Liver Diseases Associated with Inflammatory Bowel Disease

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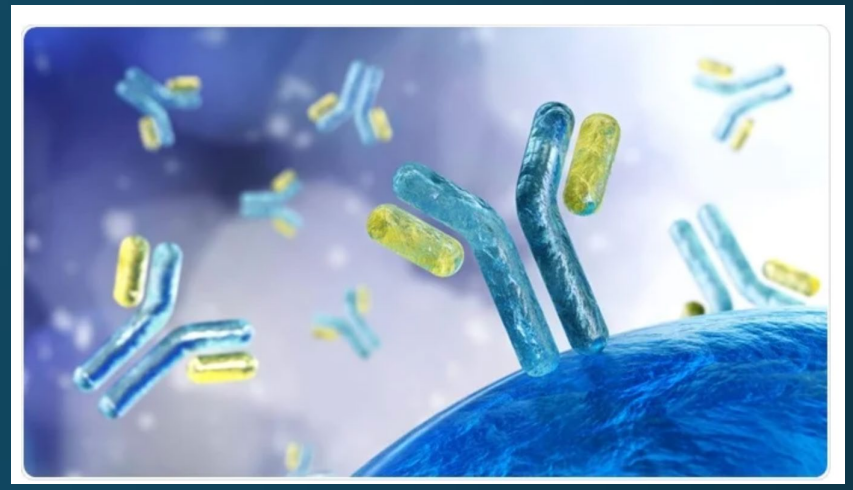
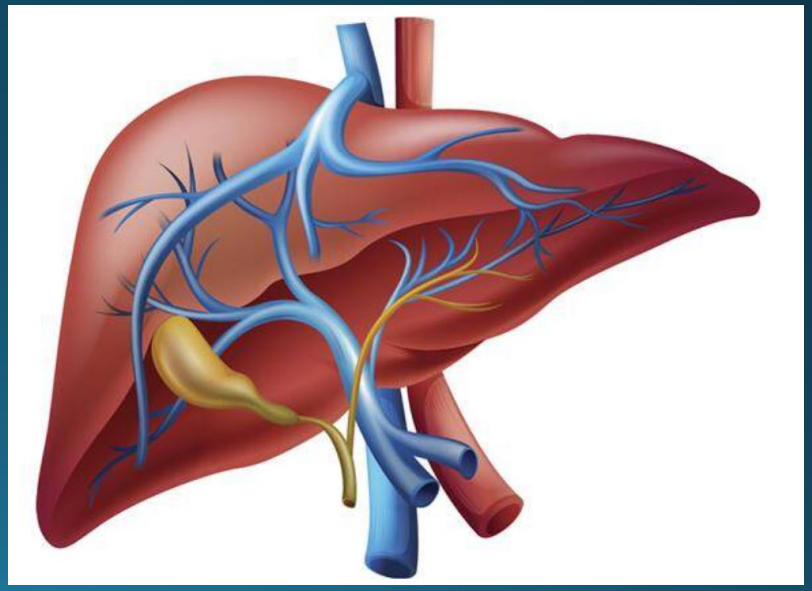
Agenda

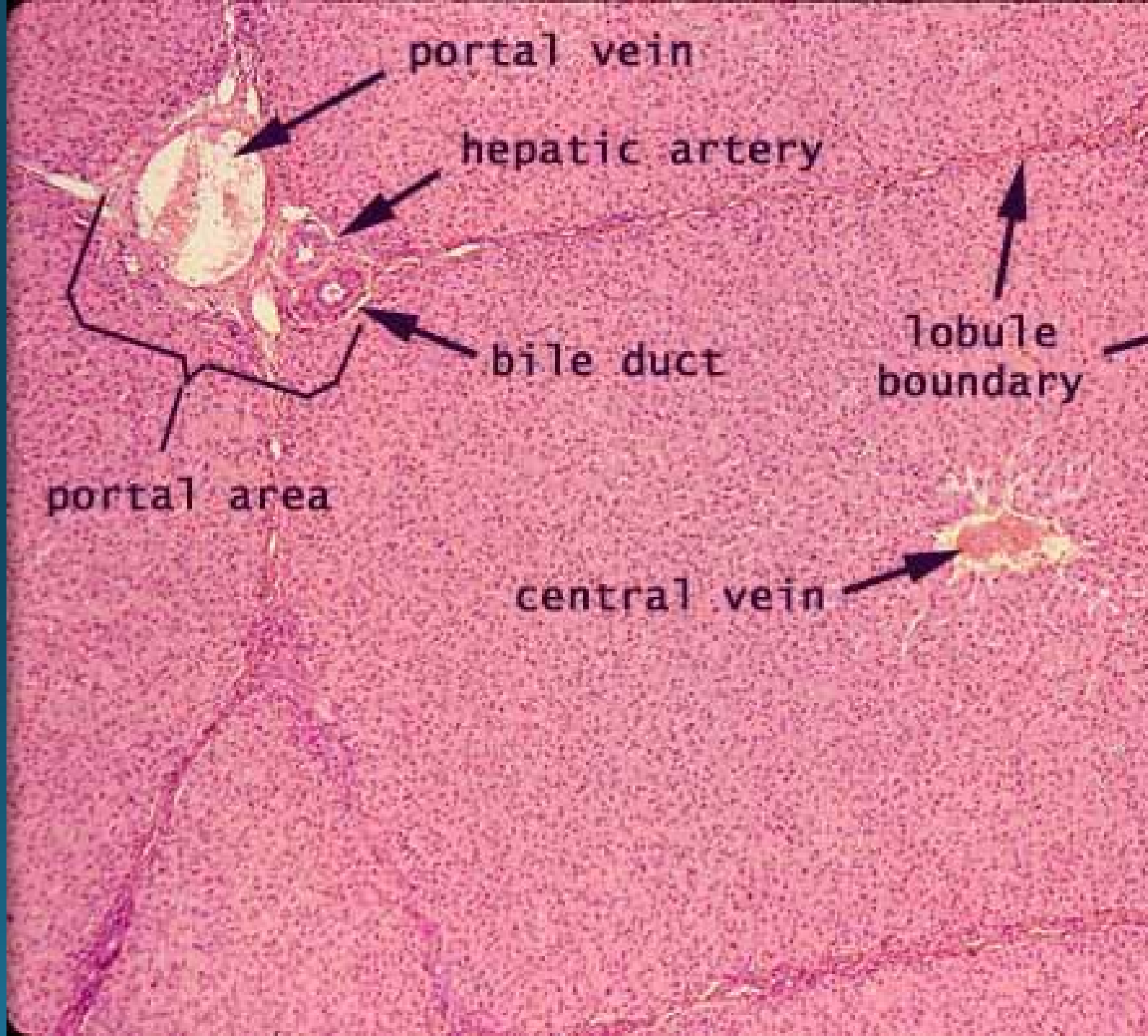
- Autoimmune liver diseases
- Drug induced liver injury (DILI)
- Metabolic-dysfunction associated steatotic liver disease (MASLD)
- Reactivation of hepatitis B





Liver histology

- Location of inflammation
- Types of inflammatory cells
- What structures are being attacked



