RESOURCE PERSONS

Prof. Madunil Niriella
Professor in Gastroenterology,
Faculty of Medicine, University of Kelaniya
Consultant Gastroenterologist - NCTH - Ragama

Dr. Kuleesha Kodisinghe
Consultant Gastroenterologist
DGH - Matara

Prof. Anuradha Dassanayake
Professor in Pharmacology,
Faculty of Medicine, University of Kelaniya
Consultant Physician - NCTH - Ragama

Dr. Uditha Dassanayake
Senior Lecturer,
Faculty of Medicine, University of Kelaniya
Consultant Gastroenterologist - NCTH - Ragama

Dr. Sanjeewa Aryasingha
Consultant Gastroenterologist
NHSL - Colombo

Dr. Tharanga Liyanaarachchi
Consultant Gastroenterologist
DGH - Gampaha

Dr. Sujeewa Kumarasena
Consultant Gastroenterologist
NH - Galle

Dr. V. Vijitharan
Consultant Gastroenterologist
TH - Batticaloa

Dr. Mananjala Senanayake
Consultant Gastroenterologist
CSTH - Kalubowila

Dr. Chinthaka De Silva
Consultant Gastroenterologist
TH - Anuradhapura

Dr. Hasitha Wijewantha
Consultant Gastroenterologist
NH - Kandy

Dr. Dhanushi Abeynayake
Consultant Gastroenterologist
DGH - Embilipitiya

Dr. Nilesh Fernandopulle
Senior Lecturer,
Faculty of Medicine, University of Colombo
Consultant Gastroenterologist - NHSL - Colombo

Dr. Hiruni Jayasena
Senior Lecturer & Consultant Gastroenterologist
Faculty of Medicine,
Kotelawala Defence University

Clinical Case Discussions and Interactive Session

Dr. Janaka Subasinghe
Senior Registrar in Gastroenterologist, NH - Kandy

Dr. Prabhath Dasanayaka
Senior Registrar in Gastroenterologist, NH - Kandy

Dr. Mohamed Nazeef
Senior Registrar in Gastroenterologist, NHSL - Colombo

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Senior Registrar in Gastroenterology, NH – Kandy

Dr. Prabhath Dasanayaka,
Senior Registrar in Gastroenterology, NH – Kandy

Dr. Mohamed Nazeef
Senior Registrar in Gastroenterology, NHSL, Colombo

Non-invasive Testing in Advanced Chronic Liver Disease

Dr. Hiruni Jayasena

MBBS (Lond), MRCP (UK), MRCP (Lond), MD (Bris), MD (Col)

Honorary Consultant Gastroenterologist and Hepatologist – UHKDU Senior Lecturer in Medicine – Faculty of Medicine, General Sir John Kotelawala Defence University

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Optimizing the Use of Non-Invasive Testing in Advanced Chronic Liver Disease

Author: Dr. Hiruni Jayasena,
MBBS (Lond), MRCP (Lond), MRCP (UK) MD (Bris), MD (Col)
Senior Lecturer in Medicine – KDU
Hon. Consultant Gastroenterology & Hepatology – UH KDU

Chronic liver disease (CLD) represents a significant global health burden, with fibrosis stage being the most important predictor of clinical outcomes including decompensation, hepatocellular carcinoma, and mortality. While liver biopsy remains the diagnostic gold standard for fibrosis staging, it is invasive, costly, and unsuitable for repeated use across large populations.

This presentation reviews the evolving role of non-invasive tests (NITs) as practical and reliable alternatives for assessing liver fibrosis. NITs include simple serum-based scores (e.g., FIB-4, APRI, NFS), proprietary biomarker panels (e.g., ELF, FibroTest), and imaging modalities (e.g., transient elastography (TE), MR elastography (MRE)). Although NITs are cost-effective, safe, they have limitations in accurately staging intermediate fibrosis and can be affected by confounders such as inflammation and steatosis.

