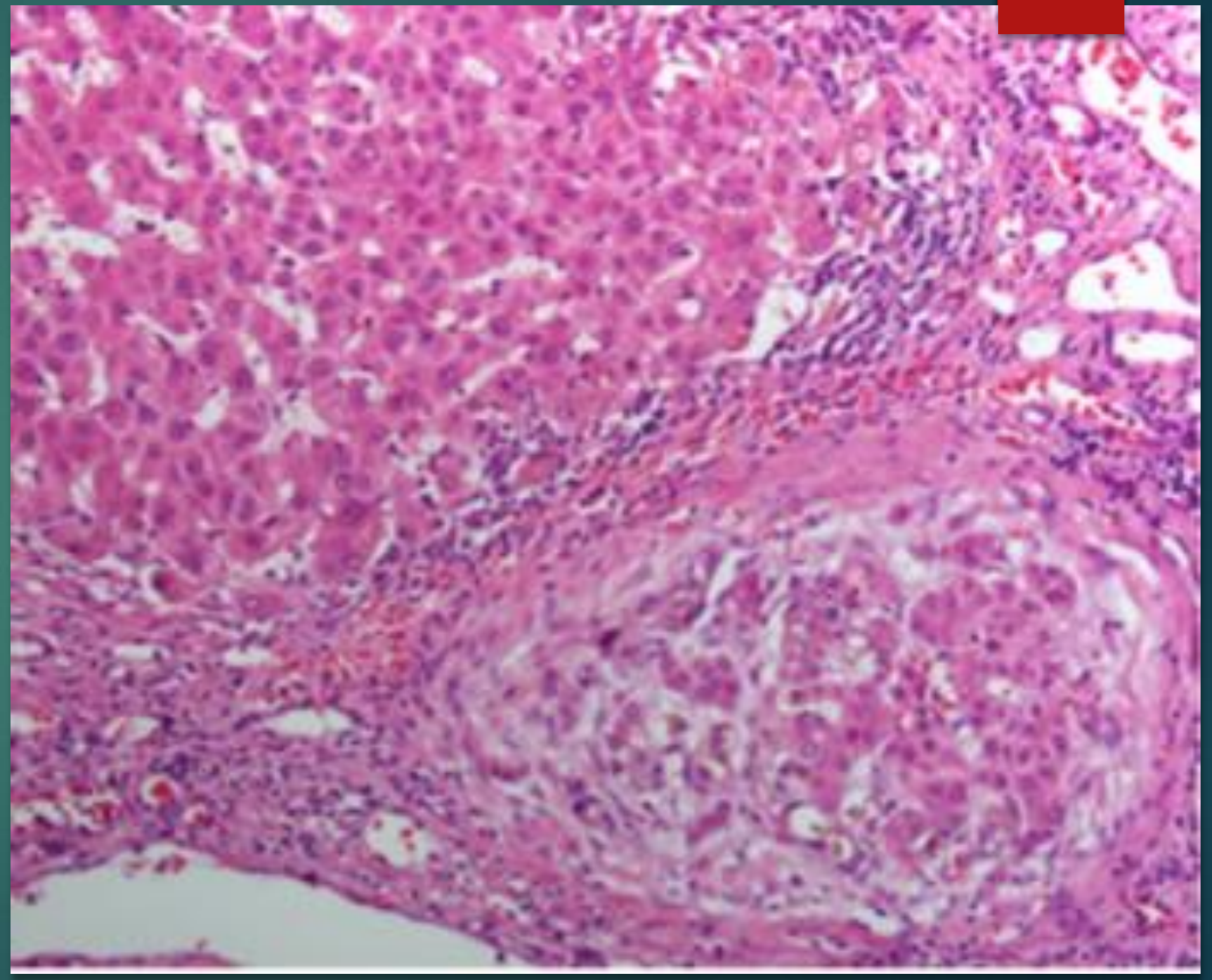
- Which of the following is the approved 2nd line agent for treatment of PBC?
  - Vancomycin
  - Fenofibrate
  - Meformin
  - Obeticholic acid