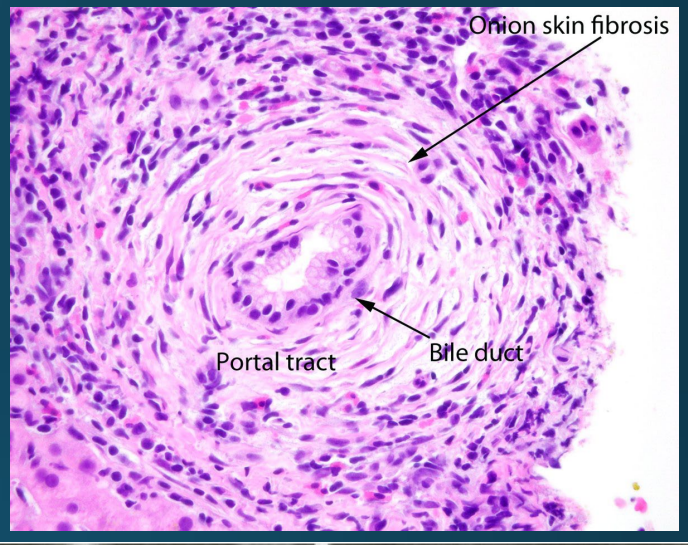
PSC and IBD

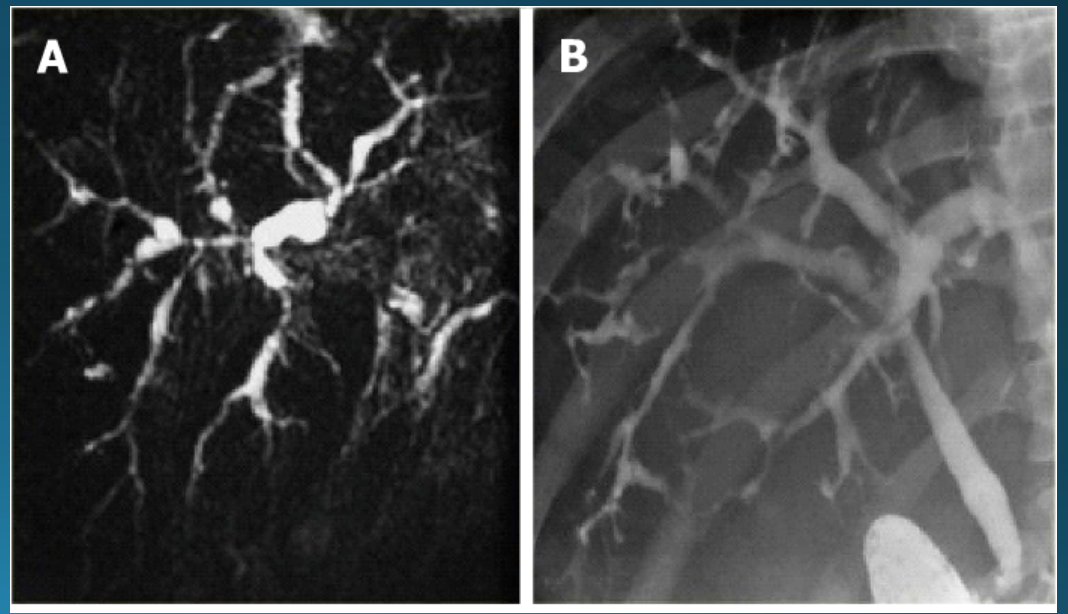
- 0.6-4.3% of patients with IBD have concurrent PSC
  - Studies of universal liver biopsies or cholangiography in IBD patients have shown a PSC prevalence of 8-9% in adults and 15% in children
- 70-80% of patients with PSC have concurrent IBD
  - 2/3 diagnosed with ulcerative colitis; PSC-IBD can be pancolitis with rectal sparing and backwash ileitis
  - 1/3 diagnosed with Crohn's disease or indeterminate colitis
- Often asymptomatic or less aggressive despite endoscopic and histologist activity
- Prone to develop pouchitis after colectomy with ileoanal anatomsis
- If portal hypertension present these patients are at increased risk of peristomal or stomal varices

AASLD practice guideline on primary sclerosing cholangitis and cholangiocarcincoma , 2023
Sauberman et al. JPGN 2017; 64: 639-652

PSC

- Destruction of the mid-larger bile ducts
- Elevation mainly in Alkaline phosphatase and/or total bilirubin
- Less inflammation than the other diseases
  - Lymphocytic infiltrate
- Onion skinning around the bile duct
- Mainly an imaging diagnosis
- Treatment: none; consider ursodiol (13-23 mg/kg in bid dosing) and monitor for labs or symptom response; consideration of vancomycin in PSC-IBD but not standard of care



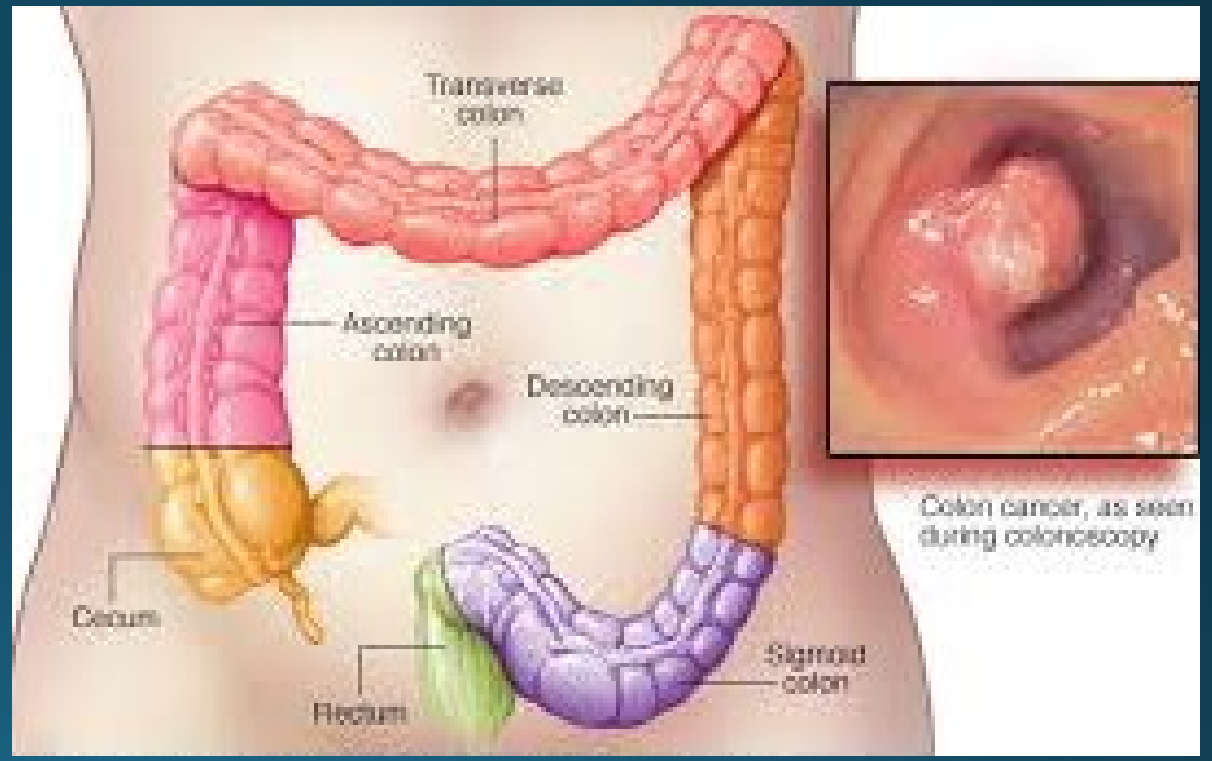


A: MRCP; B: ERCP

AASLD practice guideline on primary sclerosing cholangitis and cholangiocarcincoma , 2023

PSC-IBD and Colon cancer

- 5-12x increased risk compared to general population
- 4-5x increased risk compared to patient with IBD alone
- More endoscopically invisible dysplasia; more right sided cancer
- Younger age at diagnosis
- Patients with PSC-IBD should start colon cancer surveillance at 15 years old and need repeat colonoscopy with biopsies every 1-2 years



AASLD practice guideline on primary sclerosing cholangitis and cholangiocarcincoma , 2023.

