Managing the Immunosuppressed IBD Patient with Chronic Liver Disease

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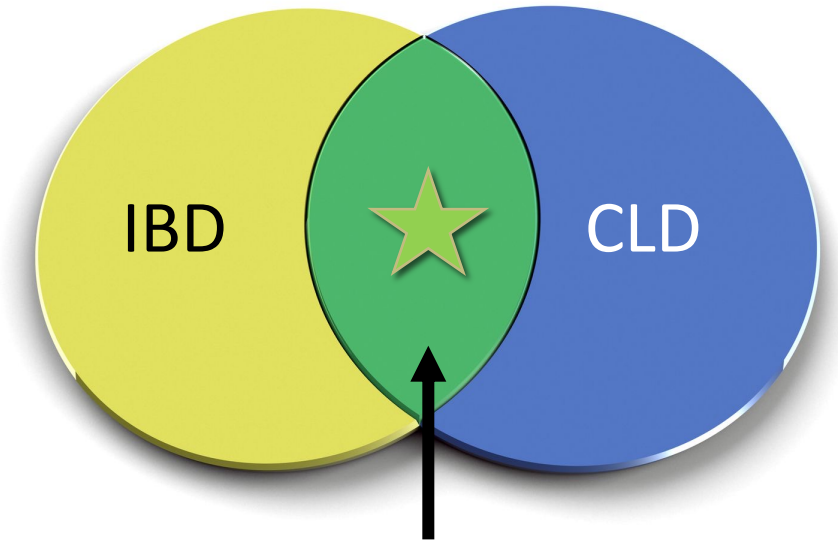
When IBD & Chronic Liver Disease Intersect:



Who to screen, how to diagnose and when to refer

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Disclosures

I have nothing to disclose.

By the end of this talk, you should:

- Know how to screen for chronic liver disease (CLD) in patients with IBD
- Recognize common causes of CLD in the IBD population
- Identify ways to optimize preventative care in this population

Agenda

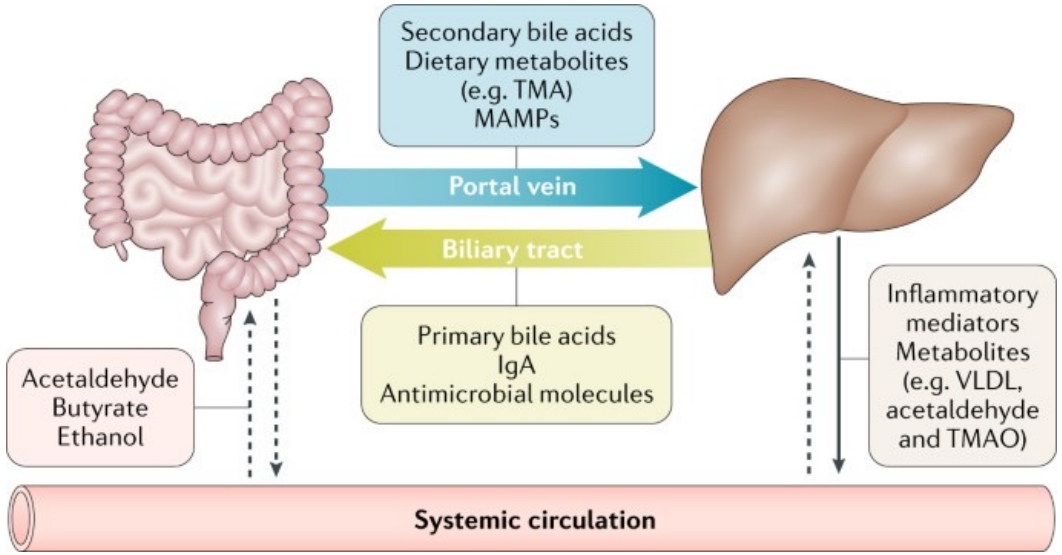
- Revisiting the gut-liver axis
- Screening for CLD in patients with IBD
- Identifying the cause of CLD in patients with IBD
- Knowing when to refer to hepatology
- Optimizing preventative care in this population
- Recognizing reasons for acute worsening

The liver and the GI system are intimately connected

The liver and intestine communicate through the biliary tract, portal vein and systemic circulation

Gut-liver axis: bidirectional relationship between the gut, its microbiota, and the liver

- integration of signals generated by dietary, genetic and environmental factors
- disruption of this axis may precipitate or worsen diseases of the gut and/or the liver



Liver products influence the gut microbiota composition & gut barrier integrity

Intestinal factors regulate bile acid synthesis, glucose and lipid metabolism in the liver.

