Work up to management of chronic liver disease

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Gastroenterology

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Conflict of Interest and Disclosures

Financial Interest or Affiliation	Commercial Enterprise(s)
Financial Disclosure	
Advisory Board or similar committee	AbbVie, Janssen, Knight, Pfizer, Merck, Takeda, GSK, Eli Lilly, JAMP
Clinical trials or studies	AbbVie
Honoraria or other fees (e.g., travel support)	AbbVie, Janssen, Takeda, Gilead, Lupin, Advanz, Pfizer, Bausch, GSK
Research grants	
Other (specify)	

Objectives

- Recognize chronically elevated liver enzyme patterns
- Utilize clinical care pathway to help with diagnosing and managing patients with chronically elevated liver enzymes and cirrhosis
- Develop approach to management of compensated and decompensated cirrhosis

CanMEDS Roles Covered

X	**Medical Expert** (as *Medical Experts*, physicians integrate all of the CanMEDS Roles, applying medical knowledge, clinical skills, and professional values in their provision of high-quality and safe patient-centered care. *Medical Expert* is the central physician Role in the CanMEDS Framework and defines the physician's clinical scope of practice.)
X	**Communicator** (as *Communicators*, physicians form relationships with patients and their families that facilitate the gathering and sharing of essential information for effective health care.)
X	**Collaborator** (as *Collaborators*, physicians work effectively with other health care professionals to provide safe, high-quality, patient-centred care.)
X	**Leader** (as *Leaders*, physicians engage with others to contribute to a vision of a high-quality health care system and take responsibility for the delivery of excellent patient care through their activities as clinicians, administrators, scholars, or teachers.)
X	**Health Advocate** (as *Health Advocates*, physicians contribute their expertise and influence as they work with communities or patient populations to improve health. They work with those they serve to determine and understand needs, speak on behalf of others when required, and support the mobilization of resources to effect change.)
X	**Scholar** (as *Scholars*, physicians demonstrate a lifelong commitment to excellence in practice through continuous learning and by teaching others, evaluating evidence, and contributing to scholarship.)
X	**Professional** (as *Professionals,* physicians are committed to the health and well-being of individual patients and society through ethical practice, high personal standards of behaviour, accountability to the profession and society, physician-led regulation, and maintenance of personal health.)

Why do a care pathway?

- Clinical care pathways becoming more common
- Allows for more timely work up and guidance
- Possible diagnosis can be made even before referral is seen
- Help “spot” serious condition which may have otherwise been delayed
- Empowers primary care with guidance and resources
- Help specialist with triaging

Moncton GI Elevated Liver Enzyme Algorithm

Moncton GI NAFLD Care Pathway Algorithm

Case 1

- Mr. Smith
- 65 year old male coming in for sore left ankle
- He was playing squash and rolled ankle and was hoping to get something for pain
- He hasn’t seen you in a few years and you tell him he should have some bloodwork
- He has no other complaints and tells you he feels fine
- He drinks moderate alcohol on weekends and a few glasses of wine throughout week

Case 1

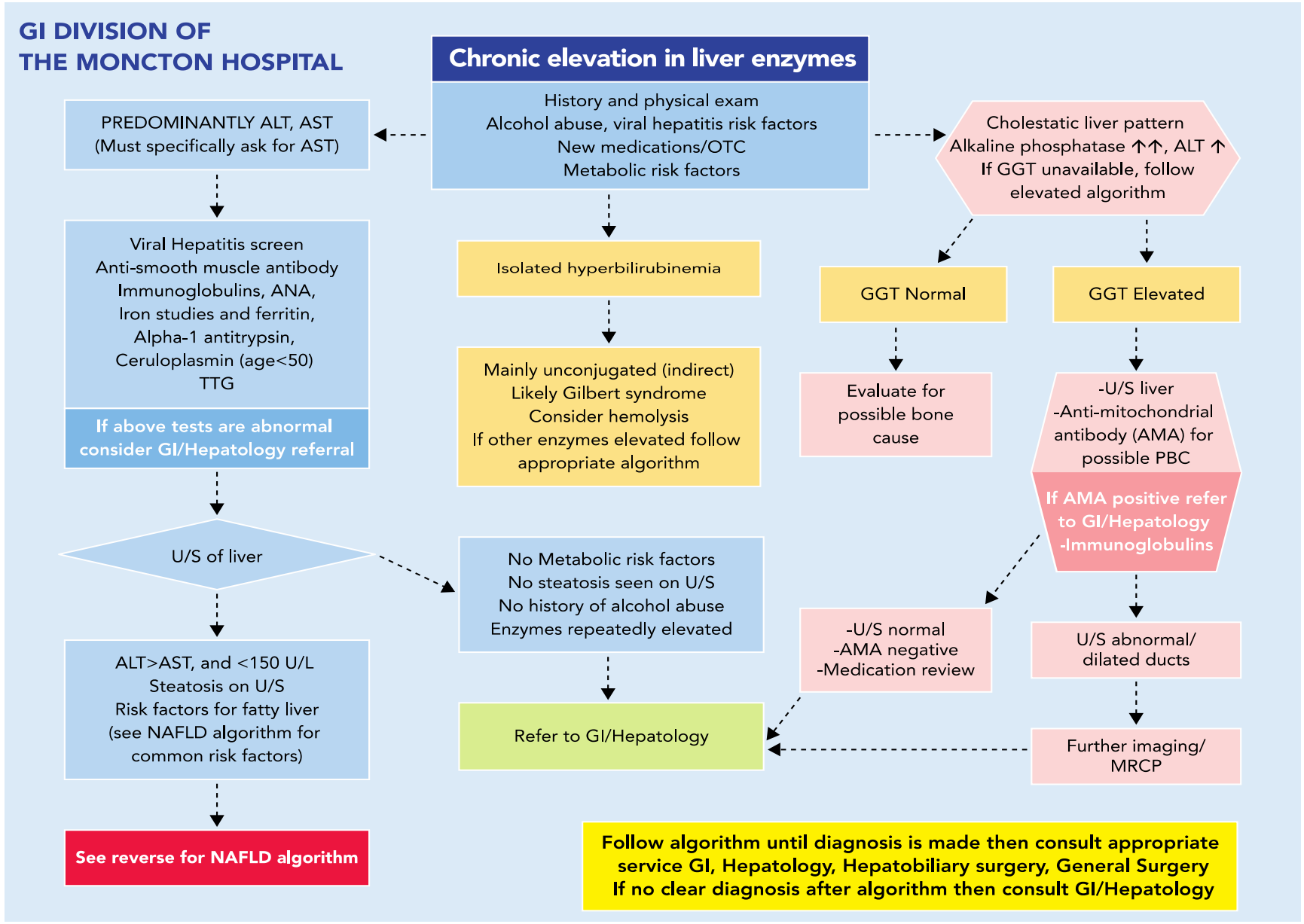
- He does not consume cannabis nor any other OTC or drugs
- He considers himself in good shape and better than majority of his friends
- He is married with 2 children and is retired lawyer who still does consulting
- On exam is he overweight at 210 lbs. and is 5’10- BMI 30.1
- His Blood pressure is 148/94 and HR 78
- He looks surprised with his results and when you tell him he is overweight

Case 1

- He agrees to some bloodwork before a Rx for pain
- His CBC shows WBC 11, HBG 156 and platelets 170
- Creatinine is 94 and lytes are normal
- ALT-140, AST- 80, T bili 16, Alk Phos 101
- You look back into bloodwork and his enzymes were similar in 2019 but he didn’t do the repeat BW due to covid restrictions and personal concerns

Case 1-poll

- You bring him back to office to discuss enzymes
    - 1) Refer to GI and let them talk to him and sort it out
    - 2) Tell him to stop drinking and repeat in 3-6 months
    - 3) Tell him to lose 20lbs and repeat in 3-6 months
    - 4) Order an ultrasound and repeat BW in 3-6 months
    - 5) all of the above


GI DIVISION OF
THE MONCTON HOSPITAL
Chronic elevation in liver enzymes
History and physical exam
Alcohol abuse, viral hepatitis risk factors
New medications/OTC
Metabolic risk factors
PREDOMINANTLY ALT, AST
(Must specifically ask for AST)
Viral Hepatitis screen
Anti-smooth muscle antibody
Immunoglobulins, ANA,
Iron studies and ferritin,
Alpha-1 antitrypsin,
Ceruloplasmin (age<50)
TTG
If above tests are abnormal
consider GI/Hepatology referral
U/S of liver
ALT>AST, and <150 U/L
Steatosis on U/S
Risk factors for fatty liver
(see NAFLD algorithm for
common risk factors)
See reverse for NAFLD algorithm
Isolated hyperbilirubinemia
Mainly unconjugated (indirect)
Likely Gilbert syndrome
Consider hemolysis
If other enzymes elevated follow
appropriate algorithm
No Metabolic risk factors
No steatosis seen on U/S
No history of alcohol abuse
Enzymes repeatedly elevated
Refer to GI/Hepatology
Cholestatic liver pattern
Alkaline phosphatase ↑↑, ALT ↑
If GGT unavailable, follow
elevated algorithm
GGT Normal
Evaluate for
possible bone
cause
GGT Elevated
-U/S liver
-Anti-mitochondrial
antibody (AMA) for
possible PBC
If AMA positive refer
to GI/Hepatology
-Immunoglobulins
-U/S normal
-AMA negative
-Medication review
U/S abnormal/
dilated ducts
Further imaging/
MRCP
Follow algorithm until diagnosis is made then consult appropriate
service GI, Hepatology, Hepatobiliary surgery, General Surgery
If no clear diagnosis after algorithm then consult GI/Hepatology

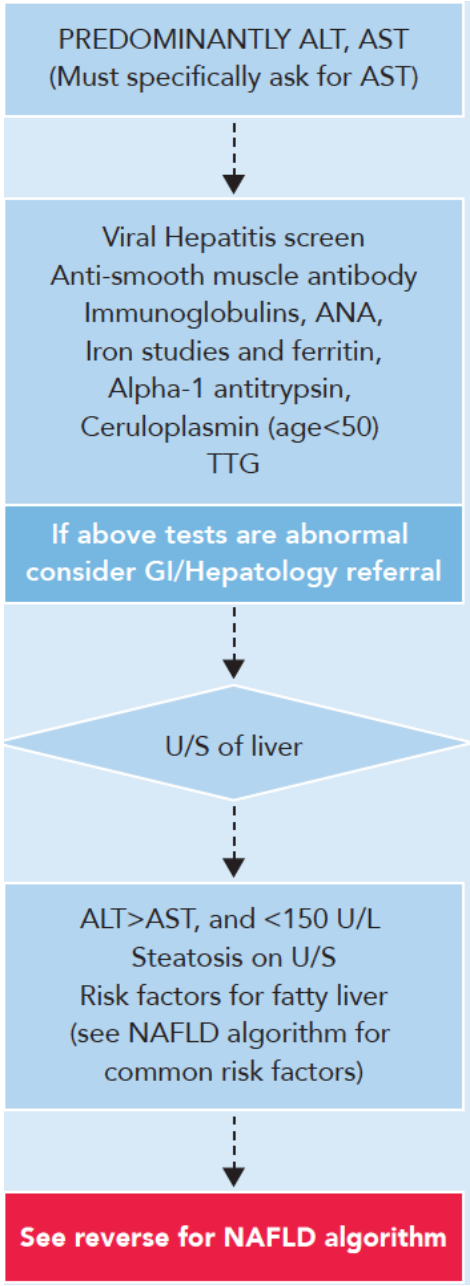
First step

- Hx and Physical important to assess for sign of chronic liver disease
- Alcohol history- sometimes difficult
- Viral hepatitis risk factors
  - Now or in past
- New Meds, OTC and herbal
- Metabolic risk factors