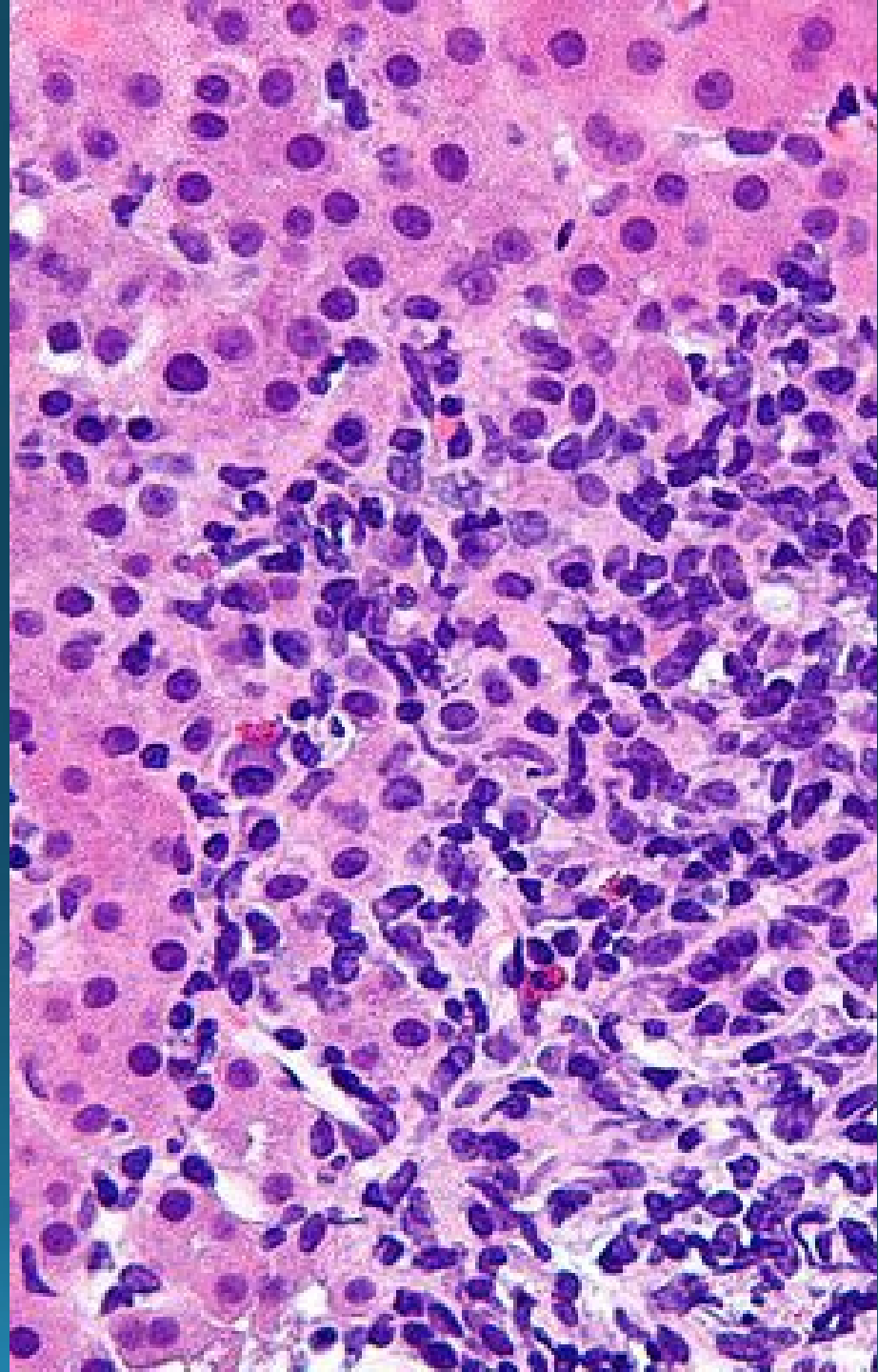
Autoimmune hepatitis (AIH) and IBD

- 0.6-1.6% of patients with IBD have concurrent AIH
- 3-10% of patients with AIH have concurrent IBD
- Limited data on PSC-AIH overlap in patients with IBD but it is likely underestimated in patients with IBD
- Compared to those with AIH alone, AIH-IBD the AIH:
  - Develops at an earlier age
  - May be less responsive to immunosuppression
- The IBD is usually UC or indeterminate colitis

Bailey, J et al. American Journal of Gastroenterology, 2014: 109, S149
Sauberman et al. JPGN 2017; 64: 639-652
Shi, H at all. Journal of Gastro and Hep; 2025

AIH

- Inflammation within the liver parenchyma
  - Elevations of AST, ALT, Total Bilirubin, Alkaline Phosphatase
- Lymphoplasmacytic infiltrate
- Interface hepatitis
- Can be difficult to diagnose
  - Variable pattern of autoimmune antibodies
  - Variable findings on biopsy
- Labs and liver biopsy used to make diagnosis
- Treatment: ***prednisone***, ***azathioprine***, cellcept, tacrolimus



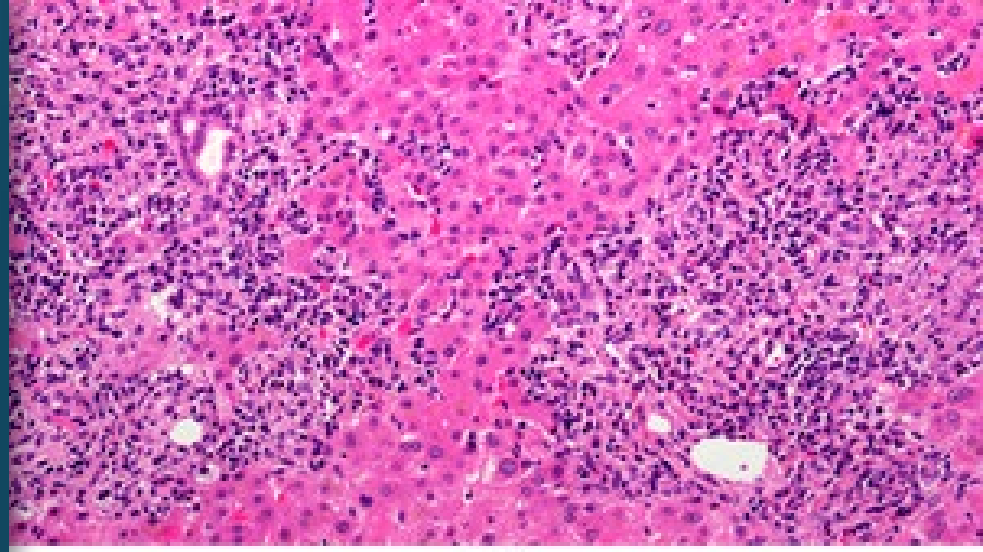
Primary Biliary Cholangitis (PBC) and IBD

- 0.3% of patients with IBD have concurrent PBC
- 2% of patients with PBC have concurrent IBD
- Limited data in IBD and PBC

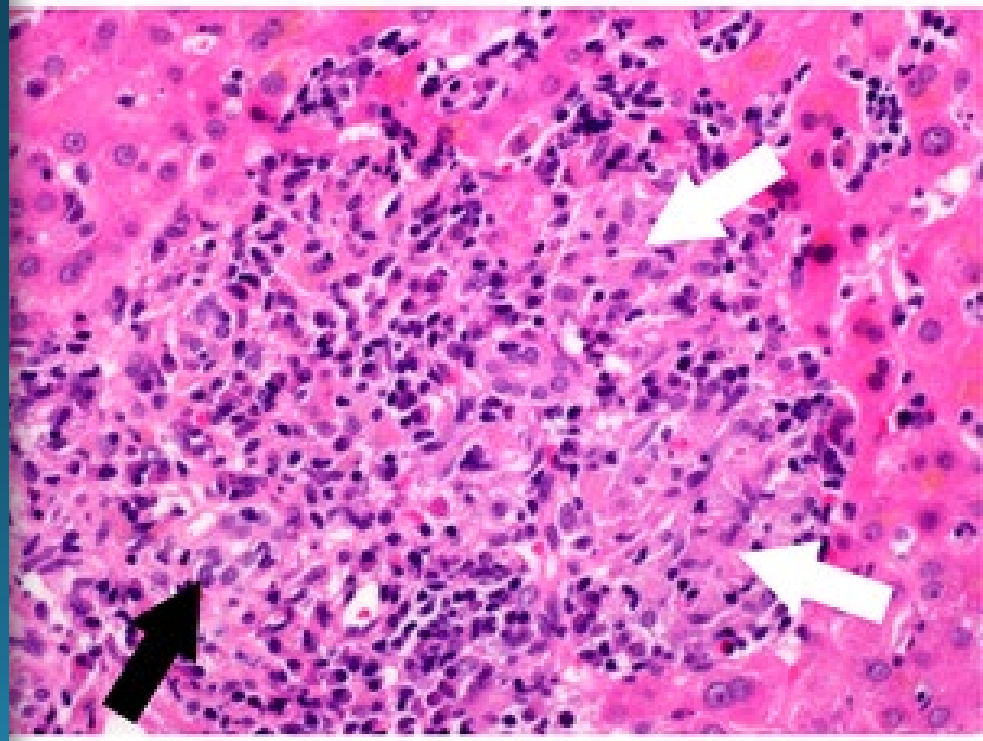
Shi, H at all. Journal of Gastro and Hep; 2025