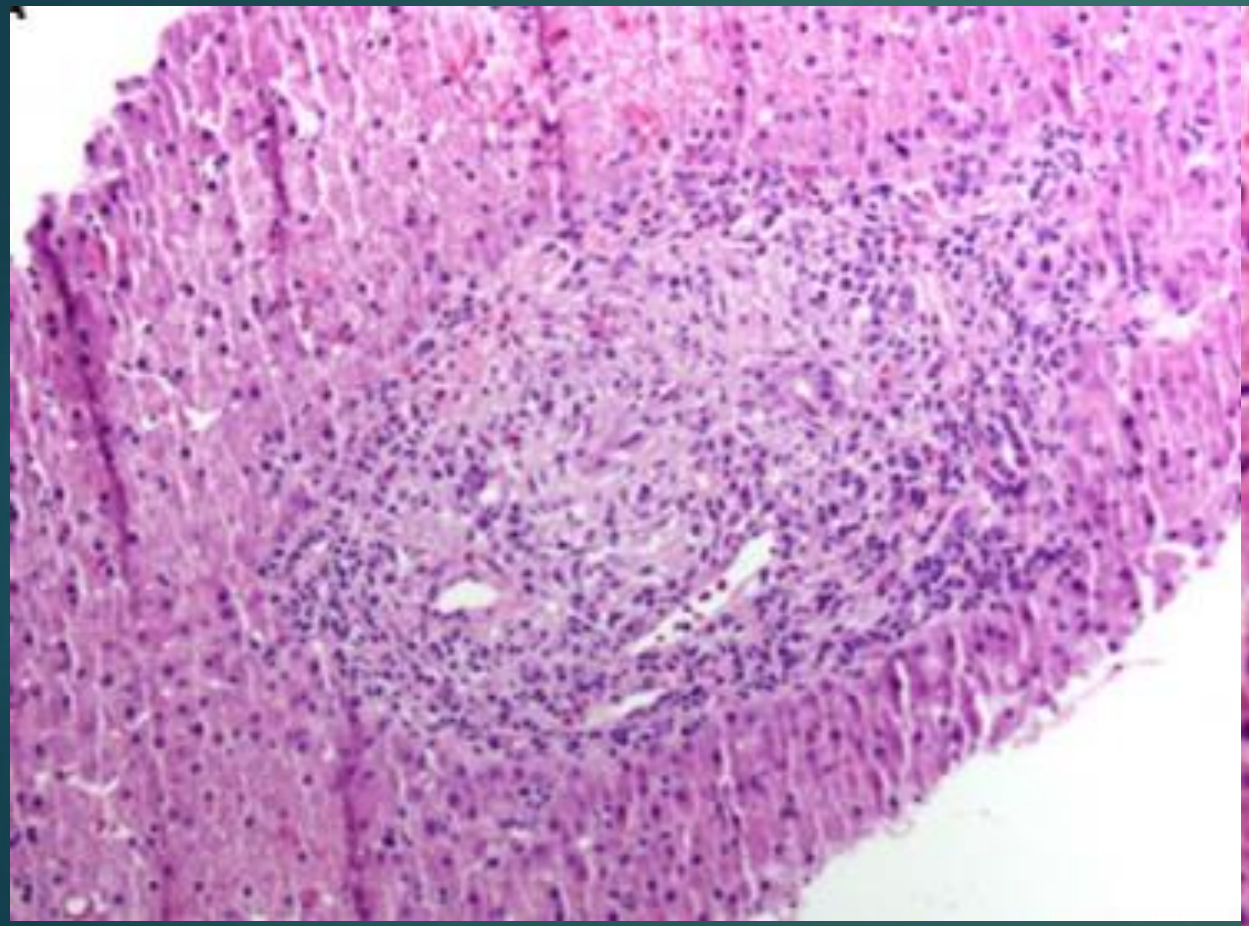
Treatment

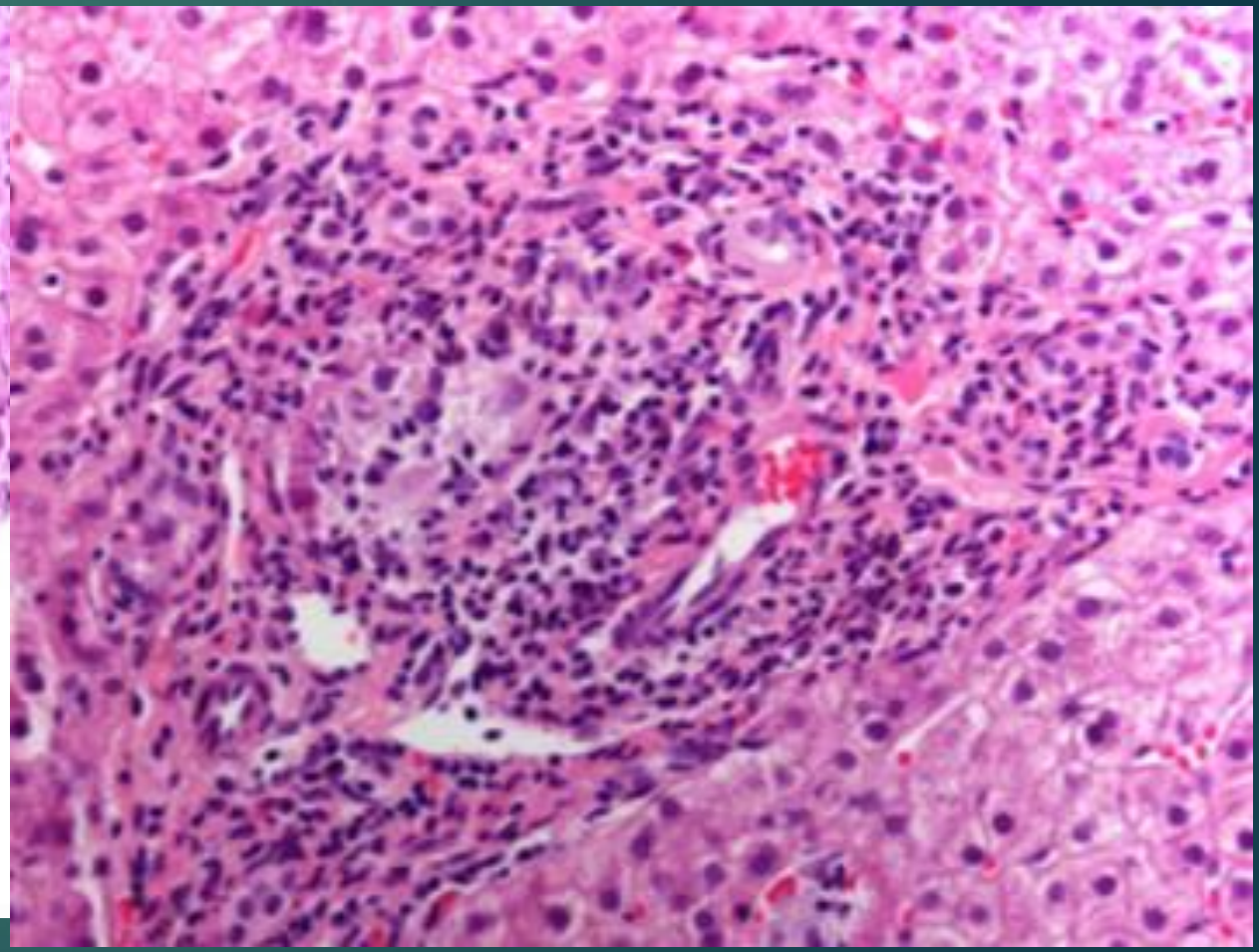
- UDCA
  - Dosing?
  - Side effects?
  - Limiting factors?
- OCA
  - Indication?
  - Evidence?
  - Side effects?