Recent evidence supports a sequential diagnostic approach. FIB-4 can be used as a first-line screening tool followed by a confirmatory tests like TE or ELF. Studies have shown that NITs allow for significant improvement of diagnostic accuracy, while reducing the need for liver biopsy.

In conclusion, NITs are indispensable tools in modern hepatology, best used in combination and tailored to patient context for effective risk stratification, treatment prioritization, and surveillance planning.

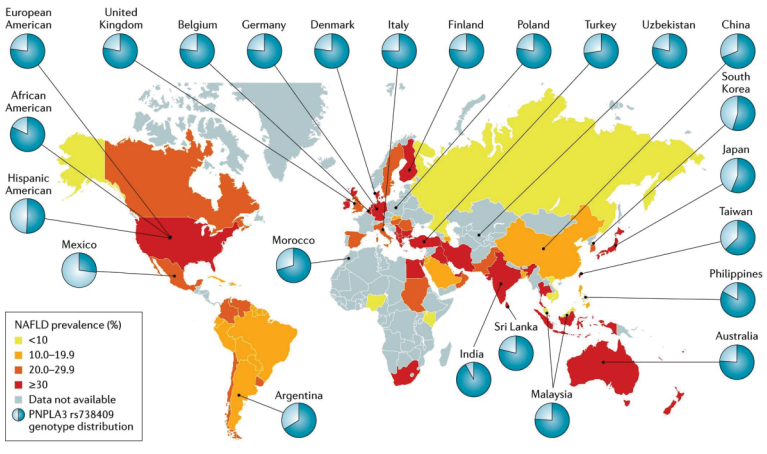
OVERVIEW

- Chronic liver disease – The problem at hand
- Why is liver fibrosis important ?
- Liver biopsy – The gold standard
- Non invasive tests (NITs)- The way forward
  - Discuss strengths, limitations, and clinical applications
- Limitations with NITs
- Optimal usage of NITs in practice

CHRONIC LIVER DISEASE (CLD): THE PROBLEM

- CLD is a **leading cause of mortality and morbidity** worldwide
  - 2 million annual deaths worldwide
- **9th leading cause of death** in SE Asia
- 15th leading cause of disability-associated life-years
- **Highest impact age : 25-49 years**
- **CLD is common – NAFLD is a global epidemic!**

Devarbhavi H, Asrani SK, Arab JP, Nartey YA, Pose E, Kamath PS. Global burden of liver disease: 2023 update. J Hepatol. 2023 Aug;79(2):516-537.

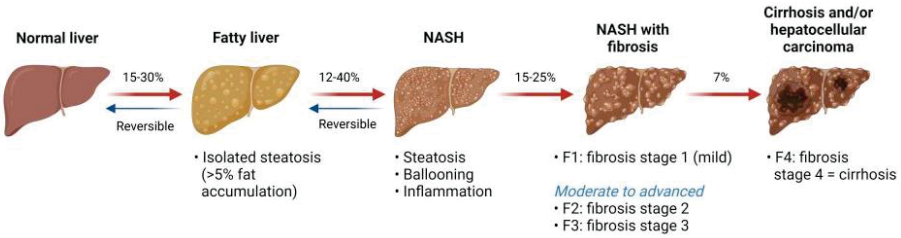


Nature Reviews | Gastroenterology & Hepatology

Younossi, Z., Anstee, Q., Marietti, M. *et al.* Global burden of NAFLD and NASH: trends, predictions, risk factors and prevention. *Nat Rev Gastroenterol Hepatol* **15**, 11–20 (2018)

WHY IS LIVER FIBROSIS SO IMPORTANT?