PBC

- Destruction of the small bile ducts
- Elevations mainly in Alkaline Phosphatase
- Granulomas and Lymphocytic portal inflammation
- Florid Duct Lesions
- Overlap can occur with AIH
- Mainly a biopsy diagnosis
- Treatment: ursodiol, seladelpar, elafibranor



(a)



(b)

a) Florid Duct Lesions
b) Black arrow lymphocytes; White arrow granulomas

Abnormal LFTs and IBD

- 20-30% of patients with IBD will develop abnormal LFTs
- Monitor liver function tests (LFTs) every 6 months
- If LFTs chronically abnormal get an ultrasound to evaluate and if the alkaline phosphatase is elevated get magnetic resonance cholangiopancreatography (MRCP) imaging
- Check autoimmune antibodies for:
  - AIH (ANA, anti-smooth muscle antibody, immunoglobulins)
  - PBC (Anti-mitochondrial antibody)
  - Titers should be higher than 1:40 to suggestion relevant disease
  - If concern for AIH or PBC then liver biopsy is needed
- If testing is positive refer to GI/hepatology for further evaluation and management; if testing negative consider other eiologies of abnormal labs

Drug-induced liver injury or disease

Drug-induced autoimmune hepatitis

Methotrexate toxicity

Azathioprine toxicity

Drug-Induced Autoimmune hepatitis

TABLE 5. Drugs Associated with Liver Injuries Resembling AIH

Definite Association	Probable Association	Possible Association
Minocycline[187,192-198]	Propylthiouracil[579,580]	Ipilimumab (anti-CTLA-4)[581]
Nitrofurantoin[187,199-205]	Isoniazid[582]	Tremelimumab (anti-CTLA-4)[581]
Infliximab[206-221]	Diclofenac[583,584]	Nivolumab (anti-PD-1)[581]
Alpha-methyldopa[585-587]	Etanercept[216,432,433]	Pembroluzimab (anti-PD-1)[230,588]
Adalimumab[216,433,589-591]	Atorvastatin[592-595]	Atezolizumab (anti-PD-L1)[581]
Halothane[596,597]	Rosuvastatin[598]	Black cohosh (herbal medicine)[599,600]
Oxyphenisatin*[601]	Clometacine[602,603]	Dai-saiko-to (herbal medicine)[604]
Dihydralazine*[573,574,605]		Germander (herbal medicine)[606]
Tienilic acid*[607]		Hydroxycut (nutritional supplement)[608]
		Trichloroethylene (toxin)[609]
		Papaverine[610]
		Indomethacin[611]
		Imatinab[612]

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Drug-induced AIH versus Primary AIH

TABLE 6. Features of Drug-Induced AIH-Like Injury and AIH

Clinical Features	Drug Induced AIH-Like Injury	AIH
Gender	Mainly women[187]	Female predominance, but men also affected[2,384,467]
Acute onset	Majority (>60%) [231]	<20%[2,136]
Hypersensitivity (fever, rash, eosinophilia)	Up to 30%[231,232,613]	Unusual[2,384,467]
Temporal relationship with drug	Positive[231-234]	Negative[2,56,188]
HLA DRB1*03:01 or DRB1*04:01 association	None[236]	Common [29]
Concurrent autoimmune diseases	Unusual[187]	Present in 14%-44% [129,149-152]
Cirrhosis at presentation	Rare [187]	28%-33%[9,104-107]
Management	Stop offending drug ± glucocorticoids [187,231,232]	Glucocorticoids with AZA[2,384,467]
Relapse after drug withdrawal	Rare [187]	60%-87%[243,244]
Progression to cirrhosis	Rare [187]	7%-40%[105]
Survival without transplantation	90%-100% [187,232]	10-year survival, 89%-91%[105,451]

Mack et al. Hepatology vol 72: No.2; 2020

Management of Drug-induced AIH

- If strong clinical evidence, then stop medication and monitor LFTs
  - Clinical decision regarding need for biopsy: response to medication withdrawal or consideration of steroids for treatment
- If LFTs significantly abnormal: ALT ≥ 3x ULN and/or Bilirubin ≥ 2x ULN then start steroids
- If relapse after withdrawal of steroids, consider a diagnosis of primary AIH

Mack et al. Hepatology vol 72: No.2; 2020

DILI

- Livertox.nih.gov

Medication	Abnormal LFTs	Clinically Significant
Risankizumab Skyrizi ®	Yes (10%)	No (self-limiting)
Upadacitinib Rinvoq ®	Yes (11%)	No (rare HBV reactivation)
Ustekinumab Stelara ®	Yes (1%)	No (rare HBV reactivation
Guselkumab Tremfya ®	Yes (3%)	No (self-limiting)

Methotrexate Hepatotoxicity

- 5% risk of advanced hepatotoxicity
  - Rarely severe drug induced liver injury when used at low doses (≤ 25 mg/week)
  - Less of a concern in IBD treatment than treatment for other rheumatologic diseases
- 15% develop intermittent transaminase elevations that are usually self-limited
- Check hepatic function every 4-12 weeks depending on duration and stability of dose
- Serial liver biopsies have fallen out of favor

Sauberman et al. JPGN 2017; 64: 639-652

Wood et al. Rheum Dis Clin N Am 44 (2018) 29-43

Histology of Methotrexate (MTX) liver disease: nonalcoholic or alcoholic

- Steatosis
- Fibrosis
- Cirrhosis
- Complication of Cirrhosis
  - Liver failure
  - Liver Cancer
  - Liver Transplantation
  - Death

Wood et al. Rheum Dis Clin N Am 44 (2018) 29-43

Methotrexate Hepatotoxicity

- Increased risk for hepatic toxicity
  - History of current use or greater than moderate alcohol consumption
  - Persistent abnormal LFT findings
  - History of liver disease including chronic hepatitis B and C
  - Family history of inheritable liver disease
  - History of exposure to hepatotoxic drugs or chemicals
  - Absence of folic acid
  - Cumulative MTX dose
  - Diabetes mellitus
  - Obesity
  - Hyperlipidemia