Pre-cirrhotic portal HTN

- NRH
- Mayo score
- Not an indication for transplant







- A 44 yo male presents to your clinic as a follow up from recent lab testing. He has history of celiac disease and adheres to GFD. He does not drink alcohol, use illicit drugs, or have high risk behaviors. Family history includes sister with Hashimoto thyroiditis.
- He had presented 2 weeks ago with worsening pruritus over a 6 month span without any rash or initiation of new medications. Topical lotions have not helped. He also has subjective fever once every few weeks and intermittent diarrhea despite dietary adherence.
- Lab testing show TBili 2.1, AST 57, ALT 48, ALP 475, IgG 1400, IgM 75, ANA neg, ASMA neg, AMA negative
- RUQ u/s showed a normal appearing liver and MRCP showed a 'beaded' appearance of the intrahepatic bile ducts.

- A 44 yo male presents to your clinic as a follow up from recent lab testing. He has history of celiac disease and adheres to GFD. He does not drink alcohol, use illicit drugs, or have high risk behaviors. Family history includes sister with Hashimoto thyroiditis.
- He had presented 2 weeks ago with **worsening pruritus** over a 6 month span without any rash or initiation of new medications. Topical lotions have not helped. He also has **subjective fever** once every few weeks and **intermittent diarrhea** despite dietary adherence.
- Lab testing show TBili 2.1, AST 57, ALT 48, ALP 475, IgG 1400, IgM 75, ANA neg, **ASMA neg, AMA negative**
- RUQ u/s showed a normal appearing liver and MRCP showed a **'beaded'** appearance of the intrahepatic bile ducts.

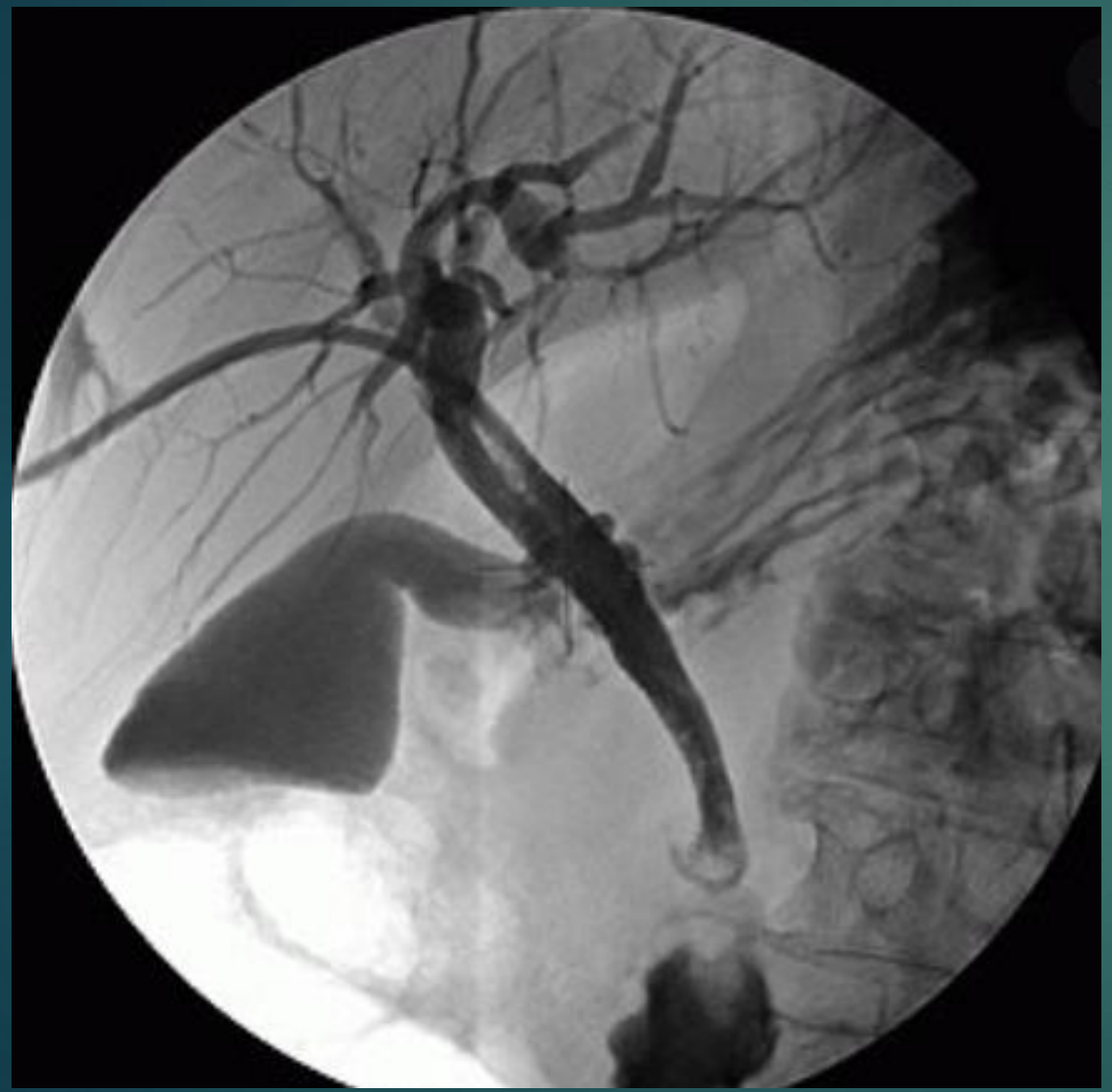
- Which of the following does this patient need to be screened for?
  - Colon cancer
  - Ulcerative colitis
  - Gall bladder cancer
  - All of the above