World J Hepatol. 2021 Nov 27; 13(11): 1534–1551.
Nature Reviews Gastroenterology & Hepatology volume 15, pages397–411 (2018)

Liver disease is common in patents with IBD

Associated diseases	Prevalence in IBD (%)	Notes
PSC	0.024-0.041	Higher risk of cholangiocarcinoma and colorectal cancer; IBD shows less severe lesions than IBD alone
NAFLD	20-30	Associated with the use of corticosteroids, long disease duration, severe disease course; Associated with metabolic syndrome
Viral hepatitis	1-9	More common in the elderly; Association with advanced liver fibrosis; Need for anti-viral treatment before starting immunosuppressive drugs; HBV vaccine recommended

HBV: Hepatitis B virus; NAFLD: Non-alcoholic fatty liver disease; PSC: Primary sclerosing cholangitis; IBD: Inflammatory bowel disease.

CLD & IBD: Special Populations

PSC patients develop IBD in 20%-70% of cases

- 80% Ulcerative colitis (UC)
- 10% Crohn's disease (CD)
- 10% Indeterminate colitis (IC)

Only 5% of patients with UC show concomitant PSC

Metabolic dysfunction associated steatotic liver disease (MASLD = NAFLD): higher in IBD patients than the control population

Chronic immunosuppressive regimens may cause a hepatitis B (HBV) flare or reactivation

- **Everyone should be screened for immunity (HBsAb), infection (HBsAg) and previous exposure (HBcAb total).** Screen all patients for HCV (HCV Ab).
- Vaccinate all non-immune patients. Include HBV and HAV vaccination.

World J Hepatol. 2021 Nov 27; 13(11): 1534–1551.

37 yo man with known UC (moderate on diagnosis)

- 1 year follow up to manage chronic disease and address health maintenance
- Followed by a GI doctor yearly. Maintained on vedolizumab monotherapy for 2 years. Colonoscopy 9 mo ago showed quiescent colitis. GI symptoms well controlled.

BP 127/74 P 68 T 37.1 BMI 33

What can you do for this patient?

Labs, initial:

Lipids- elev TG and low HDL, LDL normal fasting glc 112

Normal Hgb, Plat ct 344

AST 41 ALT 85 ALP 172 bili 0.3

Looking back, outside labs were similar 8 mo ago

Additional history:

No alcohol use

30 lb weight gain in last 2 years

Diet more limited/processed

No recent flares or med changes

No supplement use or other prescribed medications

Screening/Evaluating for Chronic Liver Disease (CLD) in Patients with IBD

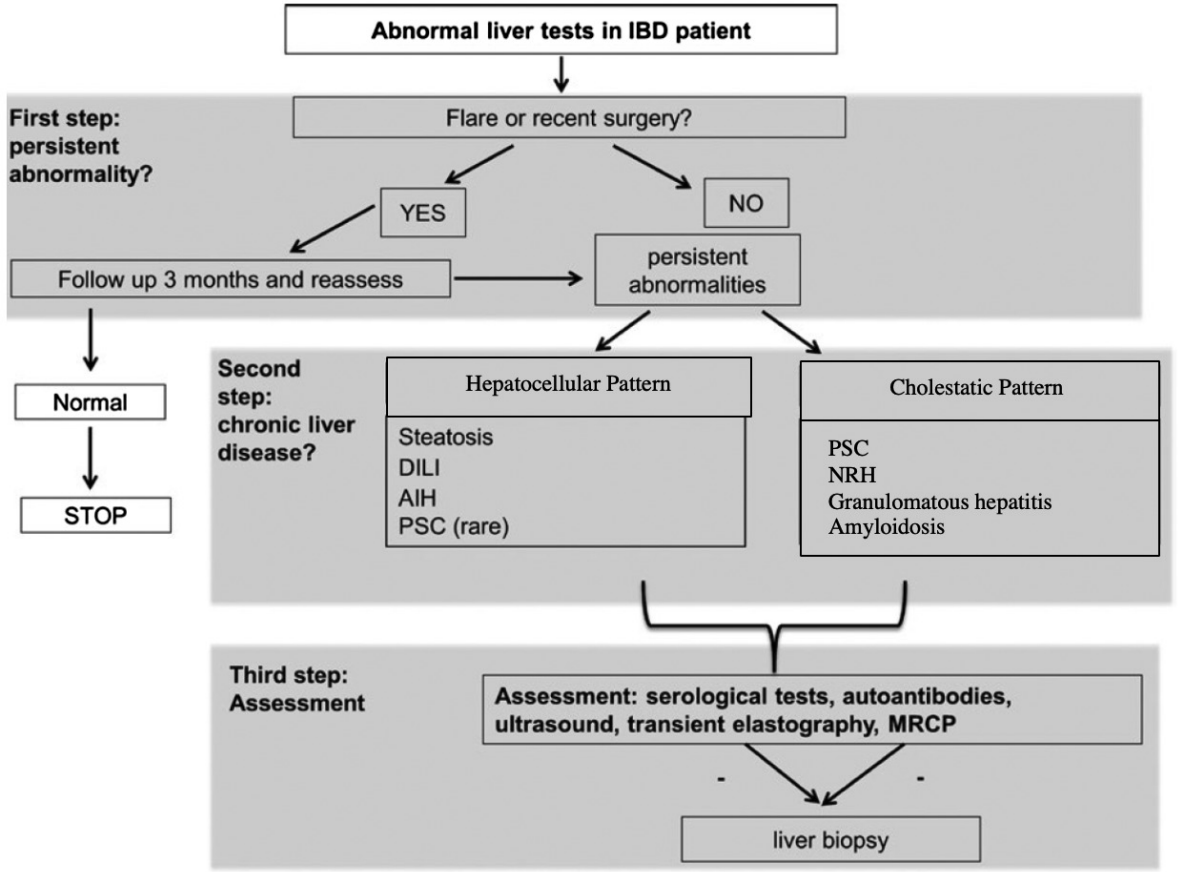
Check liver enzymes (AST, ALT, bili, alk phos) at least once a year

If there is an elevation in one of these labs:

- What is the history? Meds, alcohol use, weight change, symptoms, etc
- Acute or chronic abnormality (>6 mo)?
- Cholestatic, mixed or hepatocellular pattern?

Any platelet count <150 → consider advanced liver disease

Screen for viral hepatitis in all patients with IBD: HBsAg, HBsAb, HBcAb total, HCV Ab, HAV Ab total



Am J of Gastro. 2017 Feb;112(2):241-258. doi: 10.1038/ajg.2016.537. Epub 2017 Jan 10.

Liver International.4 Copyright 2017, John Wiley & Sons A/S.