Metabolic Risk Factors for MASLD

Wood et al. Rheum Dis Clin N Am 44 (2018) 29-43

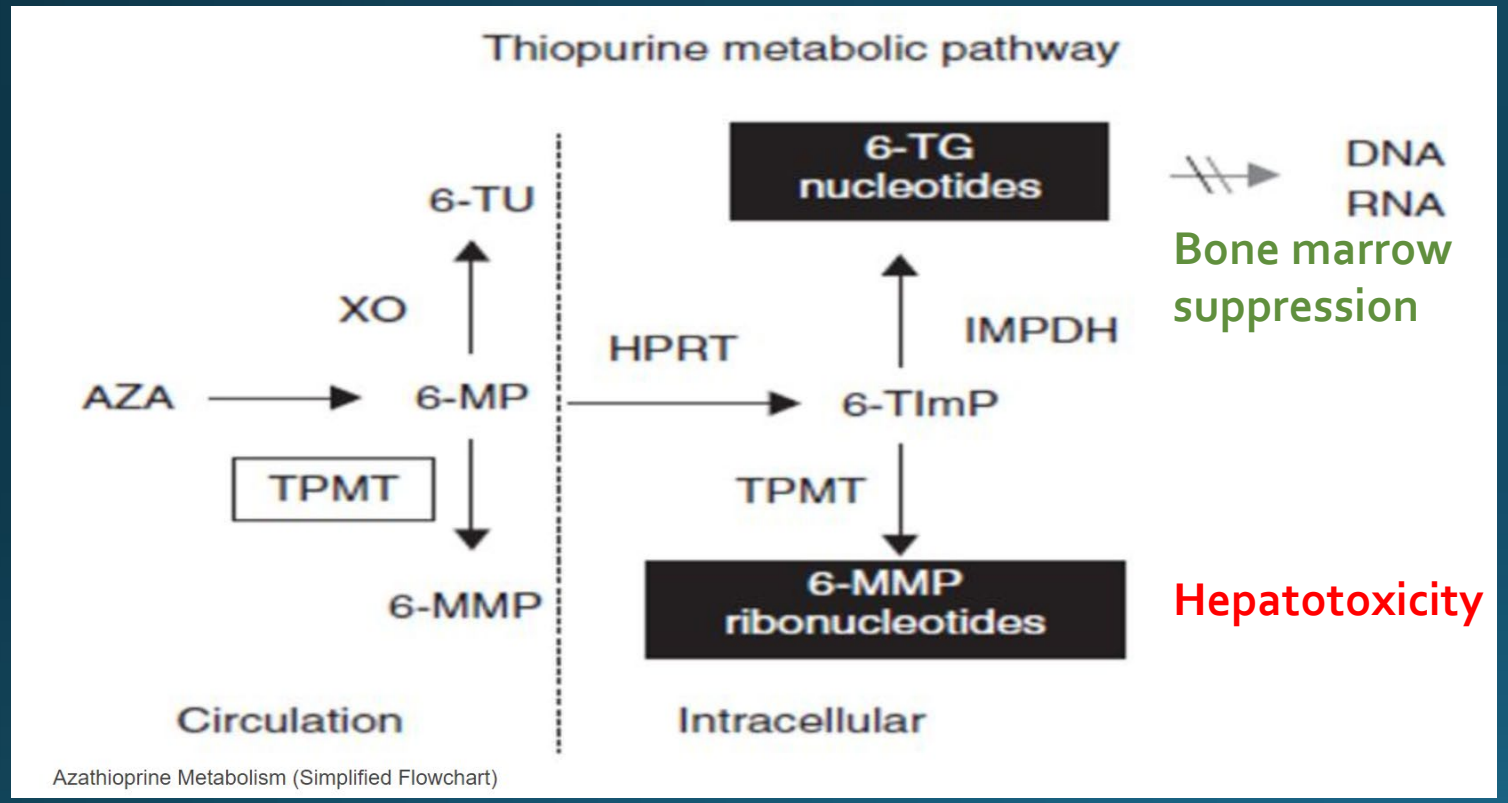
Monitoring for MTX hepatotoxicity

- Regular evaluation of LFTs
  - If there are elevations prior to starting MTX evaluate for causes
- If an elevation or change from baseline in LFTs occurs repeat labs in 2 weeks to assess for chronicity
- If persistently elevated evaluate for other causes, trial of dose reduction
  - If LFTs ≥ 3-5x normal, then discontinue MTX
- Other causes ruled-out consider a biopsy especially if no response to dose reduction
- Consider non-invasive liver fibrosis staging for monitoring

  (every 3 years)
  - Fib-4 or Fibroscan testing

Saag et al. Arthritis Rheum. 2008;59(6):762
Uptodate. Hepatotoxicity Associated with Chronic low dose MTX

Azathioprine (AZA)



- 8% have increase in LFTs usually within the 1st year
- No universal agreement on monitoring but at least every 1-24 weeks depending on duration and stability
- Consider checking AZA metabolite levels after 8-12 weeks of therapy

https://www.eventscribe.com/2019/ACG/fsPopup.asp?efp=RUxTQkhWU1g2NDI1&PresentationID=591863&rnd=0.9973644&mode=presinfo

Metabolic-dysfunction associated steatotic liver disease (MASLD)

- MASLD is present in ~34% of Americans
  - Non-alcoholic steatohepatitis (MASH) is present in 12%
- Incidence is expected to rise by 63% by 2030
- Persons of Hispanic descent have the high prevalence of any ethnicity (58.3%)
- Metabolic syndrome: obesity, insulin resistance, dyslipidemia
- Relevance in IBD
  - High prevalence of MASLD among IBD patients including lean MASLD
  - Growing liver-related morbidity and mortality with increasing prevalence
  - Prednisone can contribute to increased metabolic risk

Clinical Gastro and Hep, 2024; 22: 215-218
Inflammatory bowel disease, 2024; 30: 1274-1283

MASLD

- Entire spectrum of fatty liver disease in individuals without significant alcohol consumption

MASL: Metabolic-dysfunction associated steatotic liver

- Isolated steatosis (fat ≥5% of hepatocytes)

MASH: Metabolic-dysfunction associated steatohepatitis

Active form of the disease characterized by:

- Steatosis
- Ballooning
- Inflammation

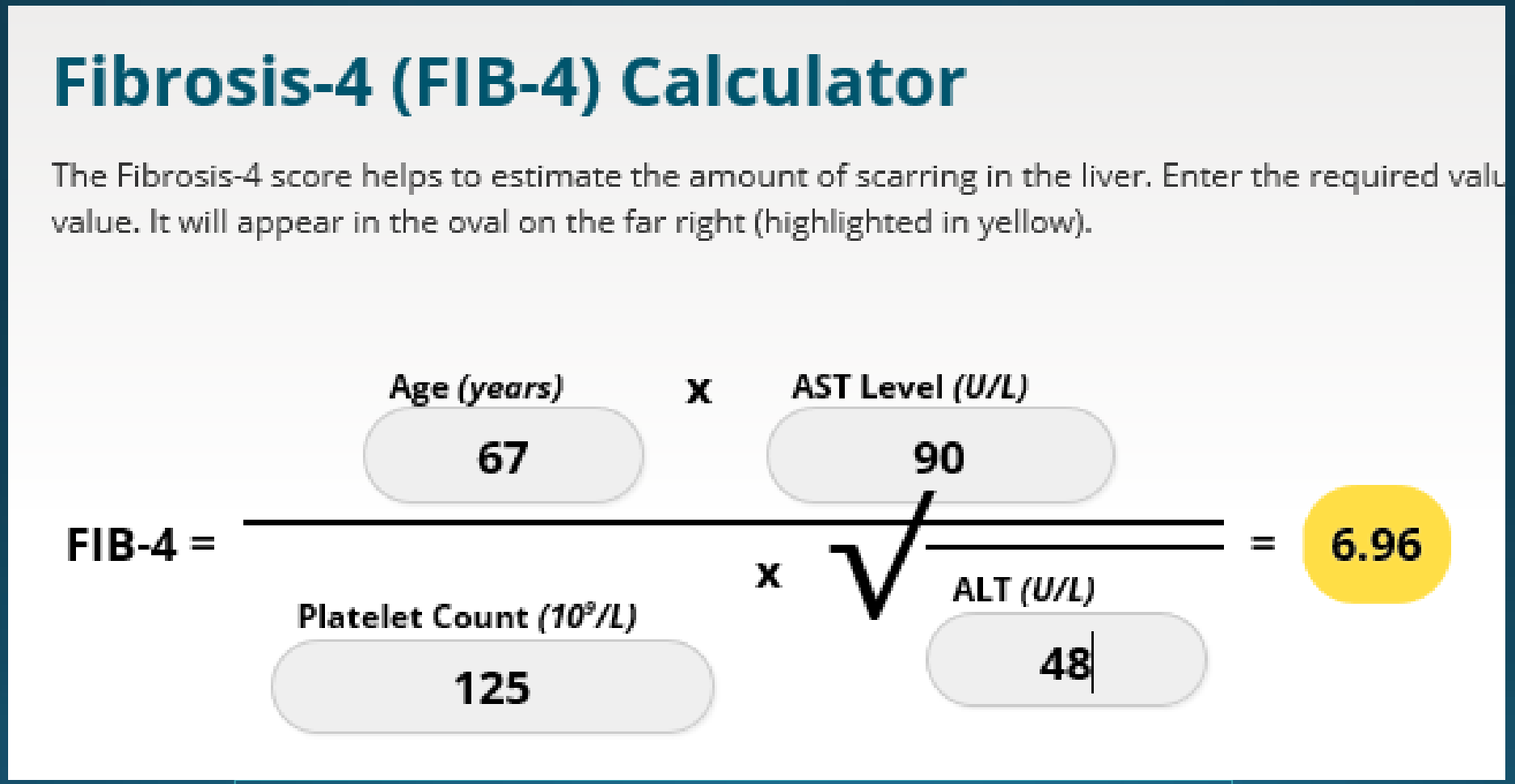
MASH with fibrosis[3,4]

MASH (steatosis, ballooning, inflammation) Stage of fibrosis:

- **Mild:** Fibrosis stage 1 (F1)
- **Significant:** (Fibrosis stages 2 and 3) F2/F3)
- **Cirrhosis:** Fibrosis stage 4 (F4)