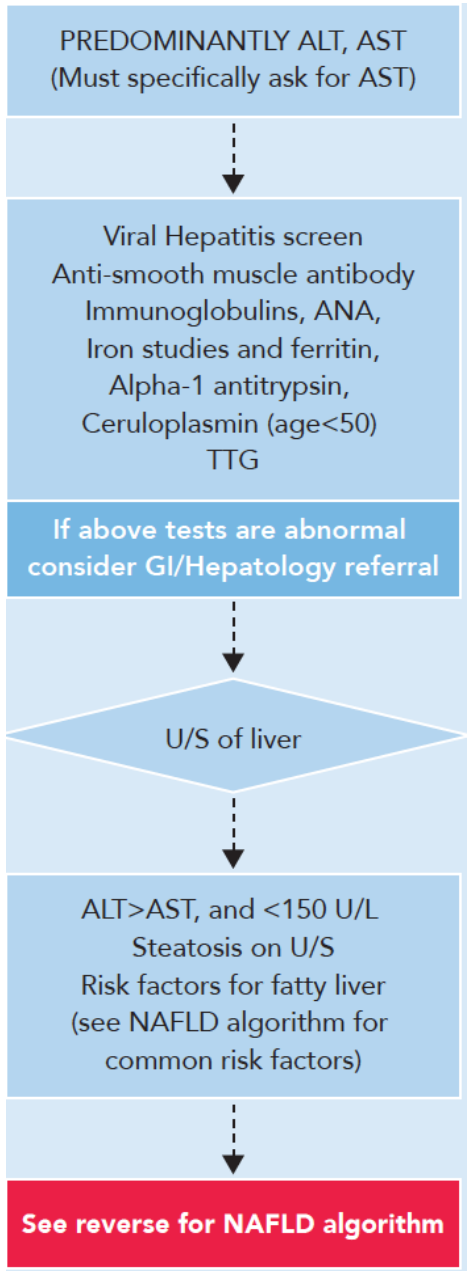
Chronic elevation in liver enzymes

History and physical exam
Alcohol abuse, viral hepatitis risk factors
New medications/OTC
Metabolic risk factors

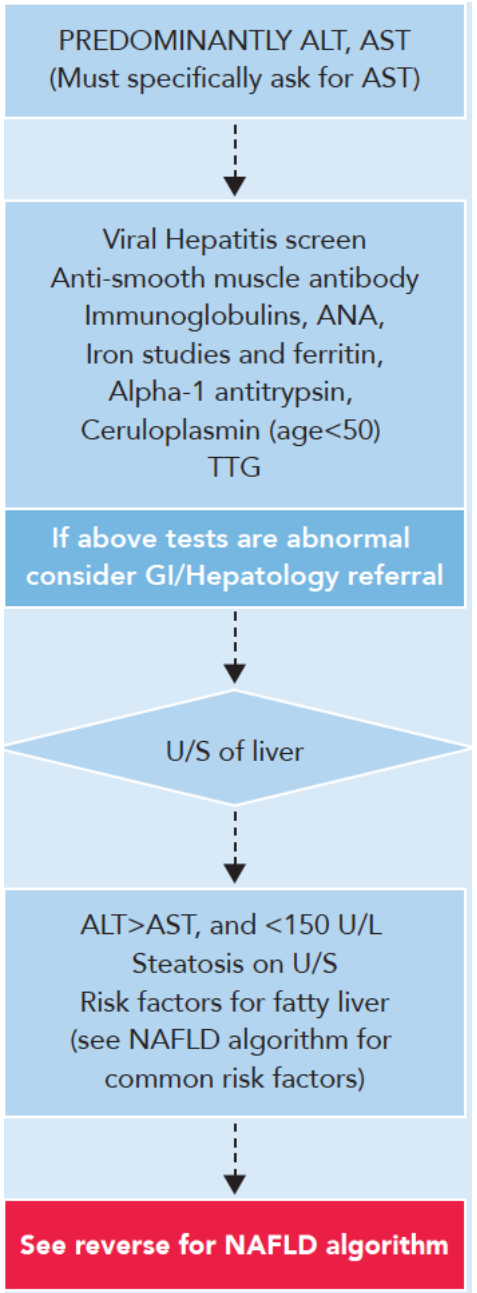
- AST helpful- especially for prognostication
  - Can you order this?
- Viral hepatitis screen
  - Hep B and C
- ASMA- looking for autoimmune hepatitis
- Immunoglobulins
  - IgA- Alcohol/Fatty liver
  - IgM- PBC
  - IgG- Autoimmune hepatitis



- ANA- Autoimmune hepatitis
- Iron studies- Hemochromatosis
  - Need more than ferritin
- Alpha-1 antitrypsin deficiency
- Ceruloplasmin
  - If young and low value
- Celiac disease
  - Can cause chronic liver disease



- If above tests give diagnosis then refer as indicated
- Imaging next but can really be done at same time
- If all w/u unremarkable has metabolic risk factors can go to fatty liver pathway



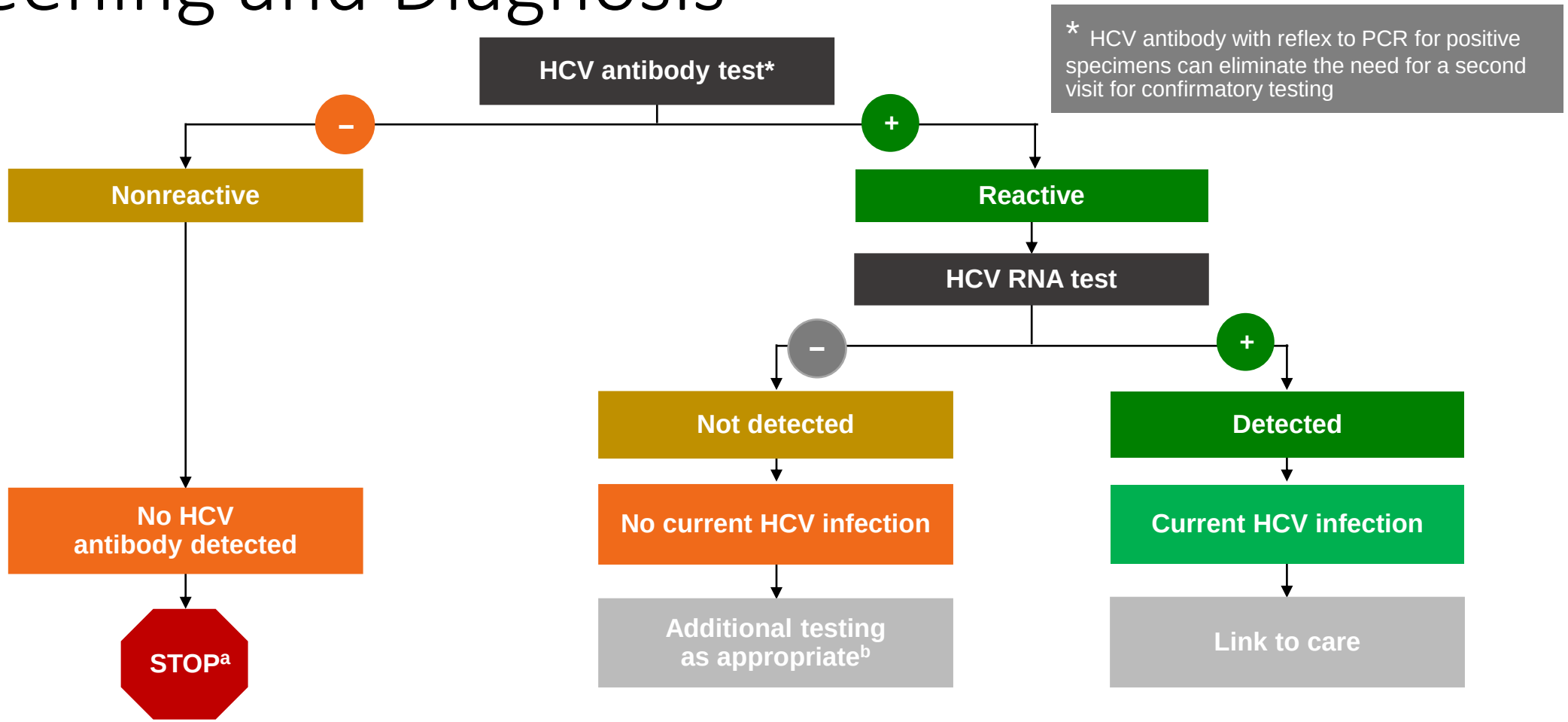
Case 1

- Mr. smith undergoes your investigations
- His ASMA, ANA and Alpha 1- antitrypsin are all normal
- TTG is negative and ceruloplasmin was not order due to age
- His iron studies show his ferritin is 430 but rest of iron studies are normal
- His viral hepatitis screen is negative for Hepatitis B but his Hep C antibody comes back positive and then his PCR confirms positive Hep C

Case 1

- When discussing results he says in his late teens he experimented with IV drugs but didn’t think that was relevant today
- He undergoes FIB-4 test which shows F3 fibrosis and he is later started on Epclusa for Hep C
- He tolerates medication very well and his SVR 12 shows virus eradicated

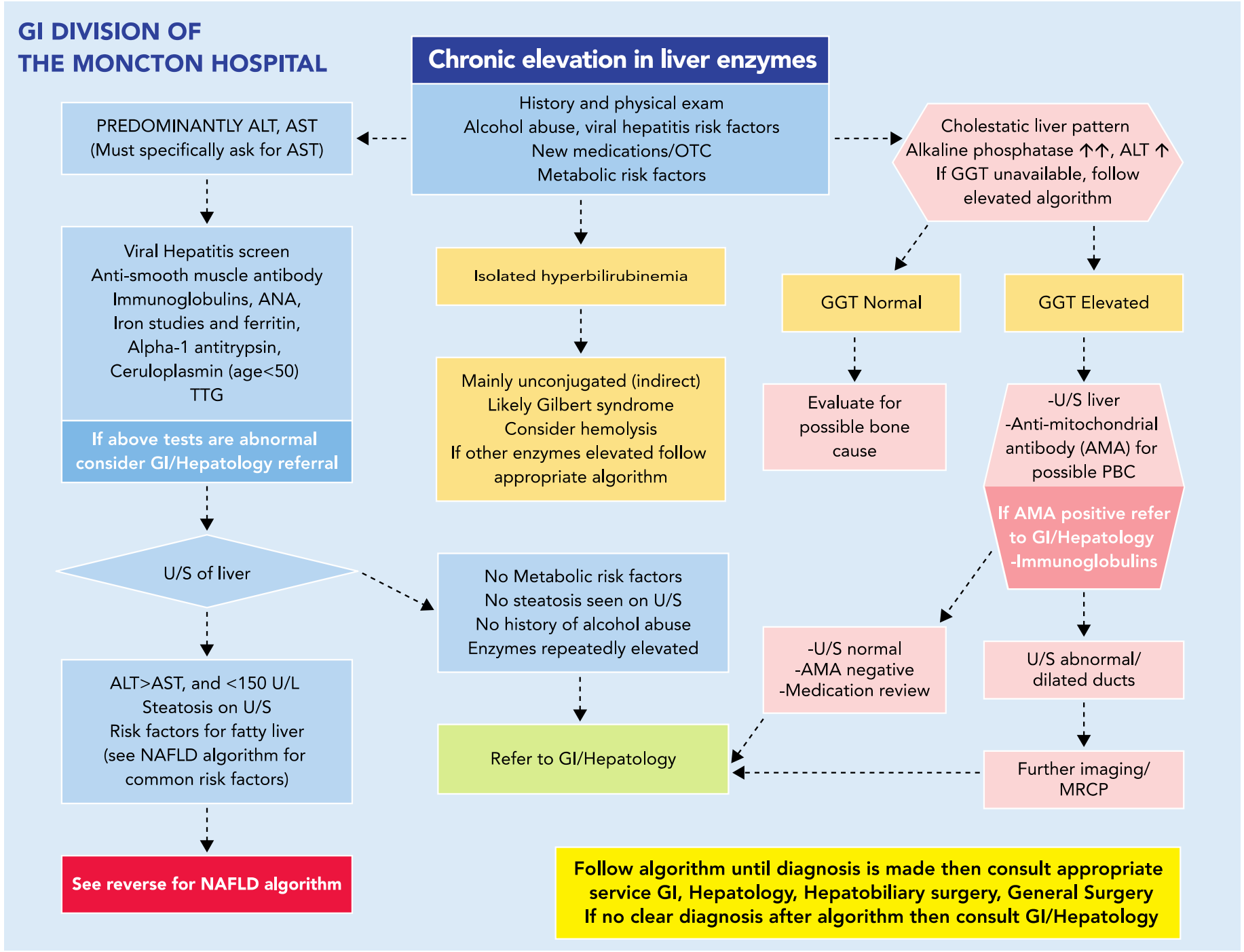
Recommended Testing Sequence for HCV Screening and Diagnosis



[a]For persons who might have been exposed to HCV within the past 6 months, testing for HCV RNA or follow-up testing for HCV antibody is recommended. For persons who are immunocompromised, testing for HCV RNA can be considered.

[b]To differentiate past, resolved HCV infection from biologic false positivity for HCV antibody, testing with another HCV antibody assay can be considered. Repeat HCV RNA testing if the person tested is suspected to have had HCV exposure within the past 6 months or has clinical evidence of HCV disease, or if there is concern regarding the handling or storage of the test specimen.