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Normal Hgb, Plat ct 344

AST 41 ALT 85 ALP 172 bili 0.3 **Chronic, Mixed pattern**

Looking back, **outside labs were similar 8 mo ago**

Making the diagnosis

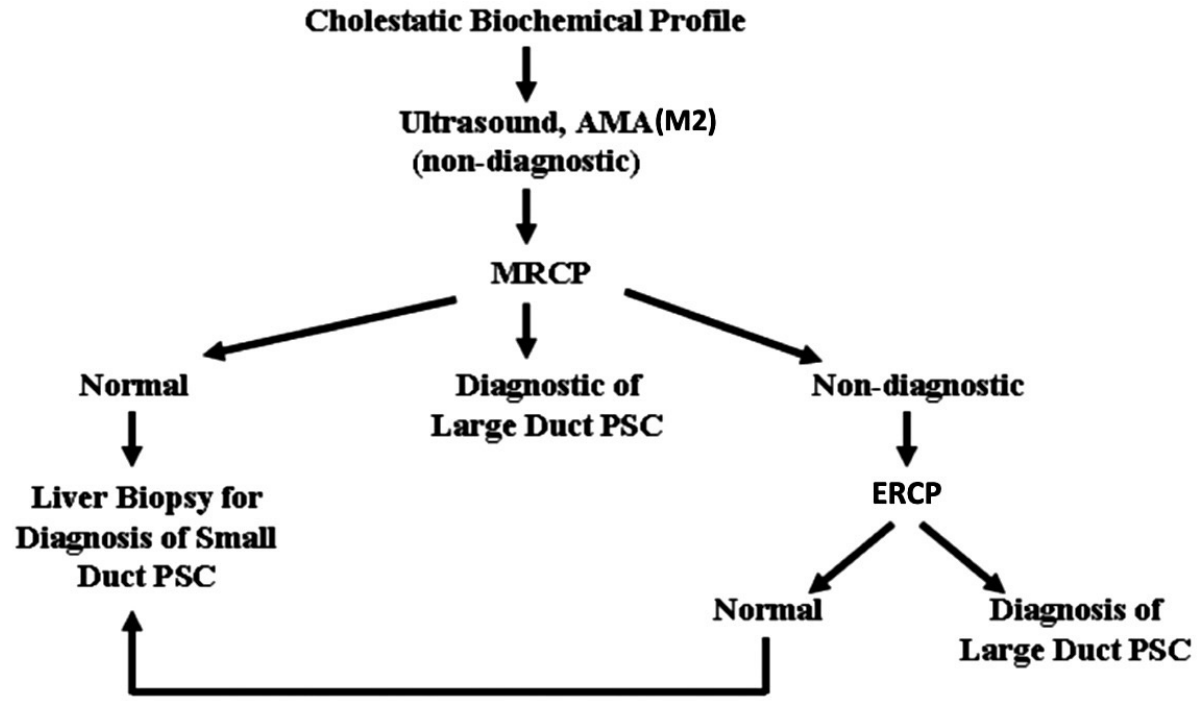
Hepatocellular pattern:

- Liver ultrasound with elastography
- ANA, ASMA, IgG total, viral hepatitis studies, A1AT level, iron profile and ferritin, ceruloplasmin
- Consider liver biopsy

Cholestatic pattern: see right fig.

Mixed pattern:

- Start with pattern that is more prominent
- If no diagnosis, complete work up of less prominent pattern



Mixed pattern → Hepatocellular pattern is more prominent:

- Liver ultrasound with elastography- **significant steatosis, grade 2 fibrosis**
- ANA, ASMA, IgG total, viral hepatitis studies, A1AT level, iron profile and ferritin, ceruloplasmin- **normal, immune to HBV, non-immune to HAV**

No support for A1AT def, hemochromatosis, HCV, HBV, autoimmune hepatitis

No risk factors for alcohol associated liver disease

Several risk factors for NAFLD, supported by US

Any chance of drug injury?

Be familiar with acute liver injury from drug induced liver injury (DILI)

Main features of drug-induced liver injury in inflammatory bowel disease

Drug	Characteristics of drug induced liver injury
Aminosalicylates	Increases in LFT; Cholestatic pattern; Rarely eosinophilia
Thiopurines	Influenced by TMPT polymorphisms > increase in 6-MMP, the hepatotoxic molecule; Increases in LFT; Idiosyncratic cholestatic reaction; Fever, rash, lymphadenopathy and hepatomegaly; Nodular regenerative hyperplasia
Anti-TNF	Idiosyncratic reaction > dose-dependent mechanism; Hepatocellular injury > cholestasis; Autoimmune phenomena
Anti-integrins	Rare; Asymptomatic LFT increase
Anti IL12/23	Mild LFT increase

LFT: Liver function test; TMPT: Thiopurine S-methyltransferase; TNF: Tumor necrosis factor.

LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet].

Vedolizumab

Last Update: August 20, 2020.

OVERVIEW

Introduction

Vedolizumab is a humanized monoclonal antibody to integrin α4β7 which is used in the treatment of inflammatory bowel disease. Vedolizumab has been linked to a low rate of serum enzyme elevations during therapy, but has not been linked to cases of idiosyncratic, clinically apparent liver injury with jaundice. Because vedolizumab is a potent inhibitor of lymphocyte function, it may cause reactivation of chronic hepatitis B in susceptible patients.