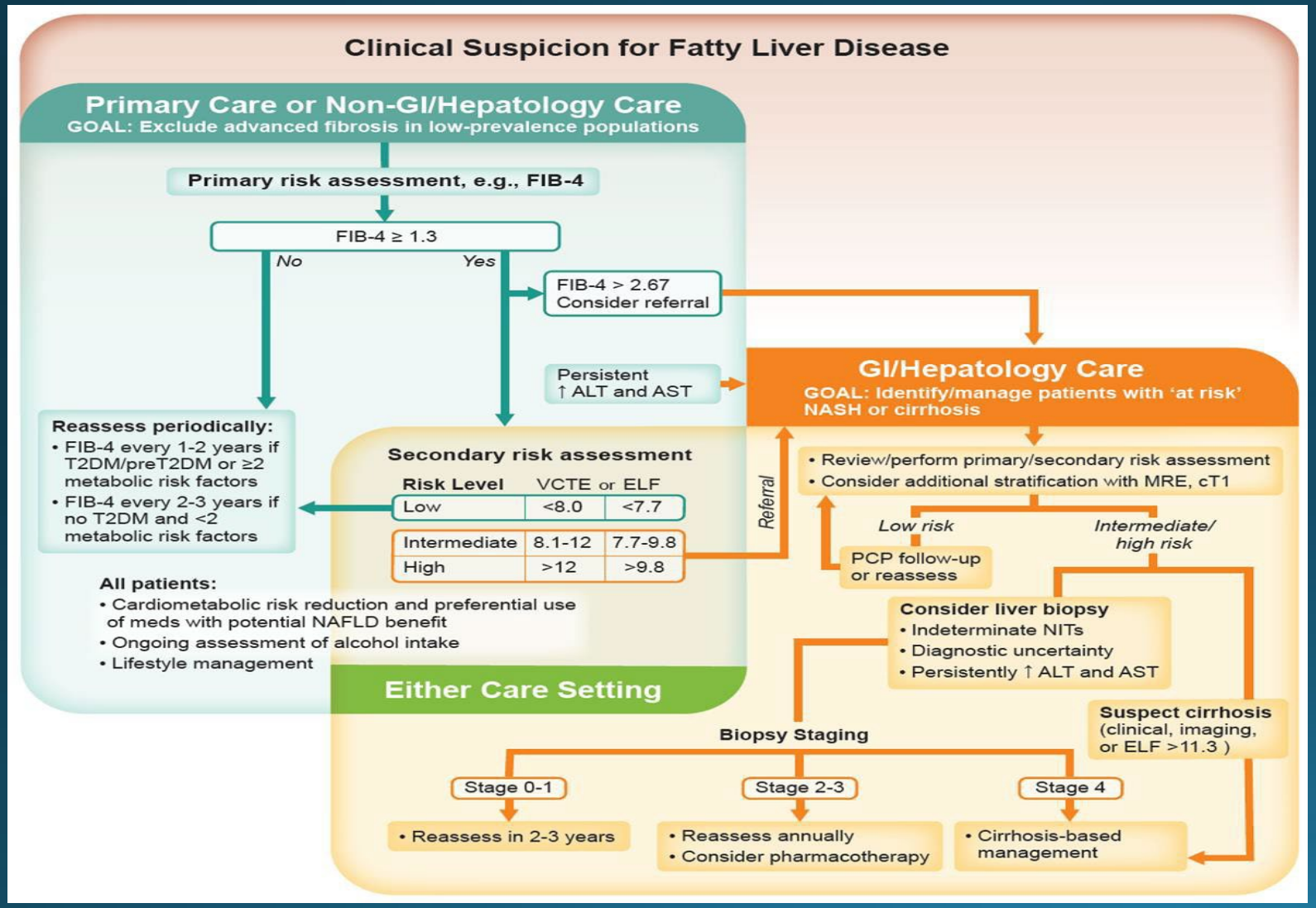
Sheka AC, et al. *JAMA*. 2020;323(12):1175-1183.
Alkhouri N, McCullough AJ. *Gastroenterol Hepatol (N Y).* 2012;8(10):661-668.
EASL–EASD–EASO. *J Hepatol*. 2016;64:1388-1402.
Diehl AM, Day C. *N Engl J Med*. 2017;377:3063-3072.

Staging Liver Disease: Non-invasive Tests (NITs)



FIB 4 ≥ 1.3 warrants additional staging
FIB 4 > 3.25; 97% specificity for cirrhosis

AASLD Screening Algorithm Related



Alcohol intake mild:
<20 grams/day in females
<30 grams/day in males

Treatment options

- Risk Factor Control
  - Weight loss
    - Diet- Mediterranean Diet; Low Carbohydrate diet
    - Exercise
    - GLP1 agonists
    - Bariatric Surgery
  - Glycemic
    - Diabetes medications
  - Lipid control
    - Statins
  - Limit amount and duration of steroids when possible or select nonsystemic steroid ie budesonide
- Prescription Medications
  - Resmetirom; Rezdiffra ®
  - Semaglutide; Wegovy ®

Evaluation and management of viral hepatitis

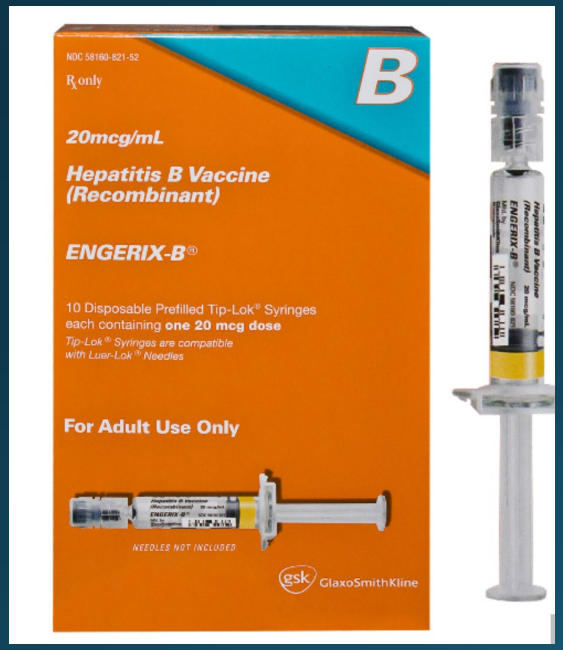
Viral hepatitis studies

HBV reactivation

Viral Hepatitis Labs

	HBsAg	HBc IgM	HBc IgG or Total	HBsAb	HBV DNA	HAV IgM	HAV IgG	HCV Ab	HCV RNA
Acute HBV infection	X	X			X				
Chronic HBV Infection (6 months)	X		X		X				
HBV Natural Immunity			X	X					
HBV Vaccination				X					
Acute HAV Infection						X			
HAV Immunity							X		
HCV exposure								X	
HCV Chronic infection								X	X