Adapted from CDC. MMWR. 2013;62:1-4.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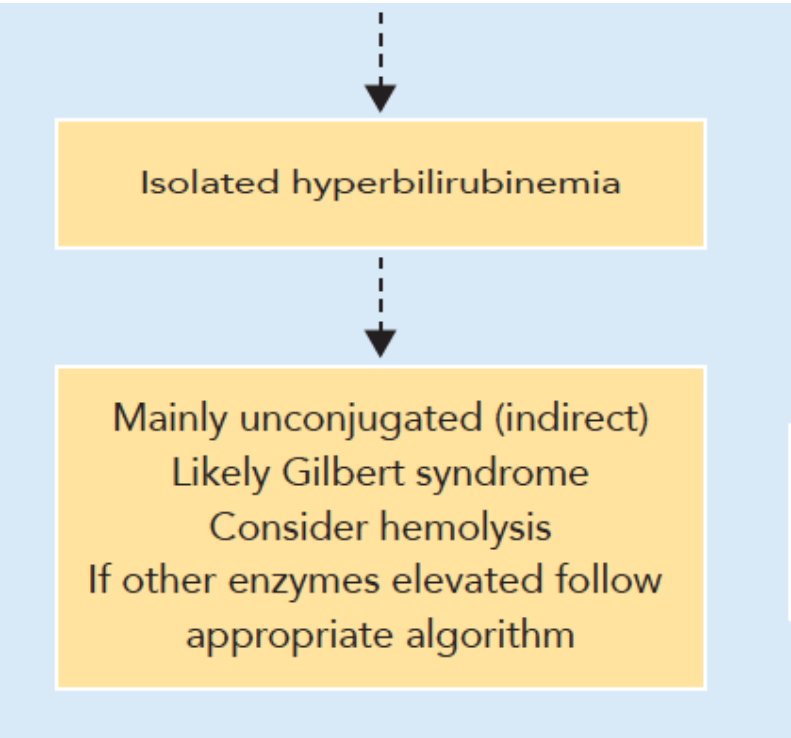
Hyperbilirubinemia



- If isolated bilirubin look at direct vs indirect
- If other enzymes elevated then follow that pathway
- Most commonly Gilbert syndrome
- Benign condition which does not require surveillance

Case 2

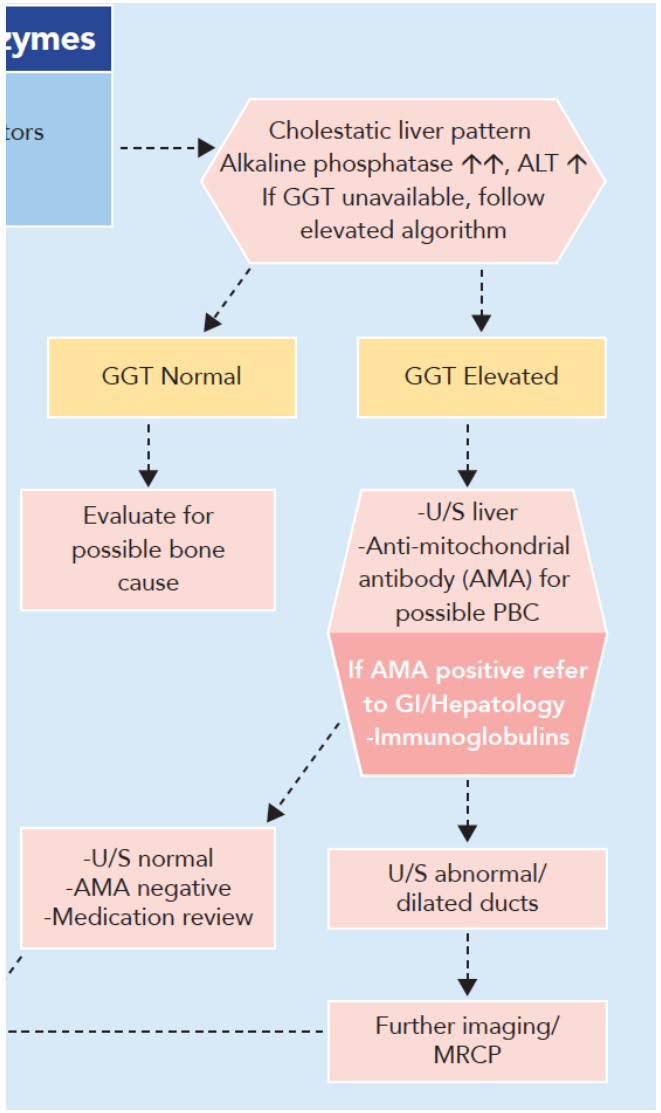
- Mrs. Smith decides she better have a check up after talking with her husband and his new diagnosis
- She is a fit 62 year old female on no meds and exercises 4/week
- She drinks 2-3 glasses of wine per week
- Her physical exam is normal with BP- 104/68, BMI- 22
- She is sent for screening blood work with hepatitis screen

Case 2

- Her WBC 9, HBG 147 and platelets 204
- Alt 48, AST 38, Alk phos 408, GGT 290 and T bili 18
- Her Hep B and C antibody is negative
- You bring her in to discuss results
- You look back and her Alk Phos was 200 in 2014
- She swears she doesn’t drink more than 2-3 glasses wine/ week
- You order an U/S to ensure no stones and U/S is completely normal
- Now what?

Case 2- Poll

1. Repeat BW in 3-6 months and hope normalizes
2. Order bone specific Alk Phos
3. Order immunoglobins and AMA
4. Refer for ERCP
5. Refer to GI to sort out

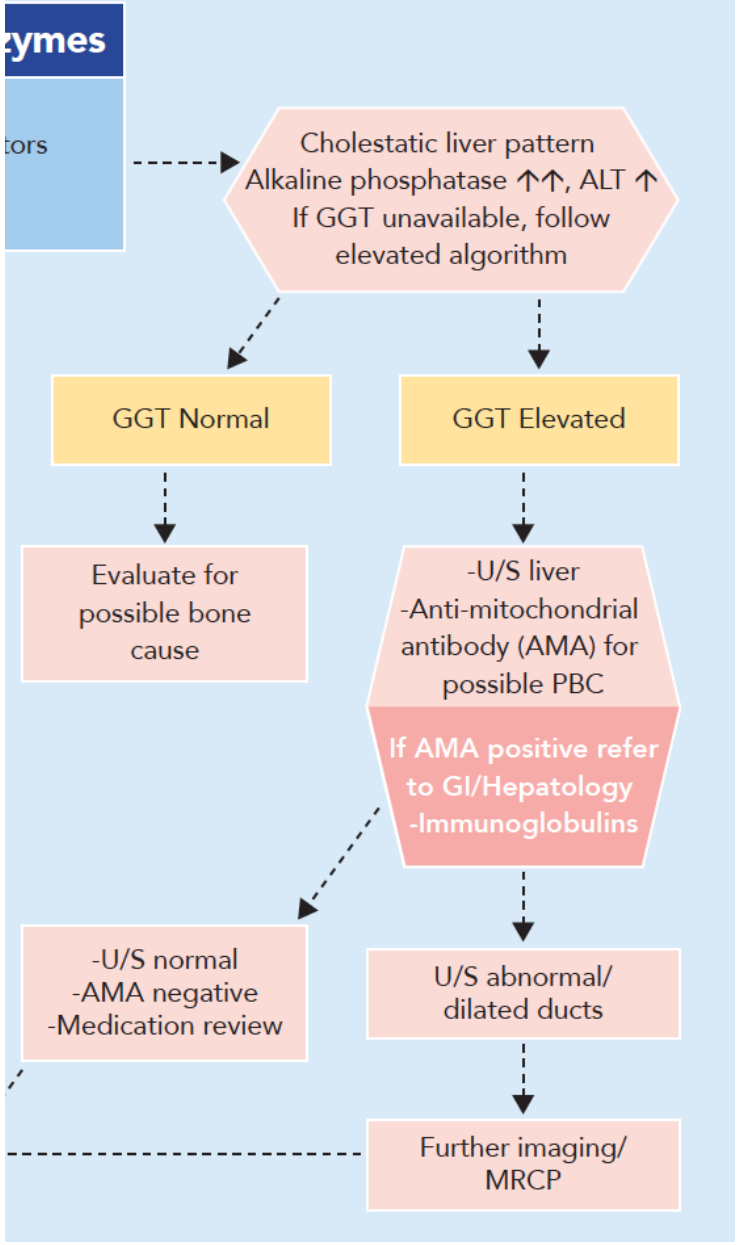


- Cholestatic liver pattern
- Alkaline phosphatase and GGT elevated more than transaminases
- GGT does not go up in bone disease

Cholestatic liver disease

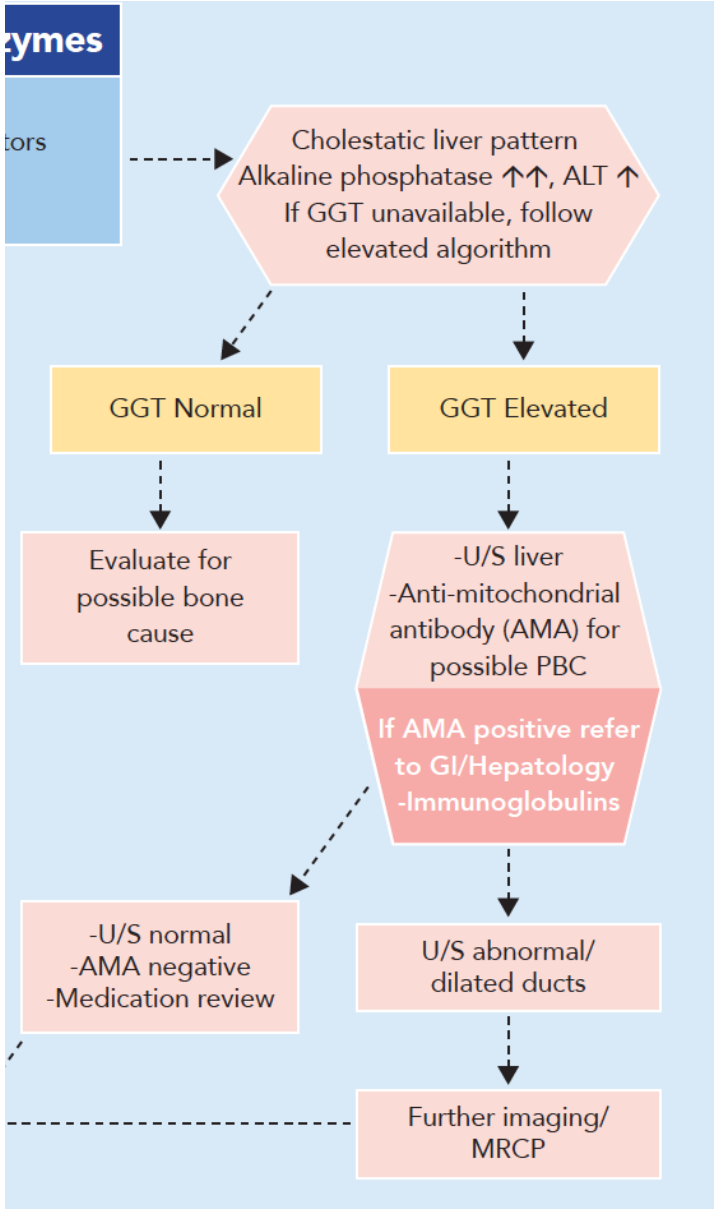
- Intrahepatic vs extrahepatic
- Drugs
- PBC
- PSC
- Granulomatosis Disease
- Viral
- Malignancy
- Infiltrative

- U/S liver to look for extrahepatic causes/ cirrhosis/ PSC
- AMA- assess for Primary biliary cholangitis
- Immunoglobulins (IgM)
- Medication review important
- Livertox.nih.gov



- MRCP helpful if abnormal Bile ducts on U/S
  - Malignancy, stricture, cysts, infections

- If work up negative and alkaline phosphatase remains 1.5x ULN then referral depending on clinical context



Case 2

- You follow algorithm and send her AMA and immunoglobulins
- You also do full med review of OTC and everything clear
- Her AMA comes back positive with IgM elevated
- She is then referred to GI and a diagnosis of Primary Biliary Cholangitis is confirmed
  - Diagnosis can be made with positive AMA and cholestatic liver pattern
  - Liver biopsy often not required

Primary Biliary Cholangitis (PBC)