Hepatotoxicity

In prelicensure controlled trials, rates of serum ALT elevations during vedolizumab were not reported, although instances of serum enzyme elevations were described. ALT elevations above 5 times the upper limit of normal (ULN) were said to occur in <2% of vedolizumab and in a similar proportion of placebo recipients, and only rare patients had to stop therapy because of serum enzyme elevations. In the prelicensure trials, 3 patients were reported to have a severe adverse reaction of hepatitis, but the specific details were not given. Since its approval and more widespread use, there have been a few isolated reports of liver injury occurring during vedolizumab therapy but usually in the presence of other competing causes.

However, vedolizumab is a potent immunomodulatory agent and may be capable of causing reactivation of hepatitis B. To date, however, neither vedolizumab nor natalizumab (another monoclonal antibody to integrin α4β7) have been linked to instances of reactivation of hepatitis B. Nevertheless, because of the possibility of reactivation, screening for markers of HBV infection before starting therapy is prudent. Patients with HBsAg or anti-HBc in serum should be monitored for evidence of reactivation and treated promptly with antiviral therapy if HBV DNA or HBsAg appear.

Finally, vedolizumab may reactivate other viral infections and acute hepatitis due to an opportunistic viral infection.

Likelihood score: D (possible rare cause of clinically apparent liver injury).

Mechanism of Injury

Why a monoclonal antibody would cause hepatic injury is unclear. The mechanism of liver injury in reactivation of hepatitis B appears to be a brisk immunological response to newly expressed viral antigens. Injury generally arises after the immunosuppressive therapy has stopped or between courses of treatment.

Patient wrap up

Picture consistent with NAFLD

Vedolizumab injury **much** less likely- no need to change the med

Try conservative treatment: weight loss (7-10% TBW), exercise, diet

Consider biopsy if not improving

Liver biopsy in inflammatory bowel disease patients with sustained abnormal liver function tests: a retrospective single-center study

Emanuel Dias,[a] Patrícia Andrade,[a] Susana Lopes,[a] Raquel Gonçalves,[a] Pedro Cardoso,[a] Rui Gaspar,[a] Hélder Cardoso,[a] Joanne Lopes,[b] Fátima Carneiro,[b] and Guilherme Macedo[a]

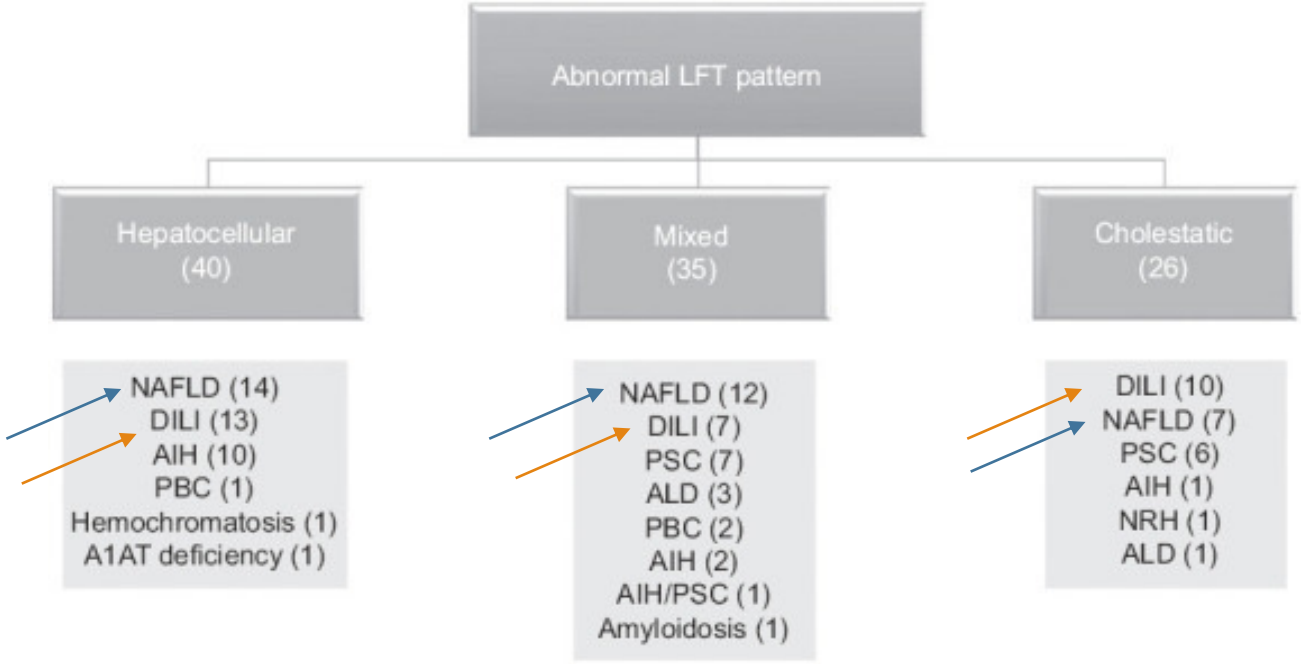
- 101 patients with IBD and >6 mo of abnormal liver enzymes
- Type of IBD:
  - 61.4% CD
  - 38.6% UC
- Pattern of liver injury
  - 40% hepatocellular injury
  - 26% cholestatic injury
  - 35% mixed liver injury