- Chronic liver injury ultimately leads to hepatic fibrosis & chronic liver disease (CLD)
- Fibrosis occurs as a gradient of severity , which increases in the presence of continuing insult
- Fibrosis may reverse with removal of insult



Clinical Outcomes in Adults with Nonalcoholic Fatty Liver Disease

MULTICENTER, PROSPECTIVE STUDY

1773 Adults with nonalcoholic fatty liver disease (median follow-up, 4 yr)

	Fibrosis Stage		
	F0 to F2 No, mild, or moderate fibrosis N=1237	F3 Bridging fibrosis N=369	F4 Cirrhosis N=167
Liver-related events		rate per 100 person-yr	
Variceal bleeding	0.00	0.06	0.70
Ascites	0.04	0.52	1.20
Encephalopathy	0.02	0.75	2.39
Hepatocellular carcinoma	0.04	0.34	0.14
Death from any cause	0.32	0.89	1.76

Increasing fibrosis stage is associated with increased risks of liver-related complications and death.

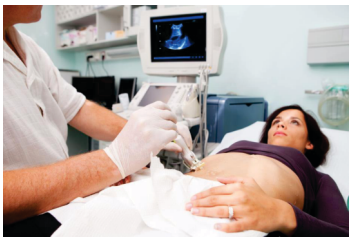
Association of liver fibrosis with prognosis and clinical progression is irrespective of aetiology!

Accurate assessment of the degree of liver fibrosis is essential in ALL individuals with CLD

1. Predict clinical decompensation, liver related mortality and HCC
2. Prognosticate, stratify therapeutic and surveillance strategies
3. Evaluate response to treatment recommendations in CLD

In doing so:
- ✓ Early referral for specialist care
- ✓ Deliver liver directed therapies
- ✓ Surveillance for varices and malignancy

Liver biopsy:
The GOLD Standard



Costly

Impractical to perform in large no: or do serially

Considerable skill of operator / Experienced histopathologist

Patient Reluctance: Pain, discomfort

Complications: Invasive, risk of rare but life-threatening complications

Redman J. CurrTreat Options Gastro2020; Loomba R. Gut 2020

Biopsy complication rate varies based on:

- Operator experience,
- Underlying Co-morbidities,
- Size of the needle,
- No: of passes
- Bleeding risk due to low platelets and/or Increased PT

Complication	Incidence
Pain at the right hypochondrium, shoulder	0.056-83%
Hemorrhagic complications: Subcapsular/ intrahepatic hematoma intraperitoneal bleeding hemobilia hemothorax	0.23-0.59% 0.03-0.7% 0.058-0.2% 0.18-0.49%
Infectious complications: transient bacteriemia septicaemia intrahepatic abscess biliary peritonitis	5,8-13.48 0.08% 0.03-0.22%
Pulmonary complications: Pneumothorax Subcutaneous emphysema	0.08-0.28% 0.014%
Arteriovenous fistula	5.4%
Reaction to anaesthetic agent	0.029%
Break of the biopsy needle	0.02-0.059%
Biopsy of other organs: lungs gall bladder kidneys colon	0.01-0.1% 0.001-0.014% 0.034-0.117% 0.029-0.096% 0.0038-0.0044%
Mortality rate	0.01-0.1%

Kobyliak N, Abenavoli L. The role of liver biopsy to assess non-alcoholic fatty liver disease. Rev Recent Clin Trials. 2014;9(3):159-69.