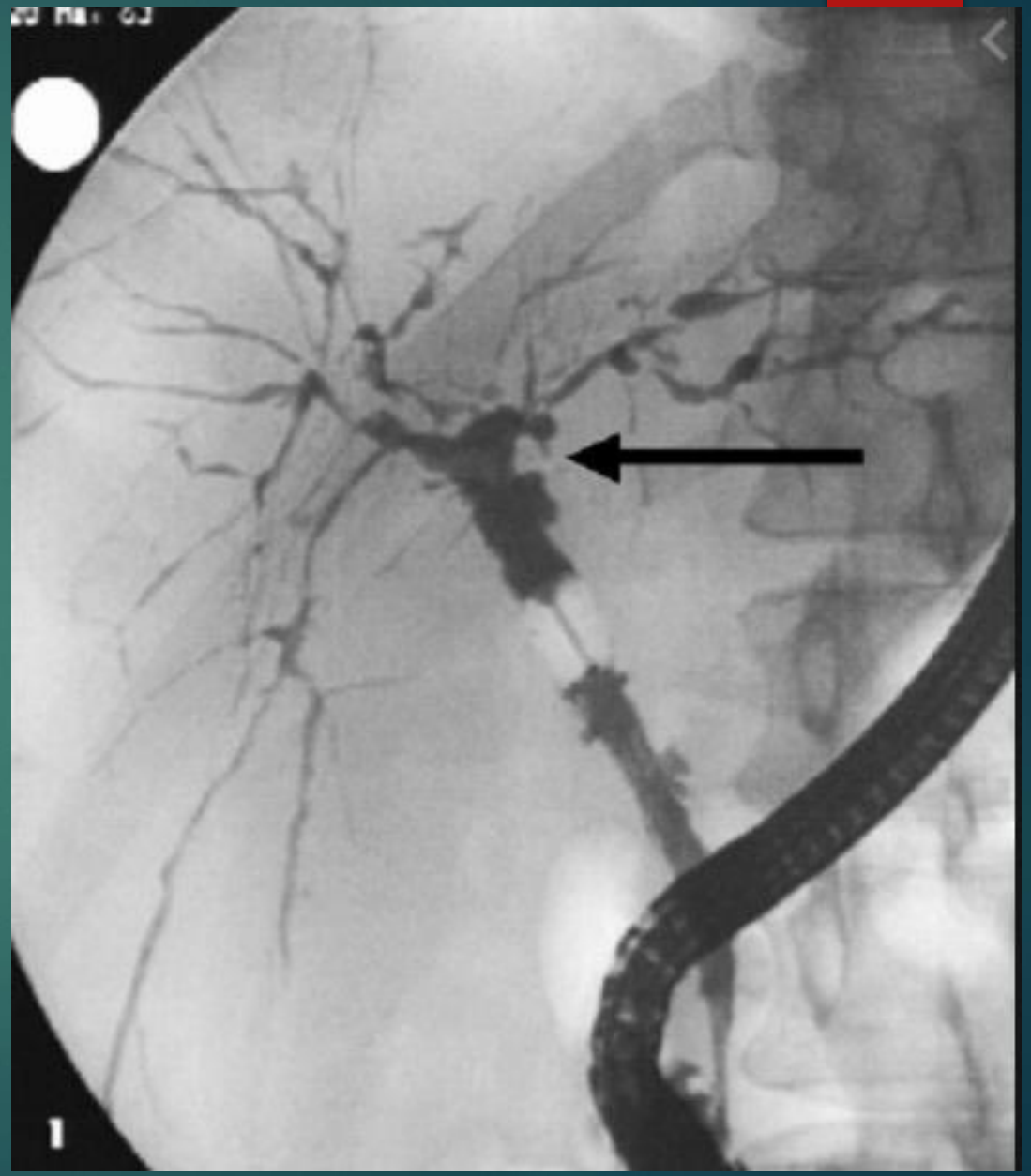
PSC

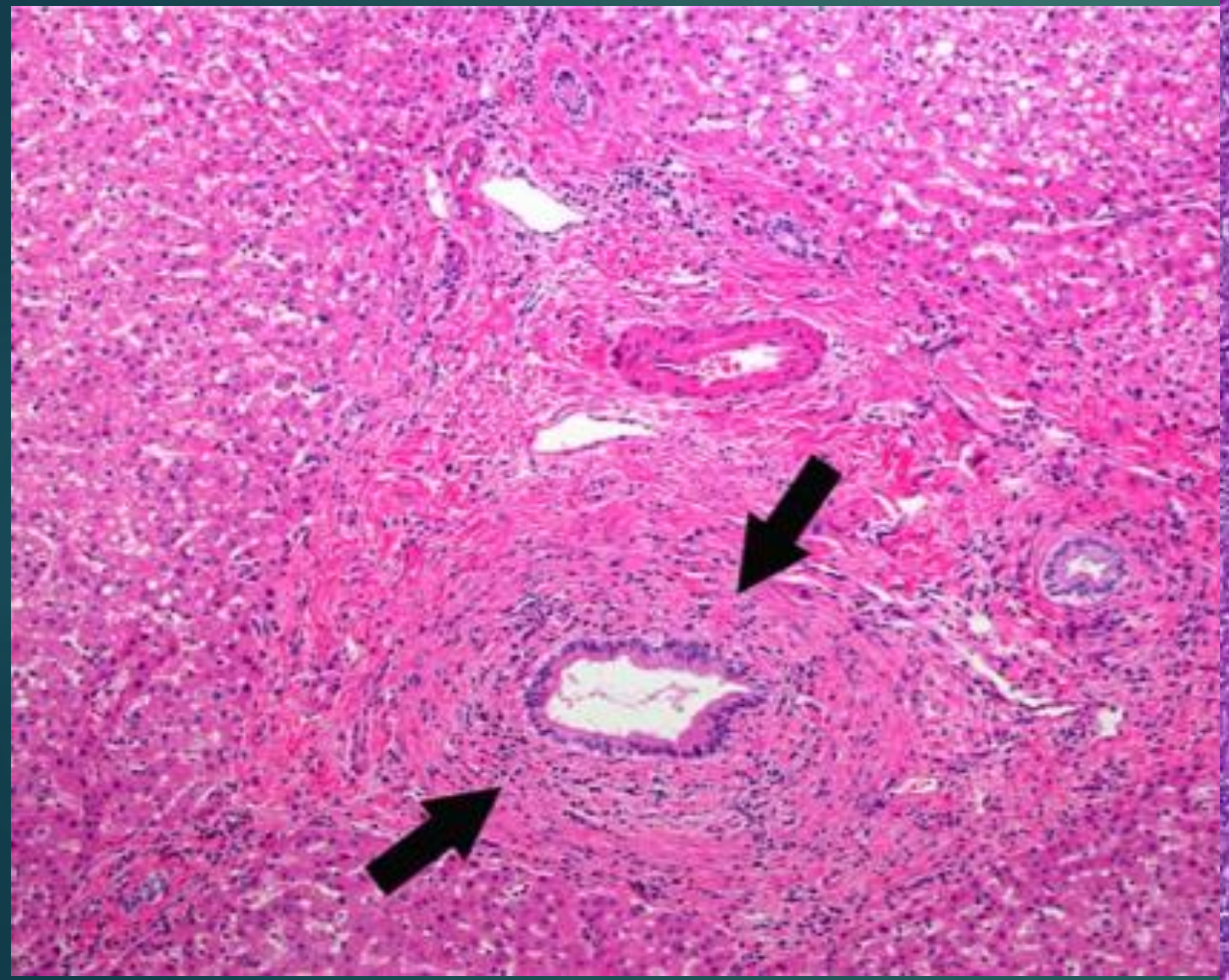
- Fibroinflammatory process
  - preferentially affects the large, intrahepatic and/or extrahepatic biliary tree
- Male 2:1
- Assoc with IBD 75%
- ~5% ‘small duct’ PSC
  - Higher correlation with IBD