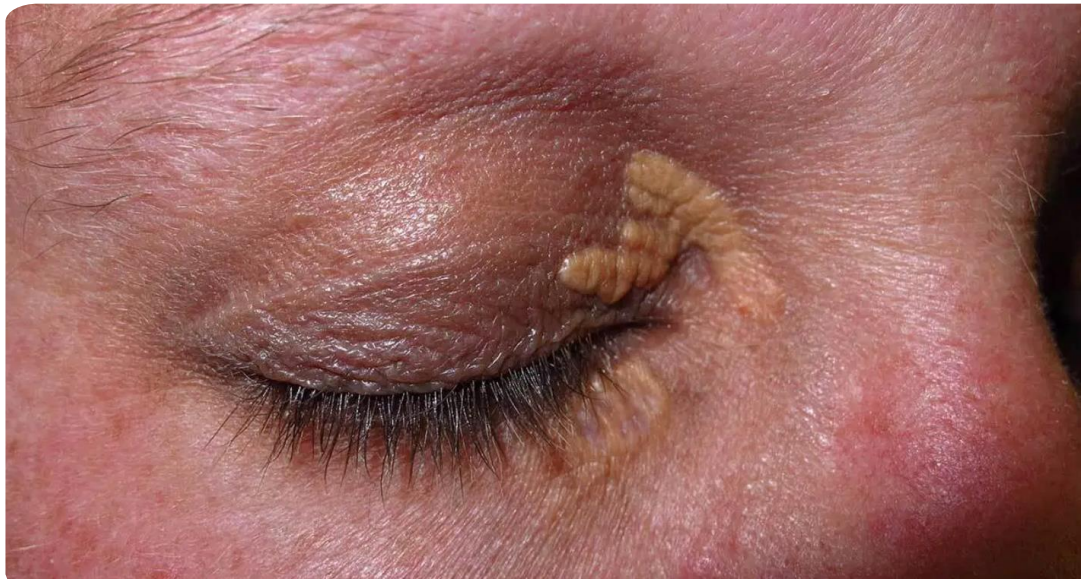
- Usually affects Middle-aged women
- Typically 9:1 women to men
- Some studies show 0.5% population test positive for AMA
- Risk is highest in daughter of index cases
- Roughly 13% of 1st degree relative with PBC have positive AMA
- AMA is present in 95% of patients with PBC

Textbook of Hepatology From Basic Science to Clinical Practice. 3rd edition

PBC

- Patients typically can have
  - Fatigue
  - Pruritis
  - Elevated cholesterol
  - Sjogren syndrome
  - Xanthelasma

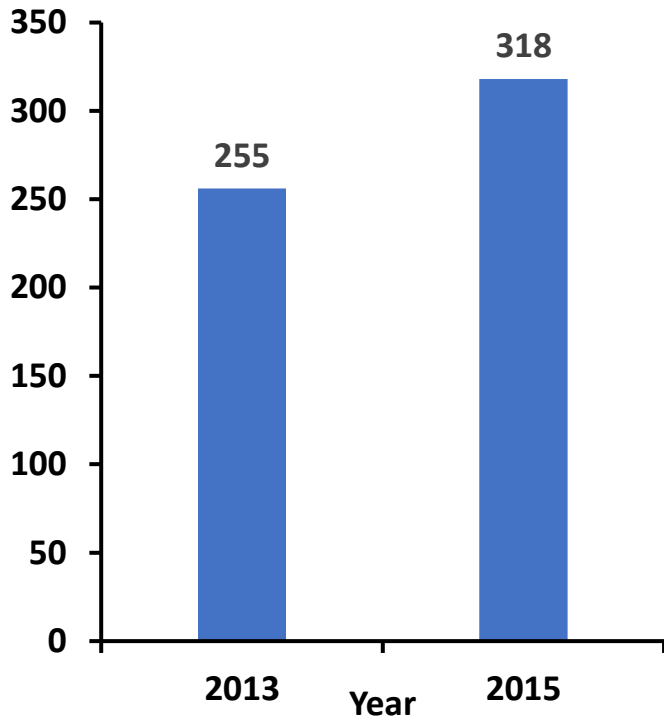
- Very treatable condition with two drugs approved for treatment
  - Ursodiol
  - Obeticholic acid



Textbook of Hepatology From Basic Science to Clinical Practice. 3rd edition

Background

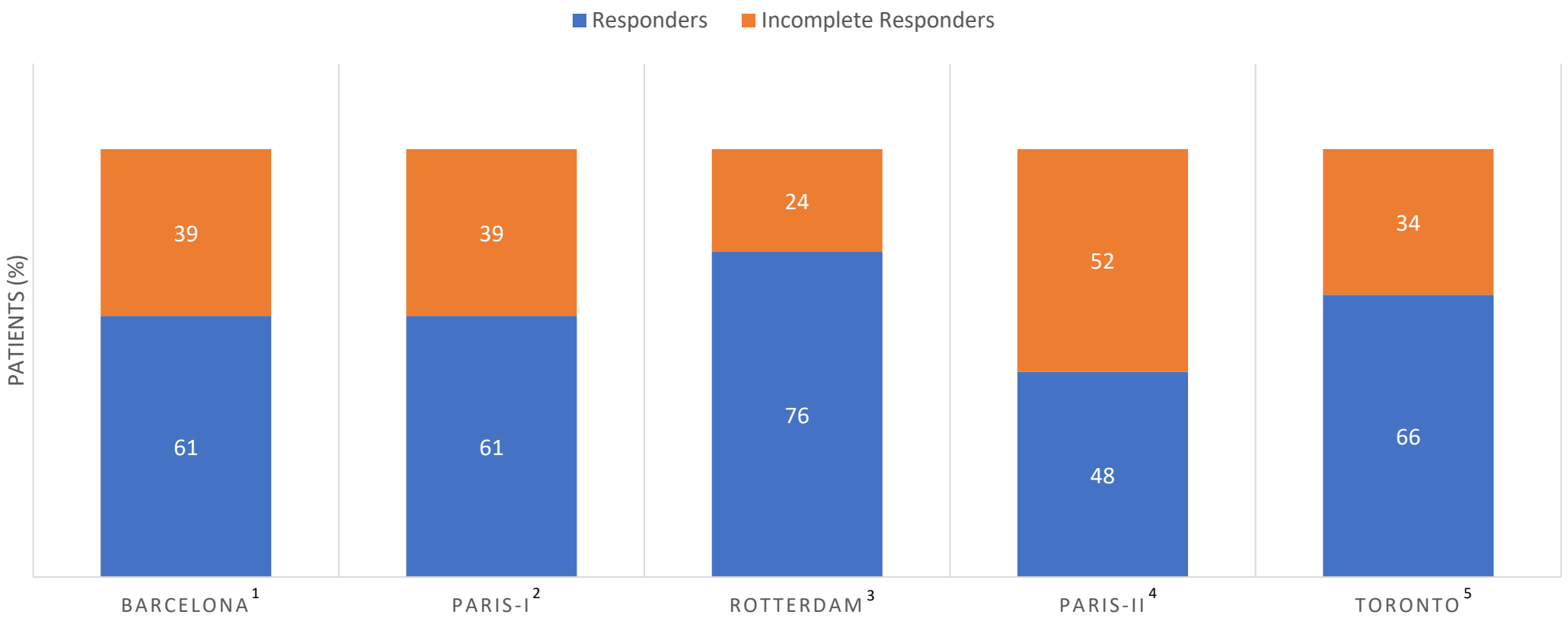
- Prevalence of PBC
  - 318 per million people in Canada



Annual prevalence of PBC in Canada 2013 and 2015

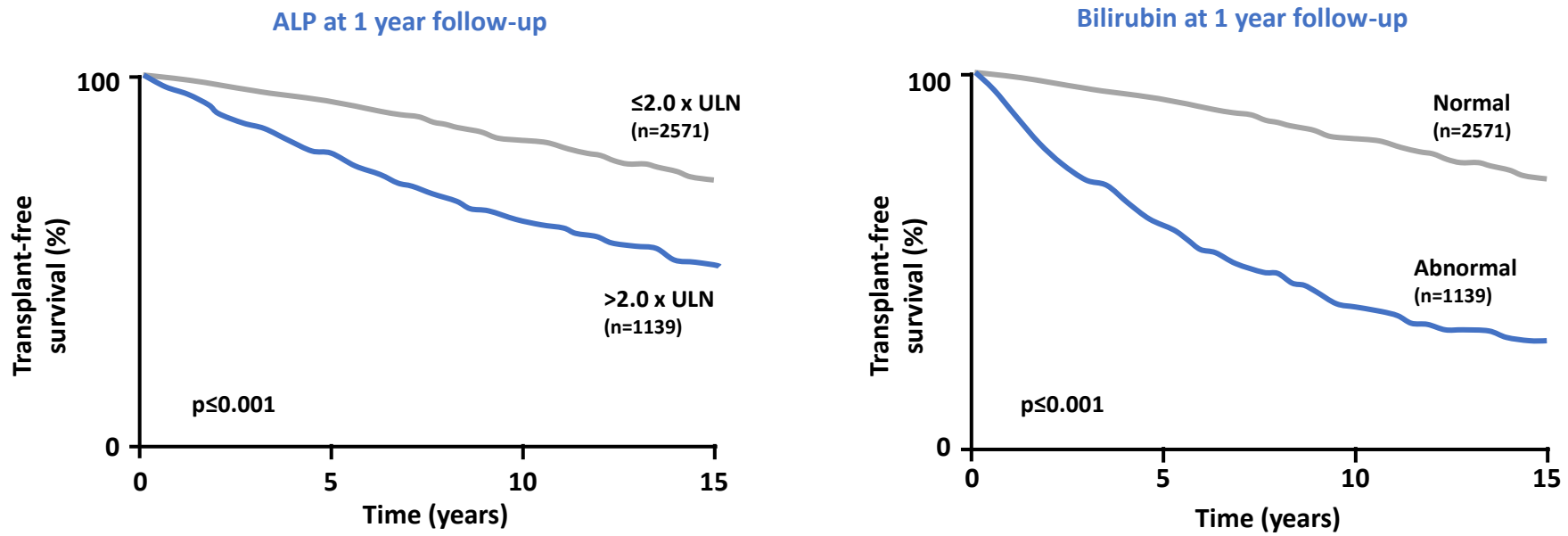
Yoshida EM *et al*. 2018. CMAJ Open 6(4):E664-E670.

Response to UDCA Treatment



. Parés A *et al*. 2006. Gastroenterology 130(3):715-20. 2. Corpechot C *et al*. 2008. Hepatology 48(3):871-77. 3. Kuiper EM, *et al*. 2009. Gastroenterology 136(4):1281-1287. 4. Corpechot C *et al*. 2011. J Hepatol. 55(6)1361-1367. 5. Kumagi T *et al*. 2010. Am J Gastroenterol. 105(10):2188-2194.

Surrogate Markers of PBC
ALP and Bilirubin



- ALP > 1.5 X ULN were independently associated with a 2.0- to 2.5-fold increased risk of LT or death when compared to normal ALP values
- TB > ULN were associated with a 5.1- to 10.7-fold increased risk of LT or death when compared to normal serum TB values

Lammers WJ *et al*. 2014. Gastroenterology 147(6):1338-1349.

OCA in PBC: Real-World Cohorts

Country	Publication and Date	Number of Patients	Duration	Key Outcomes
United Kingdom[1]	EASL 2019	65	12 months	Reduction Paris-II criteria, ALP, bilirubin, ascites, varices, variceal bleeding and liver transplantation
Austria[2]	AASLD 2019	33	Median 13 months	Reduction in ALP, ALT, GGT and bilirubin
Canada RWE[3]	**Hepatol Commun 2020**	**64**	**Median 13.1 months**	**Reduction in ALP, ALT, AST, GGT, and IgM**
France[4]	EASL 2020	128 12 months (n=50) 18 months (n=40)	Ongoing	Reduction of ALP, AST, ALT, GGT, pruritus. Increase in proportion reaching Paris-II criteria.
Spain/Portugal RWE[5]	**Aliment Pharmacol Ther 2020**	**123**	**12 months**	**Reduction in GLOBE and UK-PBC risk scores; POISE and PARIS-II criteria, ALP, ALT, AST, bilirubin, FIB-4 and APRI**
United States[6]	AASLD 2020	319	Up to 3 years	Higher proportion of patients reaching Toronto & Paris-I criteria
Global PBC Study Group[7]	AASLD 2020	290	12 months	Reduction of ALP, GGT, ALT, albumin. TB and platelets stable.
Italy[8]	**JHEP Reports 2021**	**191**	**12 months**	**Reduction in POISE criteria, bilirubin, ALP, ALT**

. Culver E *et al*. 2019. Hepatology Abstract 1271. 2. Bota S *et al*. 2019. Hepatology Abstract 1321. **3.** Roberts SB *et al*. 2020. Hepatol Commun. 4(9):1332-1345. 4. Leroy V *et al*. 2020. EASL, Abstract FRI-180. **5.** Gomez E *et al*. 2020. Aliment Pharmacol Ther. 53:519-530. **6.** Gish RG *et al*. 2020. Hepatology Abstract 1268. **7.** Gulamhusein AF *et al*. 2020. Hepatology Abstract 1267. 8. D'Amato D *et al*. 2021. JHEP Reports 3:100248.