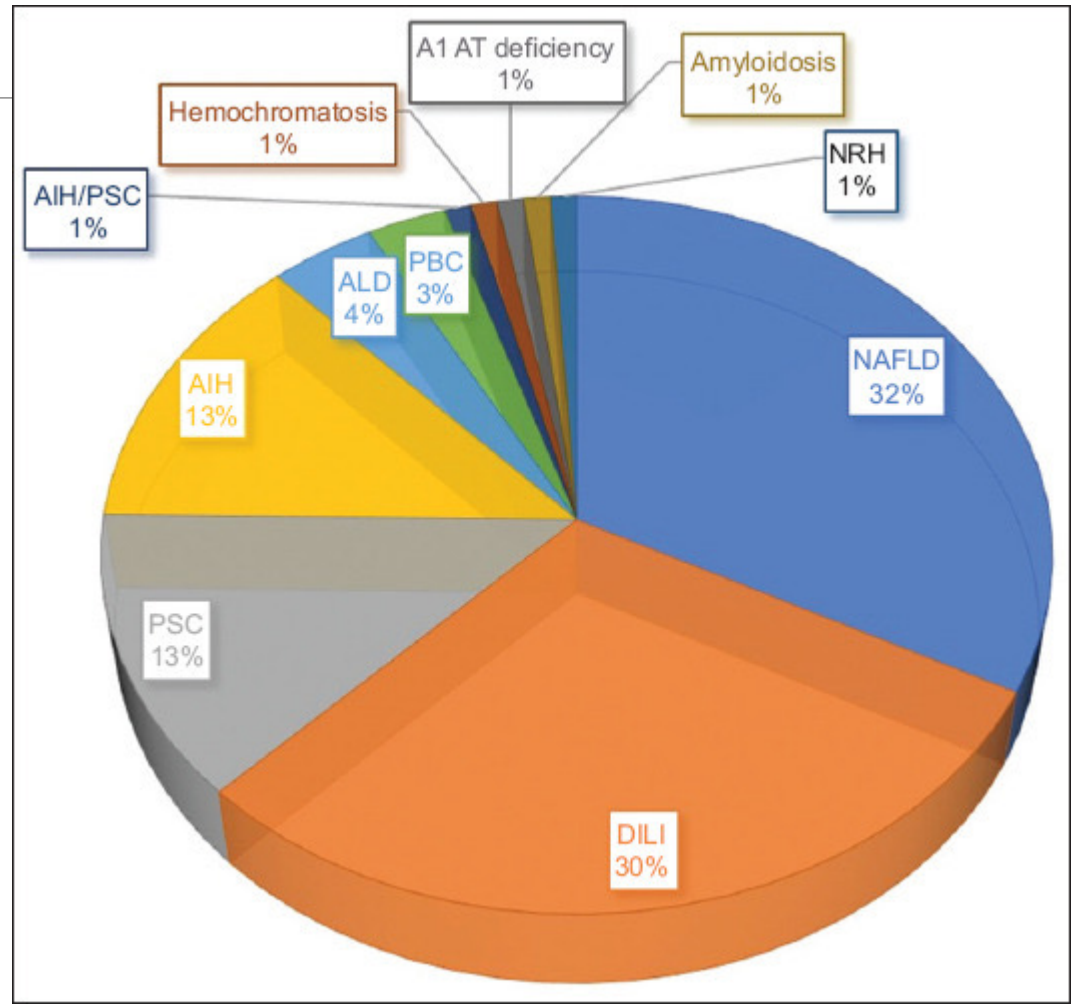
Median of 14 mo from abnormal lab until liver biopsy