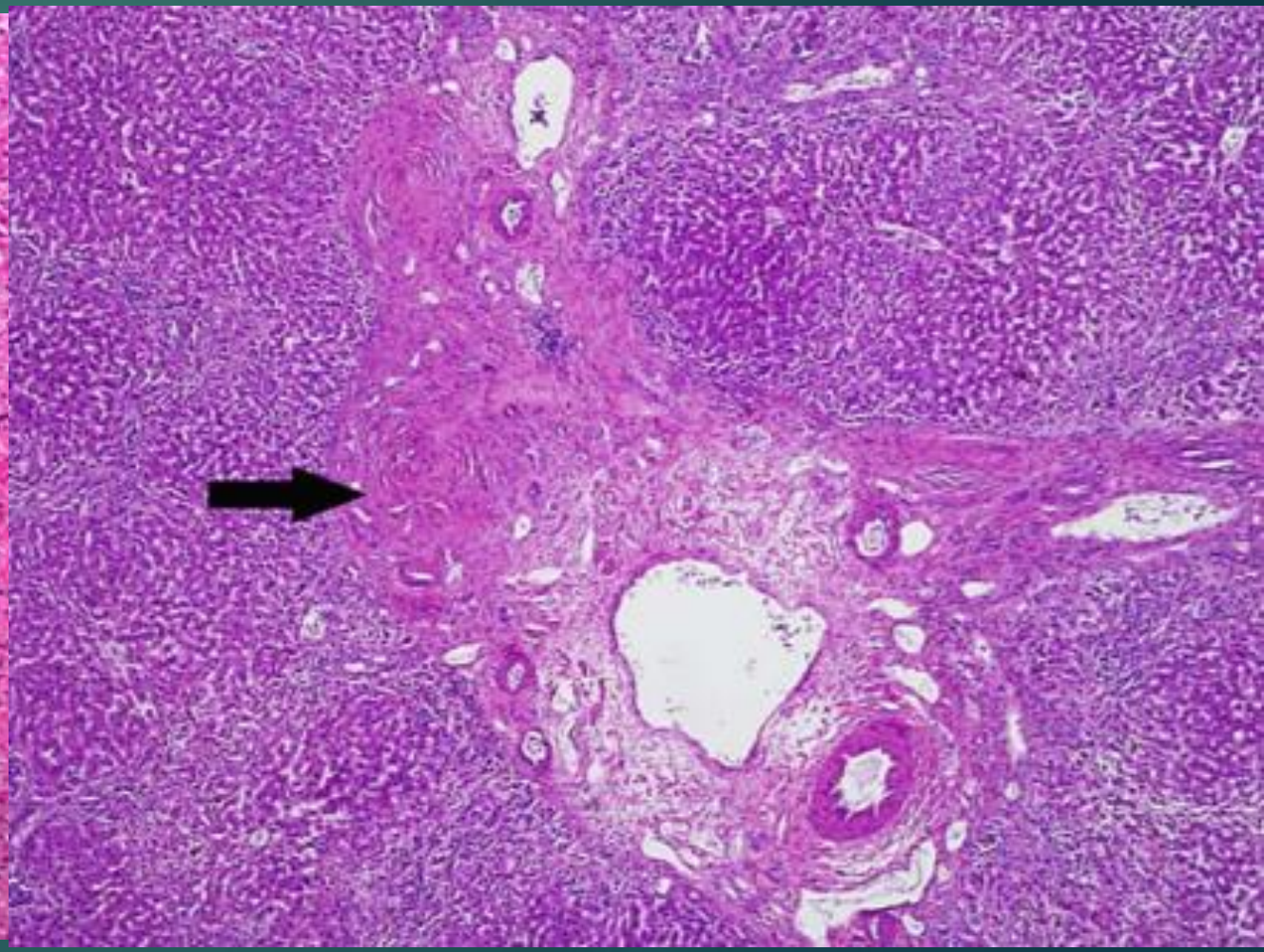
Diagnosis

- MRCP vs ERCP
- Who to biopsy?









Treatment

- Not much
- UDCA didn't work
- Investigational
- FXR agonists, PPAR agonists, FGF mimetics – none beyond phase II
- Immunomodulators/biologics - No
- Gut microbiota altering therapy
  - Antibiotics – Vancomycin, metronidazole
  - FMT

- A patient you follow with non cirrhotic PSC and ulcerative colitis in clinical remission on mesalamine presents to clinic. He notes he recently had a surveillance colonoscopy and was told there were ‘no concerning findings’. He has no acute complaints.
- You say wow that’s great and tell him his NEXT colon cancer screening should be in:
  - 1 year with colonoscopy
  - 1 year with FIT testing
  - 5 years with colonoscopy
  - 5 years with FIT testing

Management

- Symptom control similar to PBC
- PSC + GB?
  - Gallstones more common than general population
  - GB polyps
  - GB Cancer
- PSC + CCA
  - Risk factors?
  - 10 yr cumulative risk ~8%
  - Dominant strictures
  - CA 19-9 non diagnostic esp if pt symptmatic (unless very high)
  - Prognosis is poor, usually found later in course

Management

- PSC/IBD/CRC?
  - Screen for IBD at time of PSC dx if not known to be present (with protocoled biopsies)
  - If no IBD, CRC screening with colonoscopy every 5 years regardless of age
  - If yes IBD, annual dysplasia/CRC screening
  - IBD activity and PSC progression are not correlative
- Overlap syndrome?
- Indications for transplant?
  - MELD exceptions

Questions?