PBC and case 2

- She is started on Ursodiol and her Alkaline phosphatase after 12 months is still elevated at 348.
- Obeticholic acid is then added and in 6 months her Alkaline phosphatase is 148 and she is feeling well
- She develops some mild pruritis which is controlled with Cholestyramine intermittently

Case 3

- Mr. Lays is in for assessment
- He is a 71 year old retired school teacher
- Has history of diabetes, dyslipidemia, hypertension
- BMI is 34
- Does not drink alcohol and is avid stamp collector
- You review his bloodwork and see his ALT is rising and now 124
- You put AST on requisition but it wasn’t done

Case 3

- His WBC is 6, HBG 120 and platelets are 165
- Alk Phos, GGT, Bilirubin all normal
- U/S liver shows diffuse fatty liver
- He has tried exercising in past yet has bad knees and can’t do much
- You’ve followed new pathway and has come to fatty liver and asked to assess fibrosis?

What is easiest way to assess for fibrosis-poll

1) Arrange a GI referral for Fibroscan
2) Calculate Fib-4 through TMH
3) Ultrasound
4) Liver biopsy
5) Does it matter?

Test	Result	Flag	Reference
FIBROSIS-4 CALC	82.73	H	0-1.44
	Scores < 1.45 have a negative predictive value for advanced fibrosis of 90%		
	Scores > 3.25 have a positive predictive value of 65% and a specificity of 97%		
	Reference: Hepatology 2006:43:1317-1325		
	Method: *CALC* Perf Site: *ML*		
	Ent: *13/04-1608 TAYOUNG*, Ver: *13/04-1609 TAYOUNG*		
AST	1500	H	13-35 U/L
	Method: *C16000-1* Perf Site: *ML*		
	Ent: *13/04-1608 TAYOUNG*, Ver: *13/04-1609 TAYOUNG*		
ALT	50	H	7-45 U/L
	Method: *C16000-1* Perf Site: *ML*		
	Ent: *13/04-1608 TAYOUNG*, Ver: *13/04-1609 TAYOUNG*		

—— Verified Result History ——

Edited Test	Result	Entered	Verified

Case-3

- You calculate Fib-4 and comes back showing F2 fibrosis
- You tell patient they should make lifestyle changes or could run into problems with cirrhosis
- The patient seems to understand seriousness and asks what he should do moving forward

Non-alcoholic fatty liver disease

- Global prevalence 25%
- 10% go onto develop liver related complication
- MAFLD proposed as alternative name
- 47-63% of T2DM
- 80% of obesity
- Can be seen in patients with BMI<25
  - Usually have central obesity or other metabolic risk
- Obesity among children aged 2-5 has gone from 8.4% to 13.9% in 4 years

Powell E et al. Non-alcoholic liver disease- The Lancet 2021

Non-alcoholic fatty liver disease

- Pooled prevalence now in children is 7.6% in general population
- Individuals with childhood onset have a higher risk of liver related events as adult

Powell E et al. Non-alcoholic liver disease- The Lancet 2021

Natural history

- Liver disease is slowly progressive and will not result in cirrhosis or liver-related death for majority of patients
- Fibrosis most important prognostication marker
- F0 – F4
- On average moves 1 stage every 14 years in NAFLD and 7.1 years in NASH

Powell E et al. Non-alcoholic liver disease- The Lancet 2021

AASLD NAFLD guidelines

Natural History

- Leading cause of death is cardiovascular followed by extrahepatic malignancy
- NAFLD patients have 1.9 times higher rates of cancers involving liver, GI tract and uterus
- Higher risk of severe Covid-19

Powell E et al. Non-alcoholic liver disease- The Lancet 2021

Management

- Weight loss!
  - 5-7% reduces hepatic fat and steatohepatitis
  - 10% fibrosis is reduced in many patients
- Bariatric surgery should be considered in certain patients
- Currently no approved Health Canada treatments for NASH
  - Vit E
  - Pioglitazone
  - GLP-1 agonist
  - SGLT2 inhibitors
- Obeticholic acid

Powell E et al. Non-alcoholic liver disease- The Lancet 2021

The Basics-Management

- Hypocaloric, nutrient dense diet
  - Reduced by 500-1000 calories daily
  - Avoid night time snacking
- Ensure sustainable change
- Understand seriousness of condition
- Avoid fructose/ simple carbohydrates
- Consume coffee (2-4 cups, caffeinated)
  - 23% decrease rate of development of NAFLD
  - 32% reduction in fibrosis

Hayat U, Siddiqui AA, Okut H, Afroz S, Tasleem S, Haris A. The effect of coffee consumption on the non-alcoholic fatty liver disease and liver fibrosis: A meta-analysis of 11 epidemiological studies. Ann Hepatol. 2021

GI DIVISION OF THE MONCTON HOSPITAL

Non alcoholic fatty liver disease (NAFLD) Algorithm

NAFLD risk factors

Metabolic syndrome
Obesity
Diabetes mellitus
Dyslipidemia
PCOS

NAFLD/NASH likely based on elevated liver enzyme algorithm, fatty liver risk factors and/or imaging

First step is to determine risk of advanced fibrosis or cirrhosis

FIB-4 and NAFLD Fibrosis score

https://www.mdcalc.com/fibrosis-4-fib-4-index-liver-fibrosis

https://www.mdcalc.com/nafld-non-alcoholic-fatty-liver-disease-fibrosis-score

Perform a FIB-4 or NAFLD Fibrosis Score
Both are available online or on smart phone
Both require AST in measurements

NAFLD Fibrosis Score < -1.455
Fib-4 score ≤ 1.3

Advanced fibrosis unlikely

Tight control of Metabolic risk factors, dietician referral
Weight loss (aim for at least 5-7% total body weight)
Exercise (both aerobic and weight resistance)
Caloric restriction with reduction in fructose and refined sugars
Coffee consumption not to exceed 4 cups/day
Alcohol in moderation
Reassess every 2-5 years for progression of liver disease

NAFLD Fibrosis Score ≥ -1.455
Fib-4 score > 1.3

Advanced fibrosis possible

Refer to GI/Hepatology for further assessment of fibrosis
Recommendations the same for patient with low likelihood of fibrosis

Case 3

- You see Mr. Lays in Follow up
- You ask how he has done with lifestyle changes.
- He admits he hasn’t done anything and the pandemic was hard on him and he actually gained 20 lbs. and started drinking more wine
- On exam you notice some telangiectasis across his chest and palmer erythema.
- You decide to send him for some repeat bloodwork and U/S of liver

Case 3

- His bloodwork comes back WBC 4, HBG 119 and Platelets 100
- ALT 100 and you order FIB-4 which now says advanced fibrosis
- You order an U/S and it comments on coarse liver suspicious for cirrhosis
- His total bilirubin is 11, albumin is 38 and INR is 1.1.

Cirrhosis- Now what?

- Epidemiology
- Diagnosis
- Management and complications

Epidemiology- It is not going away

- Global burden is rising
- 2 million deaths yearly worldwide
  - Accounts for roughly 3.5% of deaths worldwide
- Incidence of advanced liver disease has increased 400% since 1970
- Increasing rates of all causes (HCV,HBV, ETOH and NAFLD)
- In US, predicted increase of 77% of decompensated cirrhosis from EtOH by 2040

Williams R, Aspinall R, Bellis M, Camps-Walsh G, Cramp M, Dhawan A, et al. The Lancet. 2014;384(9958):1953–97.

Huang D et al. Global Epidemiology of cirrhosis. Nature reviews. 2023

Epidemiology

- Compensated NAFLD cirrhosis- increase by 64% in Japan to 156% in France by 2030
- NAFLD could account for 75% of cases of cirrhosis in Canada in 2040
- The incidence of all cause cirrhosis expected to grow by 9% by 2040 in Canada

Huang D et al. Global Epidemiology of cirrhosis. Nature reviews. 2023
Flemming et al. NAFLD and alcohol-associated liver disease with be responsible for almost all new diagnoses of cirrhosis in Canada by 2040. Hepatology. 2021

Epidemiology- Covid impact?

- Mortality due to cirrhosis increased markedly during Covid-19 Pandemic
- Alcohol consumption increased substantially and increase was mainly alcohol related
- US National Covid cohort showed increase risk of mortality of covid (HR 3.3)
- Cirrhosis referrals decreased which may have resulted in delayed diagnosis/management
- Decrease in treatment of viral hepatitis
  - 1 year delay in Hep C in 110 countries will likely result in 72000 deaths over next 10 years

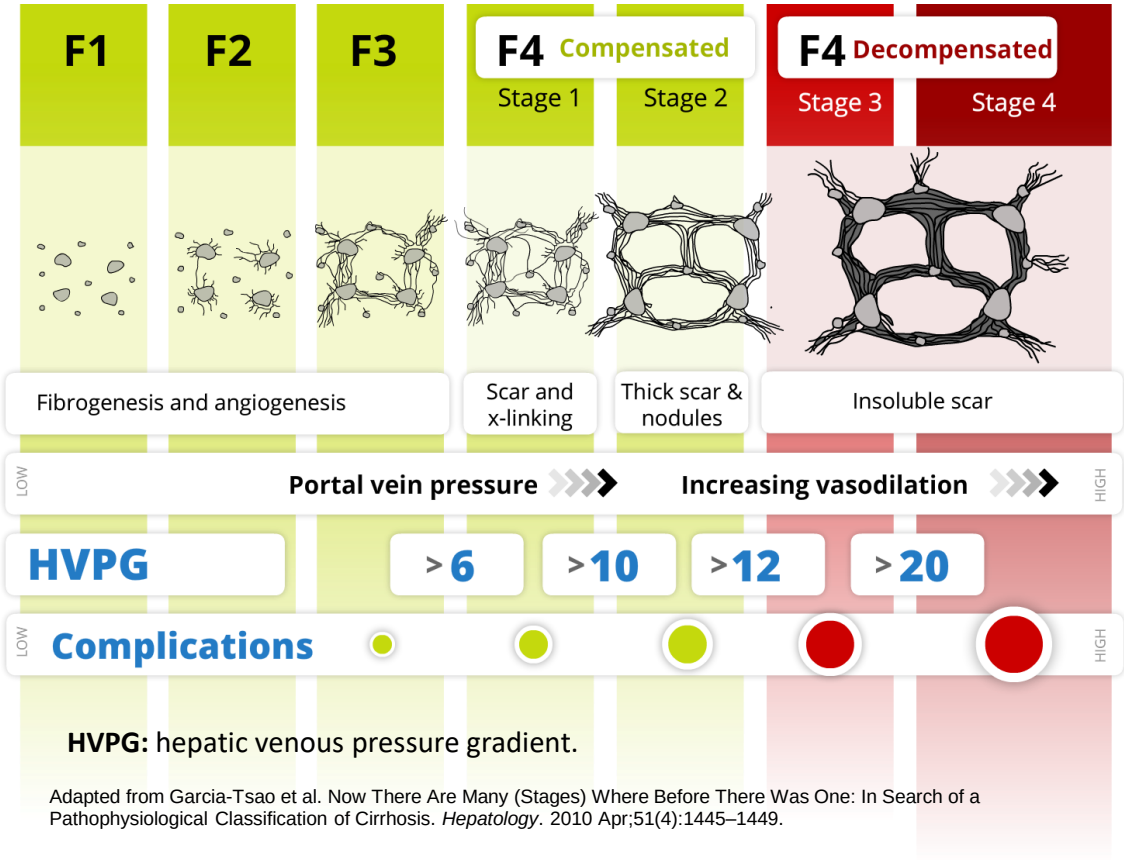
Huang D et al. Global Epidemiology of cirrhosis. Nature reviews. 2023

Diagnosis

- Assess level of fibrosis
  - Most important prognosticator
- Cause of cirrhosis
- Whether portal hypertension present
  - Which can lead to complications

Cirrhosis

- Cirrhosis represents an **advanced stage** of progressive liver fibrosis
- It is generally considered **irreversible** in its advanced stages
- The **prognosis** of cirrhosis is highly variable[1]
- A number of factors, including **etiology, severity, and the presence of complications and concomitant diseases**, can influence prognosis[2]



Adapted from Garcia-Tsao et al. Now There Are Many (Stages) Where Before There Was One: In Search of a Pathophysiological Classification of Cirrhosis. *Hepatology*. 2010 Apr;51(4):1445–1449.

1. D'Amico G, Garcia-Tsao G, Pagliaro L. Natural history and prognostic indicators of survival in cirrhosis: a systematic review of 118 studies. J Hepatol 2006; 44:217.

2. Salpeter SR, Luo EJ, Malter DS, Stuart B. Systematic review of noncancer presentations with a median survival of 6 months or less. Am J Med 2012; 125:512.e1.