Prevention of HBV: Vaccinations

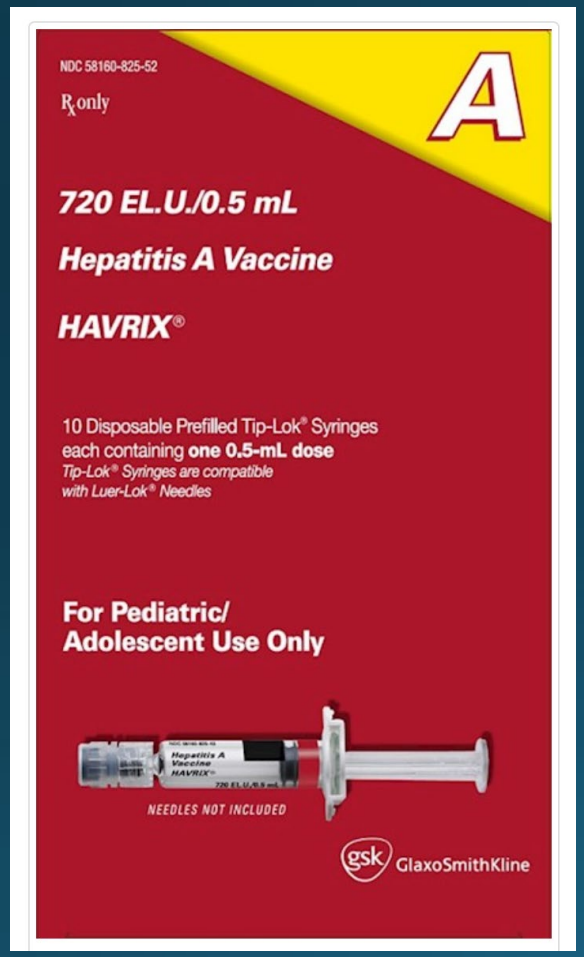


Engerix Dosing: 0, 1, 6 months

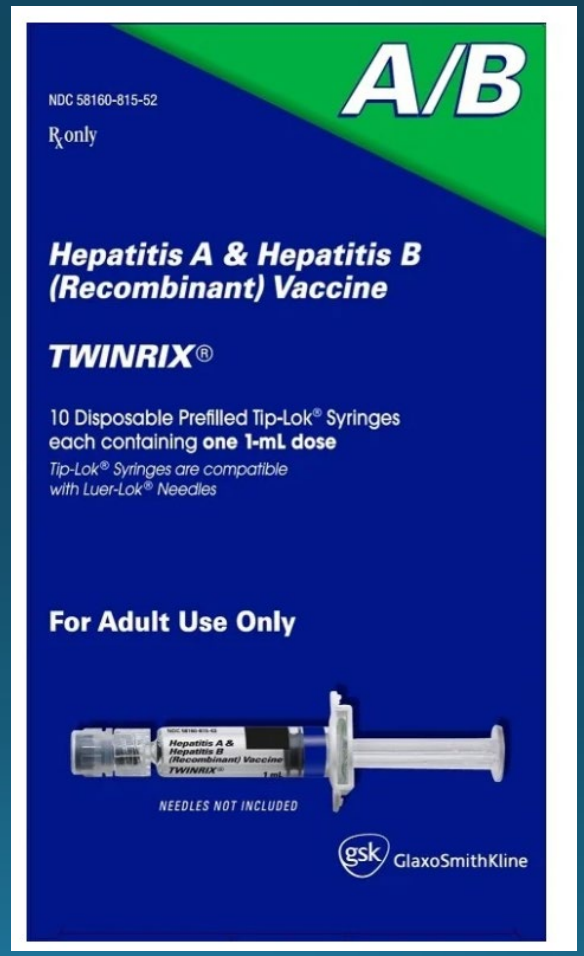
Heplisav Dosing: 0 and 1 months

Isolated HBcAb positive: Likely has natural immunity, check HBV for occult infection and consider vaccinating

Prevention of HAV: Vaccinations



Havarix Dosing: 0 and 6 months



Twinrix Dosing: 0,1 and 6 months

No available vaccine for hepatitis C

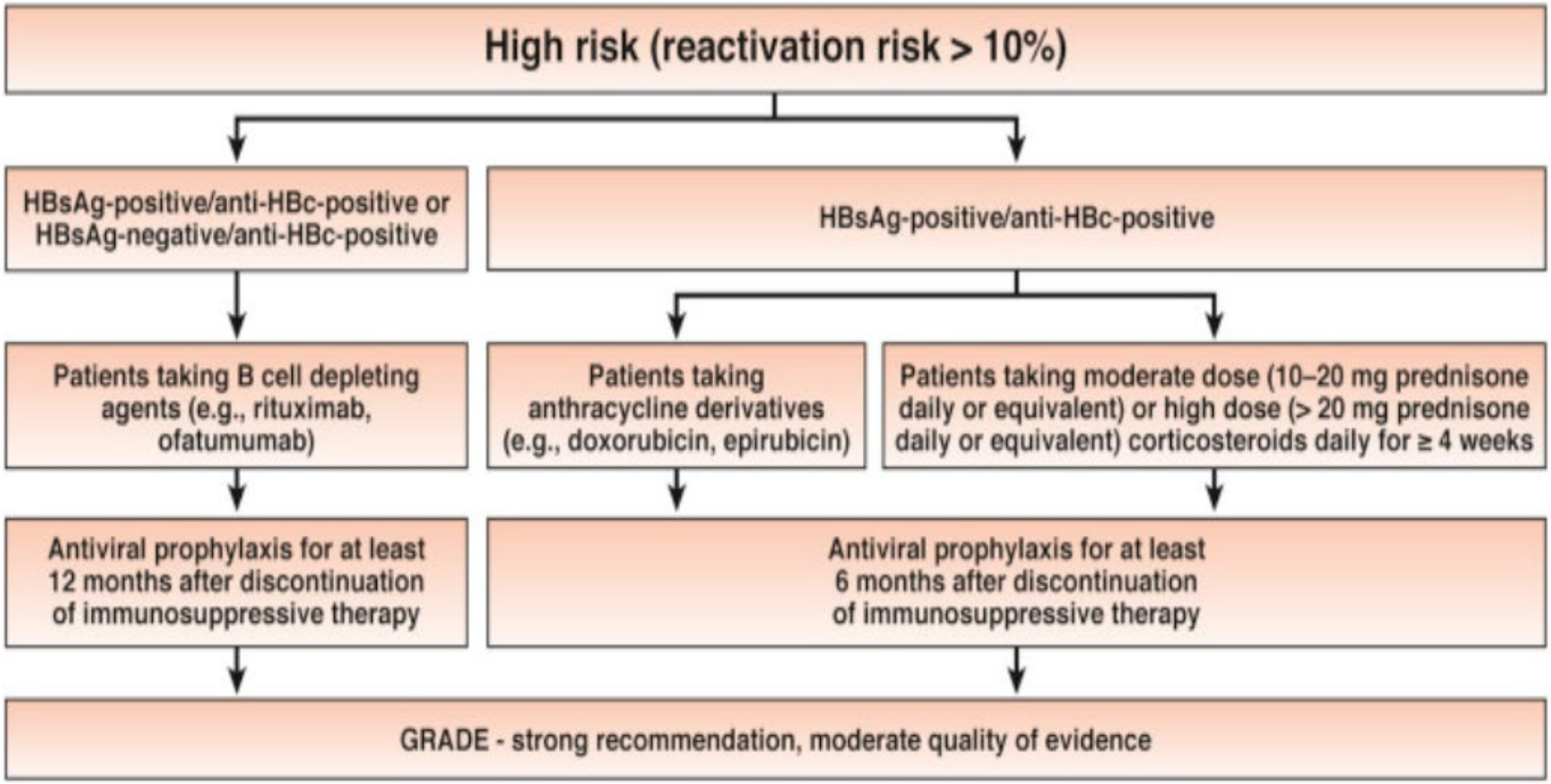
HBV Reactivation

	HBsAg Positive	HBsAg negative/HBcAb positive
HBsAg	Always positive	Seroconverts to HBsAg positive
ALT	> 3 fold rise or >100 with increase in HBV DNA	> 3 fold rise or >100 with increase in HBV DNA
HBV DNA	• Detectable when previously undetectable • ≥ 1 log rise in those previously detected	Detectable HBV DNA