Characteristics	Value	
Number of patients	101	
Age (mean ± standard deviation), years	44.4±13.2	
Sex		
Male	63	(62.4)
Female	38	(37.6)
IBD type *		
Crohn's disease	62	(61.4)
Ulcerative colitis	39	(38.6)
Disease duration (median, IQR), months	42 (8-112)	
IBD treatment		
5-ASA	68	(67.3)
Azathioprine	49	(48.5)
Azathioprine + infliximab	9	(8.9)
Infliximab	20	(19.8)
Adalimumab	11	(10.9)
Vedolizumab	3	(3.0)
Ustekinumab	3	(3.0)
Methotrexate	2	(2.0)
Abnormal LFT pattern		
Hepatocellular	40	(39.6)
Cholestatic	26	(25.7)
Mixed	35	(34.7)
Time interval between abnormal LFT and liver biopsy (median, IQR), months	14 (7-36)	

Ann Gastroenterol. 2023 Jan-Feb; 36(1): 54–60.

Causes of CLD in patients with IBD undergoing liver biopsy





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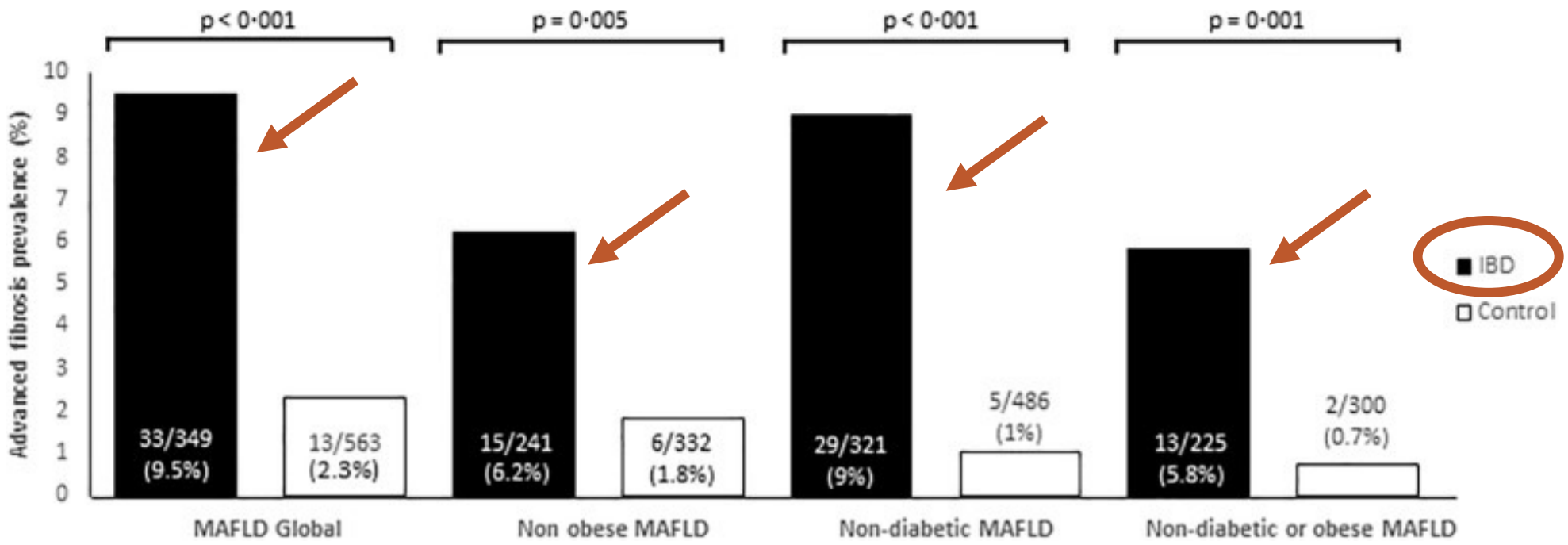
MASLD is more common in patients with IBD than weight-similar counterparts