Diagnosis

- Liver biopsy is gold standard
  - Difficult to obtain
  - Invasive
- U/S and biochemistry
  - Less than 60% sensitivity and specificity for cirrhosis
- Fib-4, NAFLD fibrosis score, FibroTest all reasonable first line tests
- Transient Elastography
  - Fasted state, absence of inflammation, congestion

Gines P et al. Liver Cirrhosis. The Lancet 2021.

Diagnosis

	Rule out fibrosis if the value is	Rule in fibrosis up to stage 2 if the value is	Rule in fibrosis stage 3 or 4 if the value is
Fibrosis-4 Index*	Lower than 1·3	Between 2·67 and 3·25	Higher than 3·25
NAFLD Fibrosis Score†	Lower than −1·455	Not established	Higher than 0·676
FibroTest‡	Lower than 0·31	Between 0·48 and 0·72	Higher than 0·72
ELF§	Lower than 7·7	Between 9·8 and 10·5	Higher than 10·5
Transient elastography	Lower than 6 kPa	Between 8 kPa and 12 kPa	Higher than 12 kPa

- All markers to rule in fibrosis shown here have a sensitivity of more than 90%.
- All markers to rule out fibrosis shown here have a specificity of more than 90%.

Gines P et al. Liver Cirrhosis. The Lancet 2021.

Compensated Cirrhosis

- Decrease risk of progression
  - Once F4 (cirrhosis) patients decompensate at roughly 3-4% per year
  - Rates of HCC 10.6/1000 person years
  - In absence of cirrhosis, HCC roughly 0.08/1000 person years
  - Median survival is greater than 12 years

- Surveillance
  - Variceal screening, Hepatocellular carcinoma screening

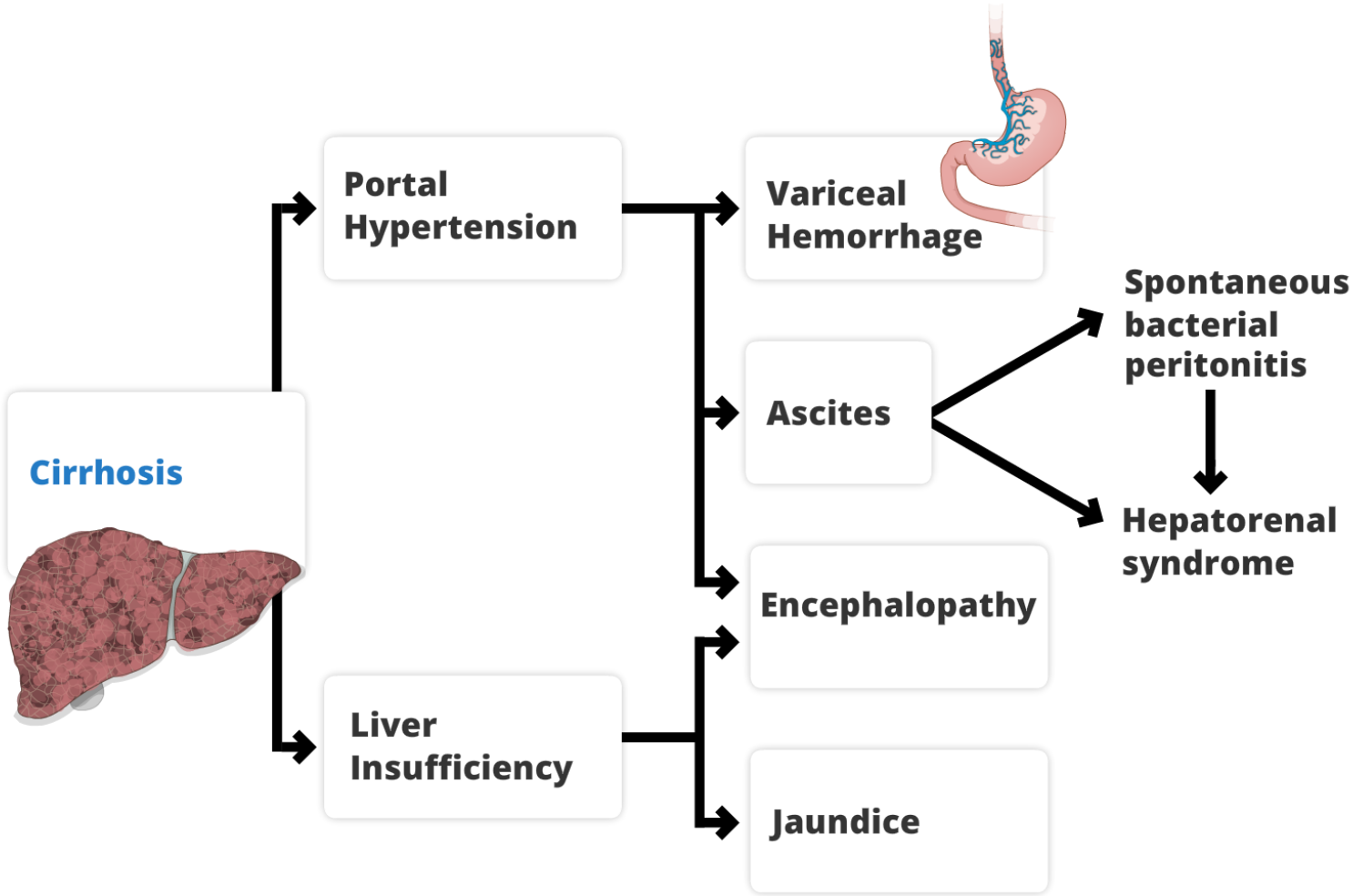
- Vaccinations

- Comorbidities

Decompensated Cirrhosis and complications

- **Ascites**
- **Portal HTN related bleeding**
- **Hepatic Encephalopathy**
- AKI and hepatorenal syndrome
- Sarcopenia
- SBP
- HCC
- Hepatopulmonary syndrome

Complications of Cirrhosis



Ascites

- Typically develops when HVPG rises above 8
- 20% of new cirrhosis present with ascites and 20% are deceased within 1 year
- First step diagnosis cause of ascites
  - Paracentesis with SAAG and cell count and cultures
- Serum Albumin Ascites Gradient (SAAG)
  - If gradient 11 or greater than portal hypertension possible
  - If gradient less than 11 then other causes
  - Total Protein greater than 25 think cardiac!

Gines P et al. Liver Cirrhosis. The Lancet 2021.

Ascites Management

- Moderate Salt restriction
  - 5-6.5 gm salt/day
  - Roughly 400mg of sodium in 1 gram of salt
- Diuretics
  - Do not change natural history- just symptoms
- Spironolactone and Lasix commonly used
  - Response rates of 95% and 52%
  - Should titrate Spironolactone q 3-4 days
- Can use Spironolactone solo or combination with Lasix
  - Typically 100mg and 40mg respectively

Portal HTN bleeding

- Second most common complication after ascites
- Variceal bleeding most common
  - 20% mortality at 6 weeks
- Best is trying to prevent bleeding
- If bleeding occurs medical emergency

- Routine screening/surveillance for patients requiring NSBB
- NSBB effective for primary prophylaxis and may have other benefits
- Unlikely to have significant portal HTN/varices if platelets greater than 110

Hepatic encephalopathy

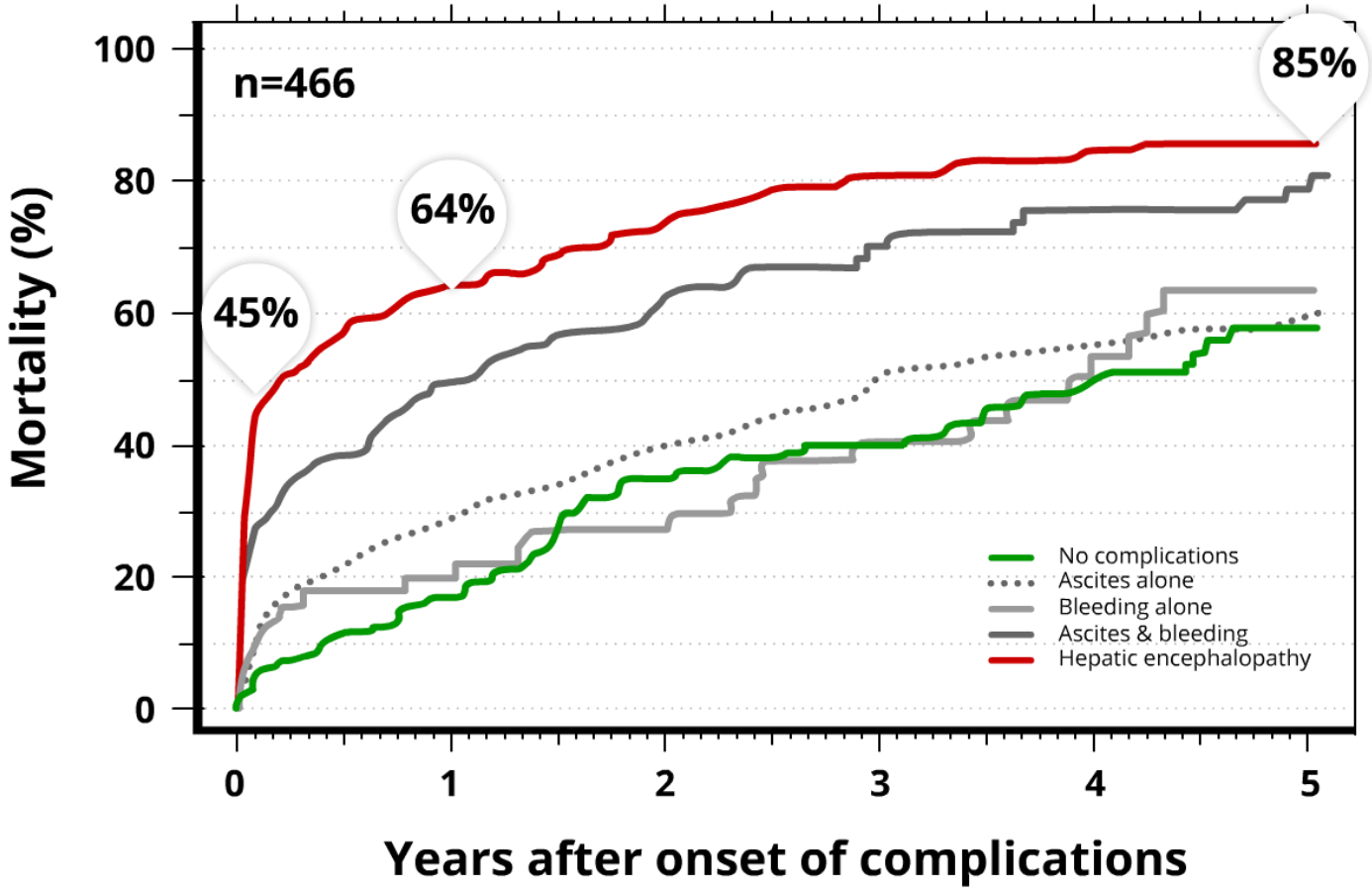
- Spectrum of potentially reversible neuropsychiatric abnormalities secondary to hepatic dysfunction, portosystemic shunting or both
- Covert or overt