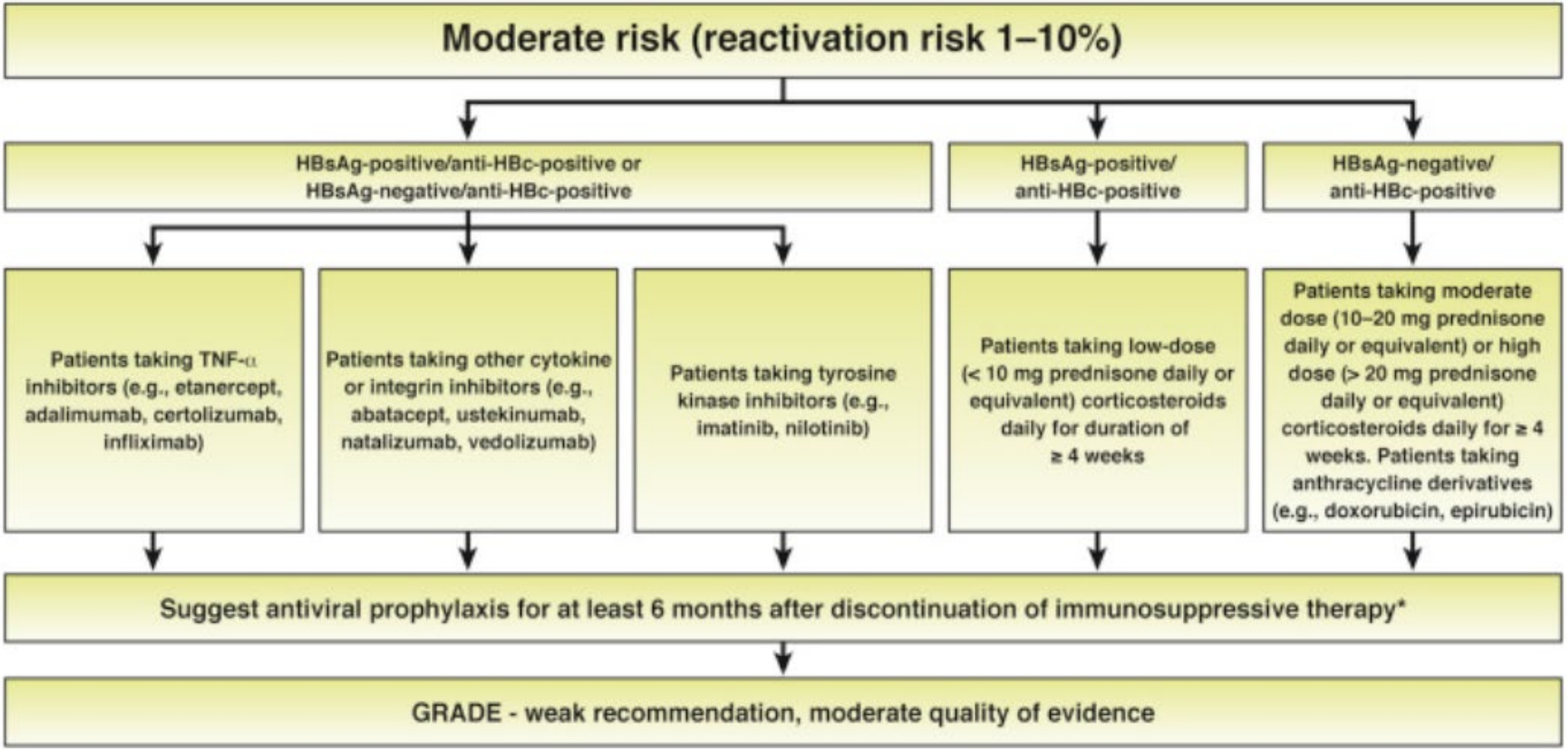
Pattulo. Clinical and Molecular Hepatology 2016;22:219-237

AGA Institute Guidelines on Hepatitis B Reactivation (HBVr)

Clinical Decision Support Tool

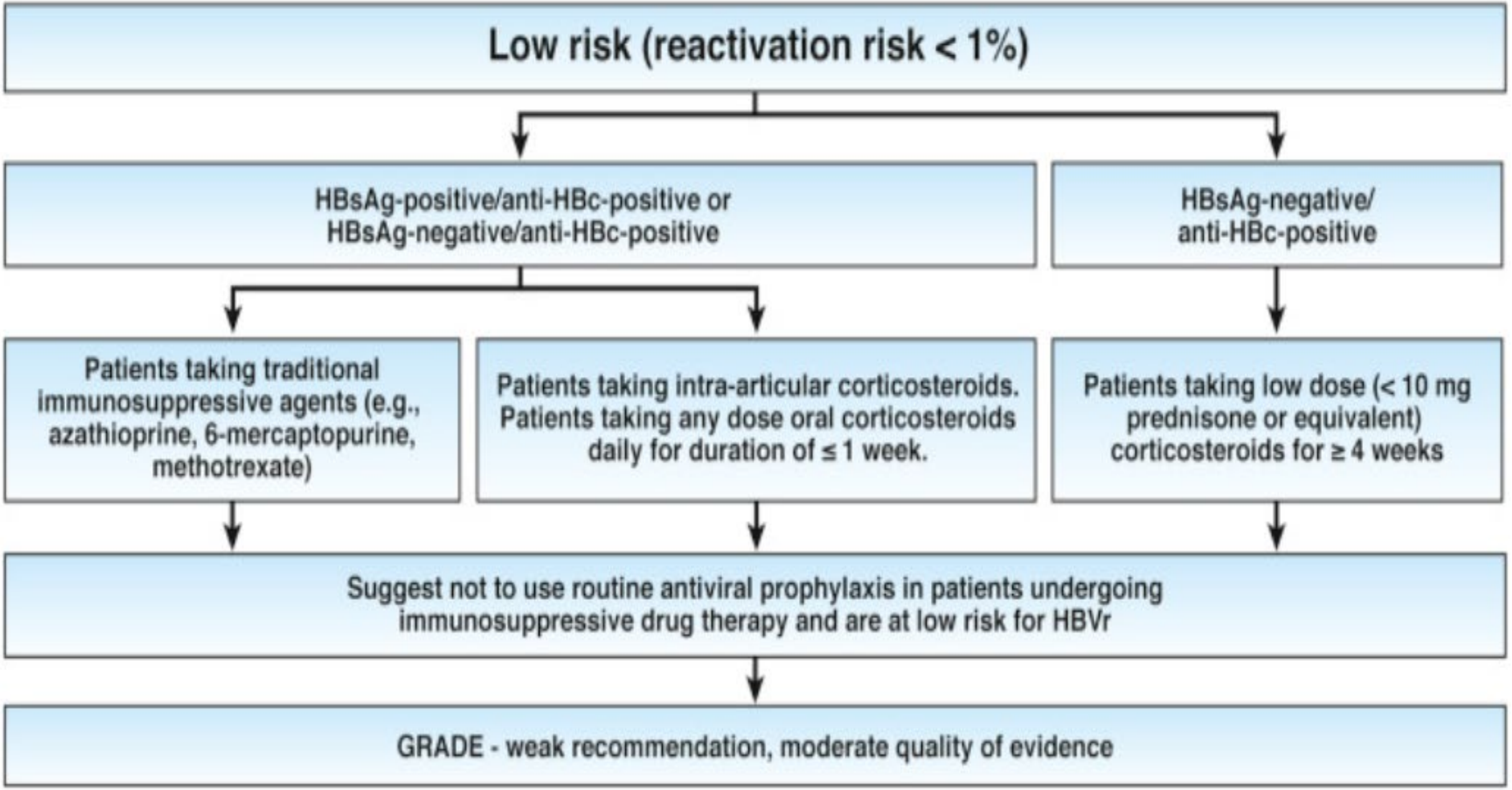


https://www.gastrojournal.org/article/S0016-5085(14)01476-0/fulltext



*Patients who place a higher value on avoiding the long-term use of antiviral therapy and cost associated with its use and a lower value on avoiding the small risk of reactivation (particularly in those who are HBsAg-negative), may reasonably select no prophylaxis over antiviral prophylaxis

https://www.gastrojournal.org/article/S0016-5085(14)01476-0/fulltext



https://www.gastrojournal.org/article/S0016-5085(14)01476-0/fulltext

Prevention of HBV reactivation

- Tenofovir-based products
  - Tenofovir disoproxil fumarate (TDF)/Viread ® 300mg daily
  - Tenofovir alafenamide (TAF)/ Vemlidy ® 25mg daily
    - Fewer potential renal and bone (osteoporosis) side effects
    - Costs more
- Entecavir-based product
  - Entecavir/Baraclude ® 0.5mg daily
- No universal guidelines for monitoring when prevention is not indicted or stopped

Conclusions

- There is liver-gut dysbiosis that connects autoimmune liver diseases and IBD, so we must be vigilant to:
  - Monitor LFTs in patients with IBD and evaluate for chronic liver disease
  - Monitor patients with autoimmune liver diseases for IBD , keep in mind IBD symptoms may be mild
- DILI with the newer IBD medications is less of an issue, but need to consider acute elevations and DI-ALH with TNF medications
- MASLD is a growing public health threat and IBD patients are susceptible so make sure to risk stratify by history and Fib-4 score
- Check HBV status with HepBsAg, HepBcAb and HepBsAb before starting immunosuppression or immunomodulating medications and decide on need for HV reactivation prophylaxis

Thank you!