JC RODRIGUEZ-DUQUE, ET AL. HEPATOLOGY. VOL 21, ISSUE 2, P406-414.E7, FEBRUARY 2023

Know when to refer to hepatology

- Any patient with cirrhosis
- New decompensating event (ascites,
- MELD score >10
- Dominant stricture in patient with PSC
- New diagnosis of autoimmune hepatitis
- New diagnosis of hepatitis B
- Worsening liver enzymes or hepatic synthetic dysfunction
- **Whenever you need another opinion**
- New onset of jaundice
- Liver mass concerning for malignancy

The work is never done

Picture consistent with NAFLD

Vedolizumab injury **much** less likely- no need to change the med

Try conservative treatment: weight loss (7-10% TBW), exercise, diet

Consider biopsy if not improving

Anything else you can do for this patient?

Optimize preventative care

Vaccines:

- PCV20 pneumococcal vaccine
- HBV and HAV vaccinations
- COVID vaccination, seasonally
- Zoster vaccination
- Influenza vaccine yearly

Colorectal cancer screening- per IBD guidelines PLUS **yearly in patients with PSC**

Mental health check ins and depression screening

Bone mineral density testing at diagnosis

Decrease risk of MASLD:

- Encourage healthy diet- limit alcohol and high fructose corn syrup
- 30 min moderate exercise daily
- maintenance of health weight (5-10% TBW loss if obese/overweight/MASLD)
- Close screening and aggressive treatment of metabolic derangements: DM, HTN, HLP

All patients with cirrhosis: remember varices and HCC screening

Stop/minimize alcohol use

Curr Treat Options Gastroenterol. 2021; 19(4): 583–596.

Don’t forget pneumococcal and Zoster vaccines!

For those who have not previously received any pneumococcal vaccine†, CDC recommends you:

- Give 1 dose of PCV15 or PCV20.
  - If PCV15 is used, this should be followed by a dose of PPSV23 at least one year later. The minimum interval is 8 weeks and can be considered in adults with an **immunocompromising condition, cochlear implant, or cerebrospinal fluid leak**.
  - If PCV20 is used, a dose of PPSV23 is NOT indicated.

† Also applies to people who received PCV7 at any age and no other pneumococcal vaccines.

What is already known about this topic?

Immunocompromised persons experience a higher incidence of herpes zoster and related complications. On July 23, 2021, the Food and Drug Administration expanded the indication for use of recombinant zoster vaccine (RZV) to include immunodeficient or immunosuppressed adults.

What is added by this report?

On October 20, 2021, the Advisory Committee on Immunization Practices recommended 2 RZV doses for prevention of herpes zoster and related complications in immunodeficient or immunosuppressed adults aged ≥19 years.

What are the implications for public health practice?

RZV is the first herpes zoster vaccine approved for use in immunocompromised persons. With moderate to high vaccine efficacy and an acceptable safety profile, RZV has the potential to prevent considerable herpes zoster incidence and related complications.

https://www.cdc.gov/vaccines/vpd/pneumo/hcp/who-when-to-vaccinate.html

Recognize acute worsening of liver injury

Watch for: Liver enzymes increasing, signs of portal hypertension, weight loss, jaundice, pruritis, RUQ pain/fever/chills

Questions to ask yourself:

- Any new medications? Map out the time course. Be familiar with LiverTox through the NIH
- Any herbal/dietary supplements?
- Flare of autoimmune hepatitis?
- Signs of biliary obstruction?
- Is patient up-to-date with HCC, CRC and varices screening?
- Any signs of infections?

In Summary…

Keep in mind that chronic live disease and IBD frequently cross paths

Be sure to occasionally screen for liver injury in patients with IBD

Know how to work up chronic liver enzyme abnormalities in this population based on pattern of liver disease

UC patients with PSC need YEARLY colonoscopy due to higher risk of CRC

Do not miss an opportunity to vaccinate these patients!

All IBD patients are higher risk for MASLD → address risk factors early

Know you can refer/defer to us at any time!

Thank you!