- Covert is subclinical
  - Increase MVC and decrease quality of life

- Overt is clinically detectable

HE carries a higher mortality than other cirrhosis complications

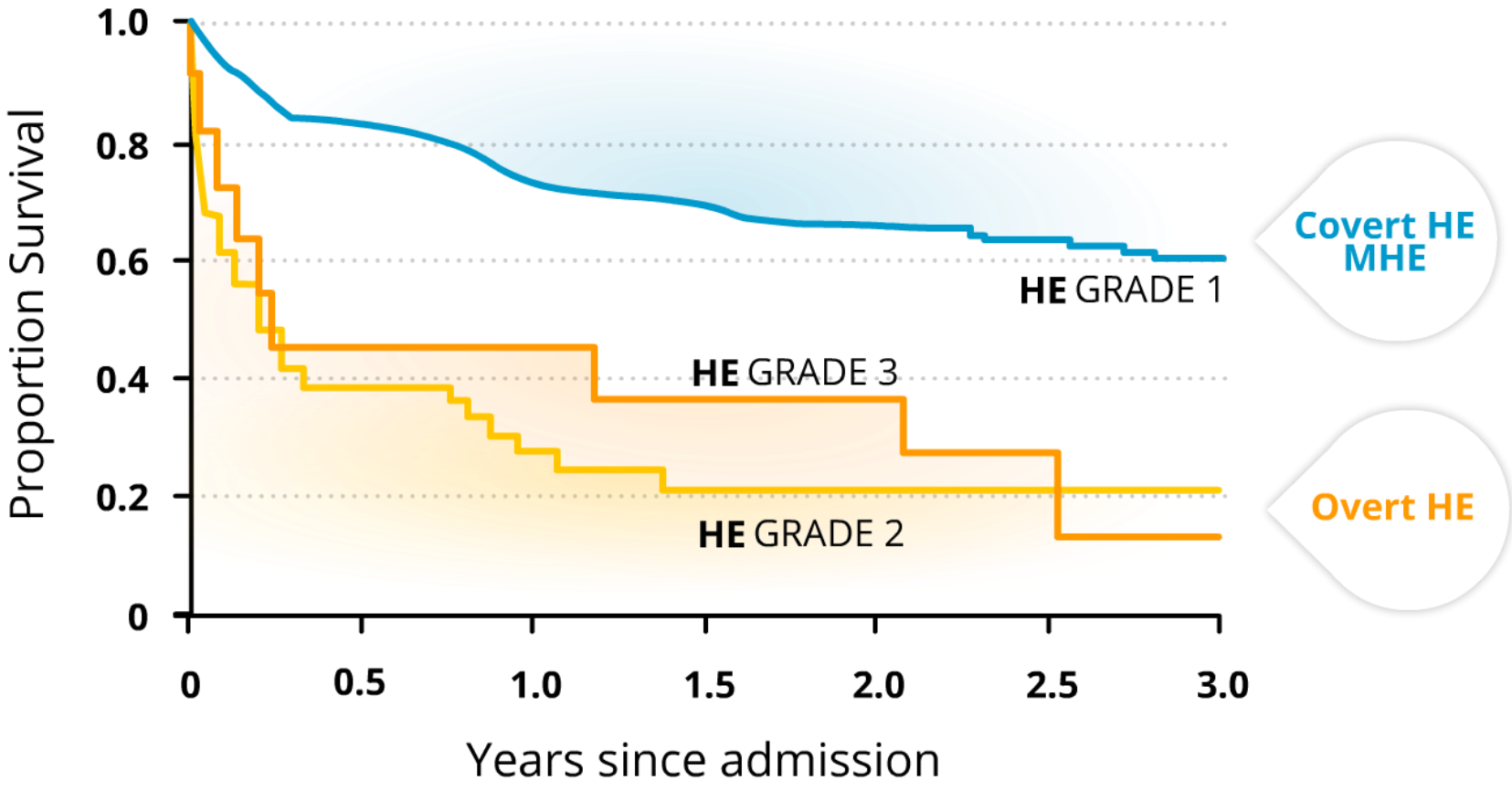
- Danish Cohort: Alcoholic Cirrhosis.
- 12-year study (1993-2005)
- 45% death rate in first month



Jepsen P, Ott P, Andersen PK, Sørensen HT, Vilstrup H. The clinical course of alcoholic liver cirrhosis: a Danish population-based cohort study. *Hepatology*. 2010;51:1675-1682.

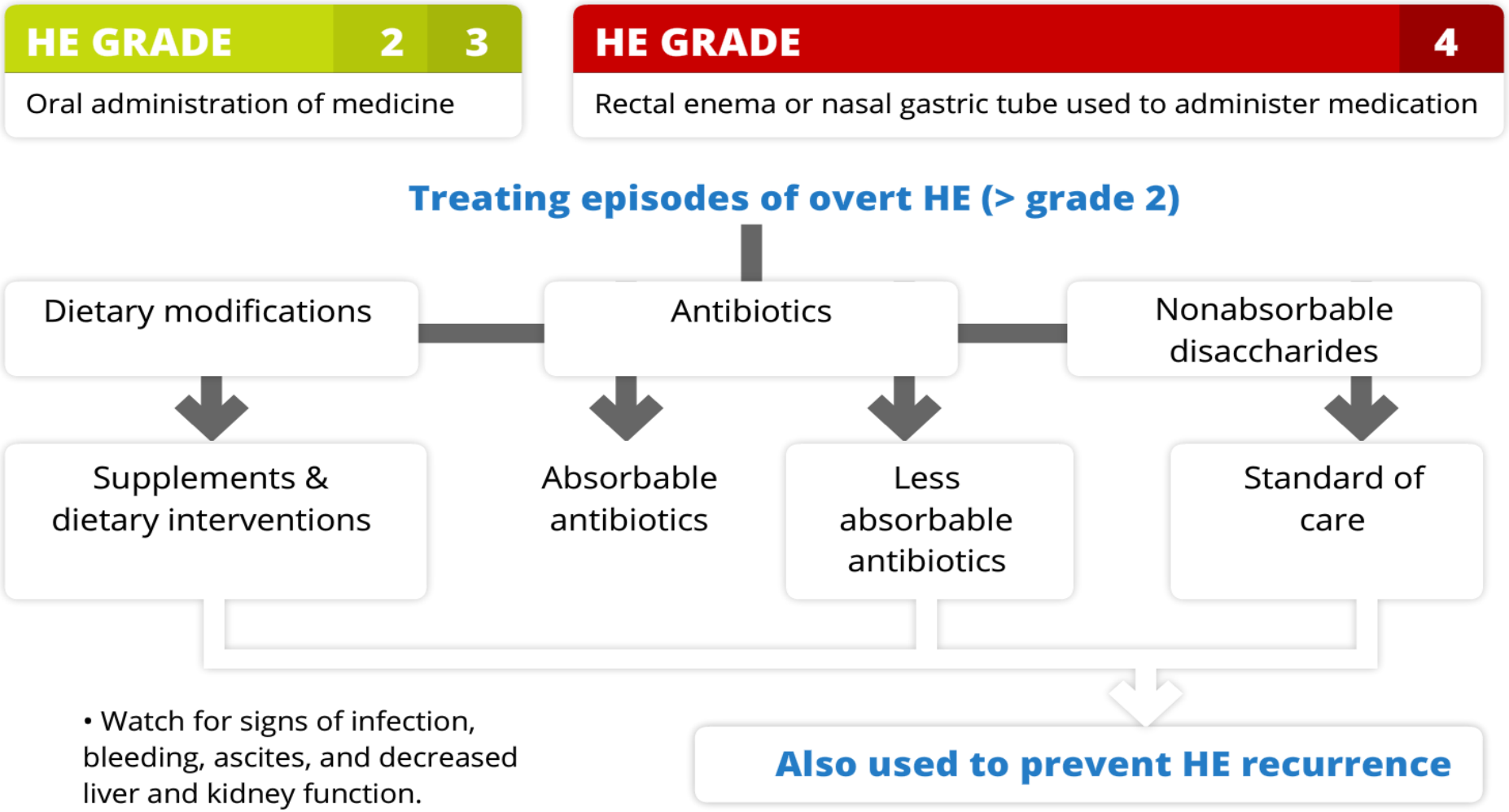
A poor predictor of survival

42% survival at 1 year
23% survival at 3 years



Stewart CA, Malinchoc M, Kim WR, Kamath PS. Hepatic encephalopathy as a predictor of survival in patients with end-stage liver disease. *Liver Transpl*. 2007 Oct;13(10):1366-71.

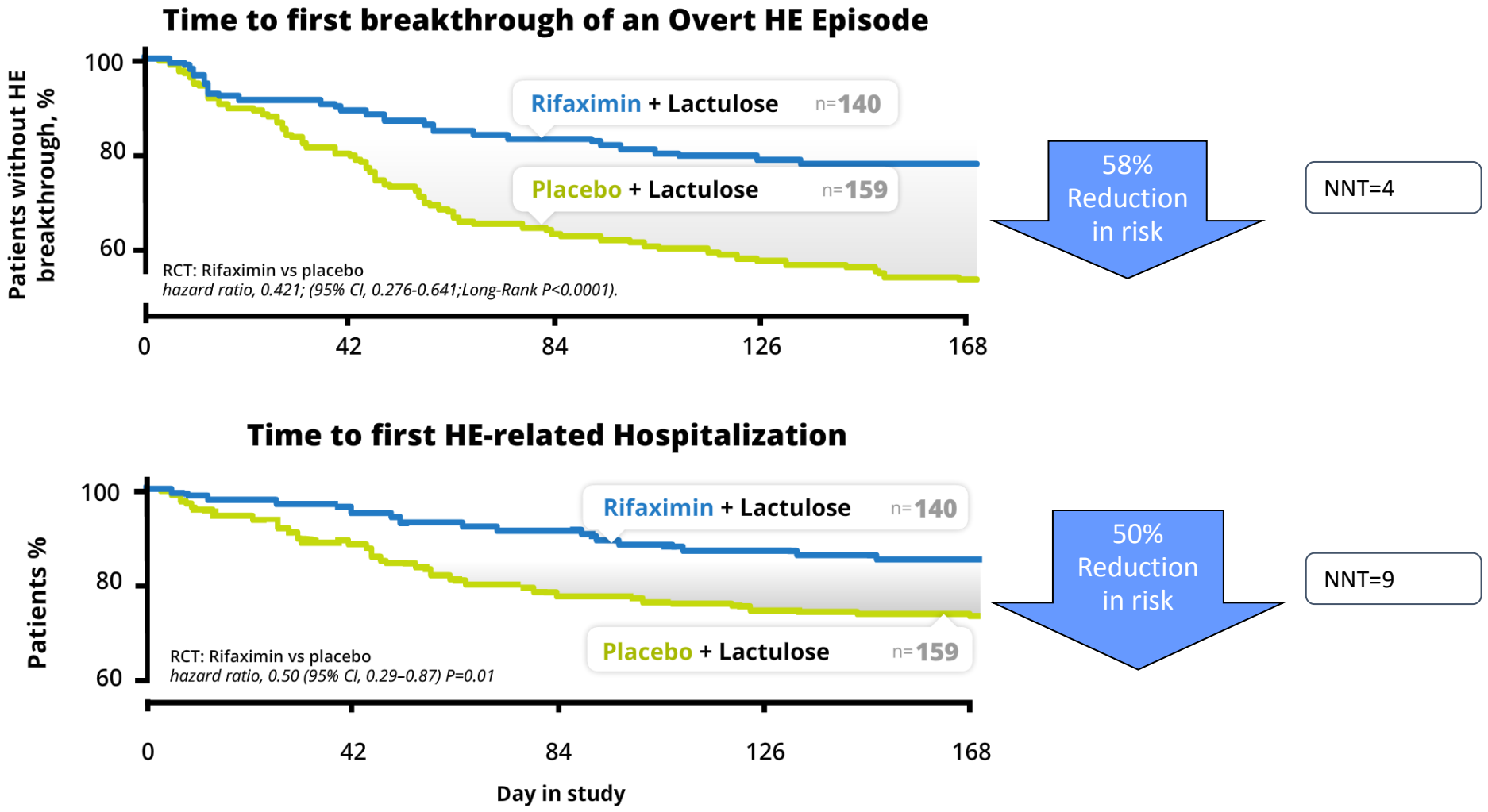
Treatment of Overt HE



Management

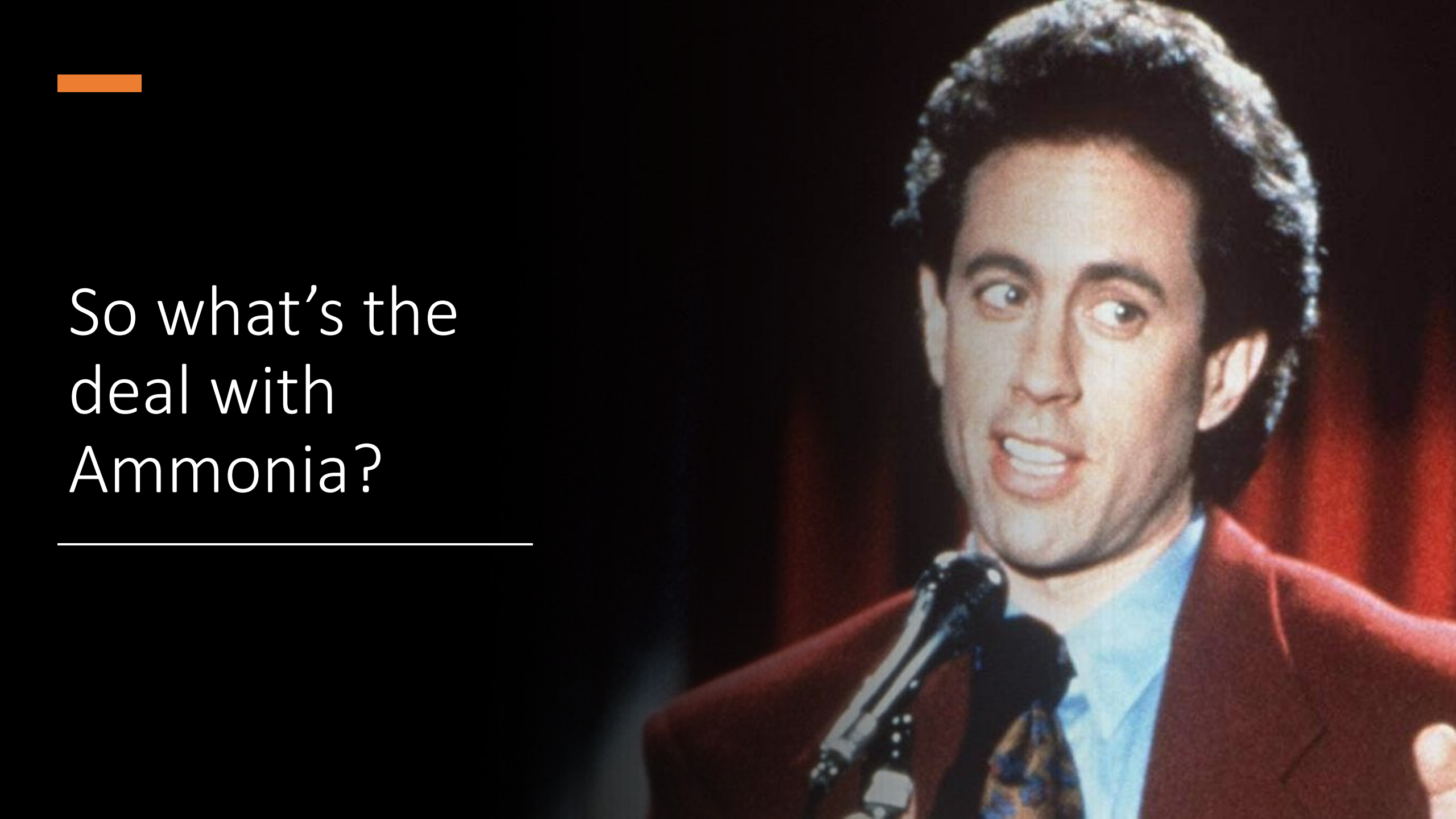
- High protein diet and try to prevent sarcopenia
- Lactulose to aim for 2-3 Bm/day
- Rifaximin 550mg po BID to prevent recurrence

Rifaximin in Prevention of Recurrence of HE



Bass NM, et al. Rifaximin treatment in hepatic encephalopathy. *N Engl J Med*. 2010;362:1071-1081.

So what’s the deal with Ammonia?



Ammonia

- Overlap with mild cognitive impairment and HE
- In patients presenting with delirium a normal ammonia level brings the diagnosis of HE into question
- Level of Ammonia can correlate with severity of HE
- Use in clinical context

EASL Clinical Practice Guidelines on the management of hepatic encephalopathy.2022

Dietary clinical pearls

- Generally 35-40 kcal/kg/day to promote anabolism
  - 1.2-1.5gm/kg/day of protein if muscle wasting
  - BCAA vs AAA can improve survival/ encephalopathy

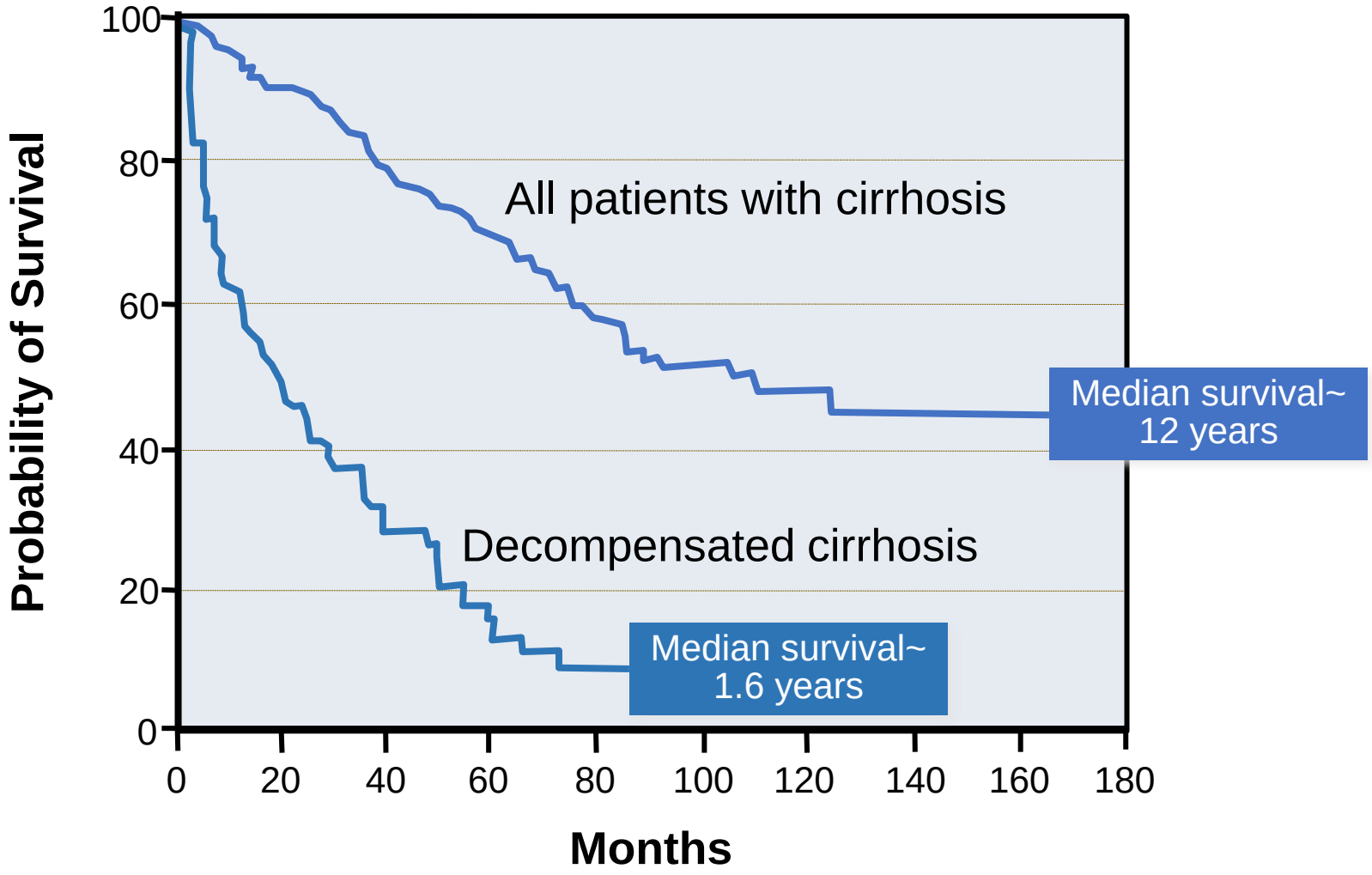
- Carbohydrates should compose ~50%
  - Avoid simple carbohydrates

- Fats should comprise roughly 10-20% and mainly in form of mono-polyunsaturated fats

Cup of Joe?

- Coffee has been shown to decrease risk of hepatocellular carcinoma and mortality in chronic liver disease
- the prevailing thought is that coffee has beneficial antioxidant and anti-inflammatory effects on those with CLD
- Coffee protective in development of non-alcoholic liver disease yet also in liver fibrosis
- Coffee drinking associated with reduced risk of death from various causes

Patients with cirrhosis - decompensation shortens survival



Ginés P, et al. Compensated cirrhosis: natural history and prognostic factors. *Hepatology* 1987; 7:122-8.

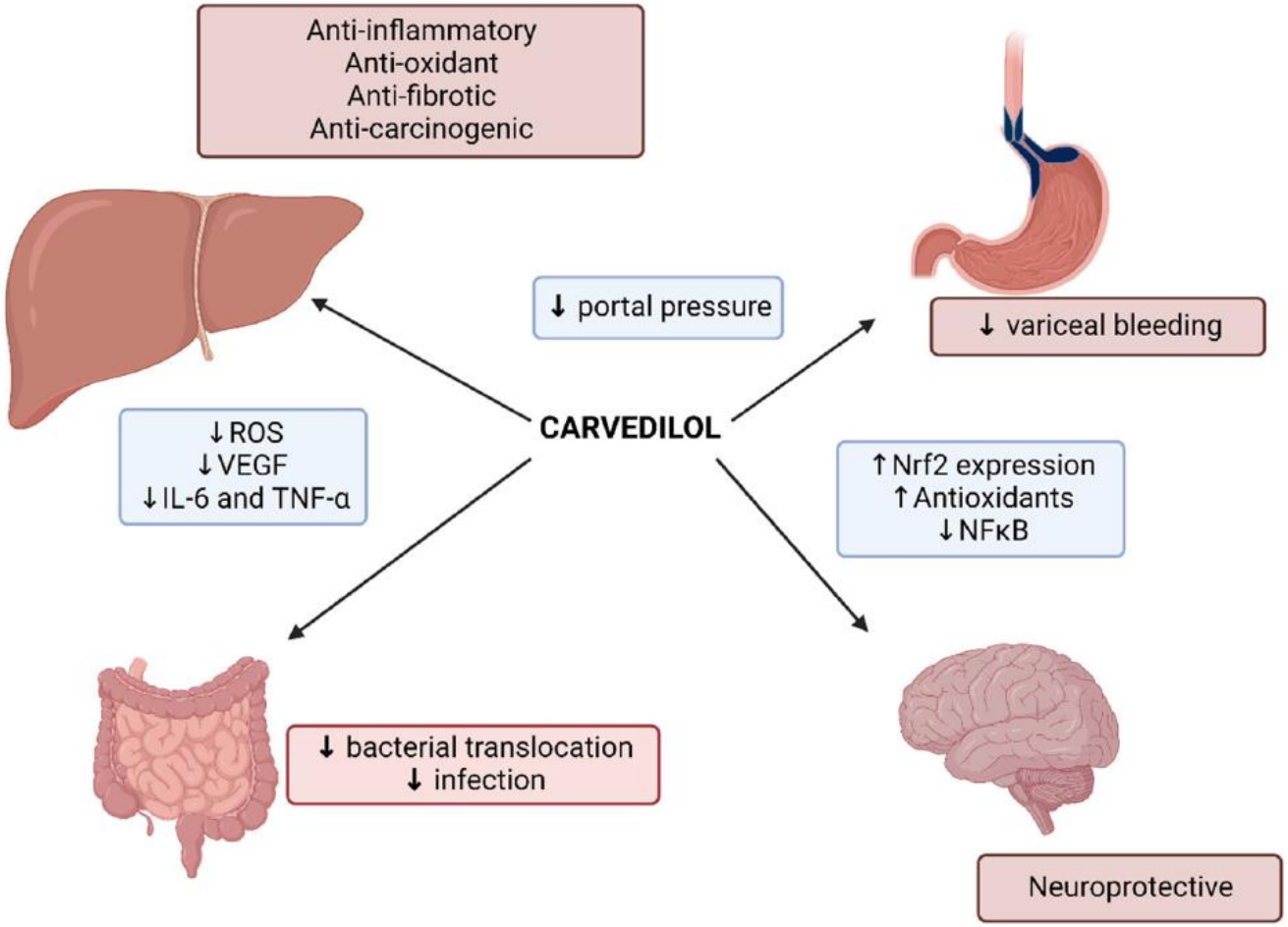
Prevent decompensation?

- Treat cause
- Nutrition, Immunize and lifestyle
- Multidisciplinary clinics/ Liver failure clinics
- New antifibrotic agents
- Use of carvedilol as NSBB
  - The number needed to treat to prevent one decompensating event over a median of 37 months was 9; comparably the NNT for statins for primary prevention of cardiovascular events is 20–25 over 10 years
- Start in all cirrhotic cirrhosis with evidence of any decompensation or significant portal hypertension (Any of: Child-Pugh Score >5, Platelet count <150, Grade 1 OV or Liver stiffness >20 kPa)

Villanueva C, Albillos A, Genescà J, Garcia-Pagan JC, Calleja JL, Aracil C, et al. β blockers to prevent decompensation of cirrhosis in patients with clinically significant portal hypertension (PREDESCI): Lancet. 2019;393(10181):1597–608.

Aliment Pharmacol Ther. 2023;57:454–463

Carvedilol



Aliment Pharmacol Ther. 2023;57:454–463

Take Home points

- Care Pathway can help in the work up of chronic liver disease and lead to timely diagnosis and management
- Diagnosis of cirrhosis can be made clinically with use of noninvasive scoring methods
- Lifestyle, surveillance and treatment of underlying comorbidities plays huge role in management of patients with cirrhosis
- Consider using Carvedilol in patients with compensated cirrhosis early which may help prevent decompensation

Thank You- Questions/Discussion

Moncton GI Elevated Liver Enzyme Algorithm

Moncton GI NAFLD Care Pathway Algorithm