NON-INVASIVE TESTS (NITs) FOR LIVER FIBROSIS

Cost effective & reproducible

Safe, non invasive

Simple way to monitor

Assess fibrosis

Sequential check will help to identify advanced fibrosis

Redman J. CurrTreat Options Gastro2020; Loomba R. Gut 2020

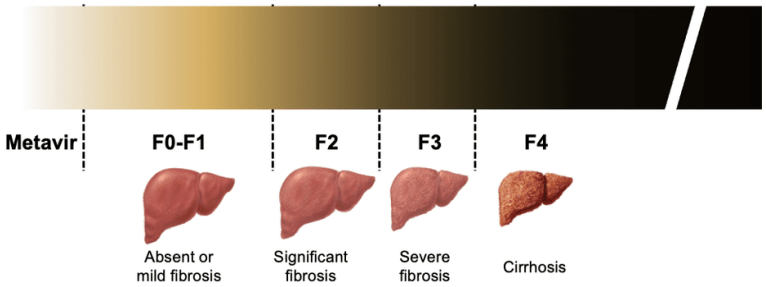
NITs FOR LIVER FIBROSIS

SIMPLE SCORES	• APRI (AST-Platelet Ratio Index) • FIB-4 (FIBROSIS -4) • NFS (NAFLD Fibrosis Score) • BARD score	"Wet" tests
PROPRIETARY SERUM TESTS	• FibroSure®(FibroTest®outside of the US) • Fibrometre • ELF™ (Enhanced Liver Fibrosis) • HepaScore	
IMAGING TECHNIQUES	• Velocity Controlled Transient elastography (e.g. FibroScan®) • Shear Wave Elastography (e.g. 2D-SWE, pSWE) • MRE (Magnetic resonance elastography)	"Dry" test

Loomba R, Gut 2020

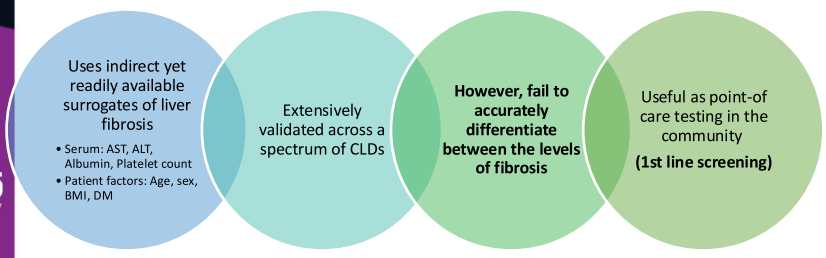
Stages of Fibrosis

METAVIR is a gold standard for assessing liver fibrosis
NITs aim to **identify and stratify hepatic fibrosis**

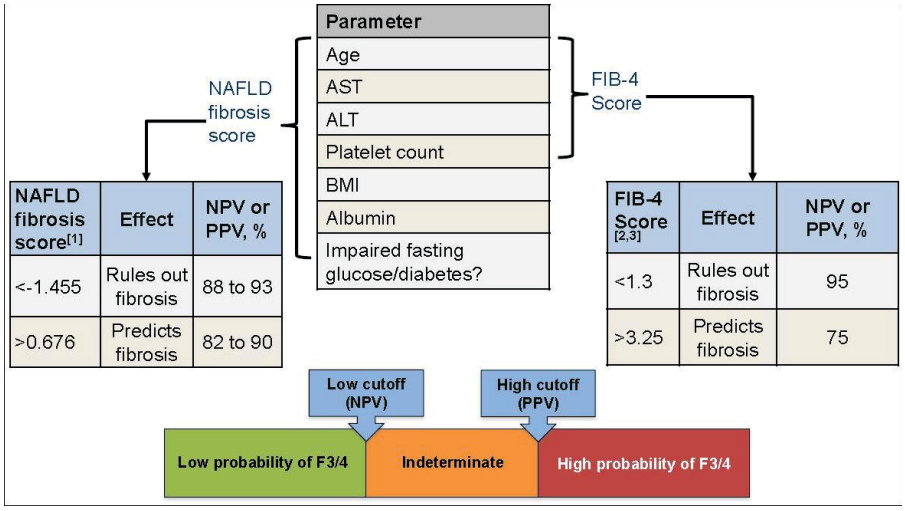


Clinically significant fibrosis (SF) if the METAVIR score **is ≥F2**
Advanced hepatic fibrosis (AF) if the METAVIR score**is F3 or F4**

What the Simple Scores aka "WET TESTS"?



NITs	Best For	Inputs	Ease of use	Target Disease	Key Advantage	Disadvantages
FIB-4	HCV, NAFLD	Age, AST, ALT, Platelets	✅	All CLDs	Good balance of sensitivity and specificity	Less accurate in younger pts (<35), in elderly > 65yrs or those with normal AST/ALT; indeterminate range (1.3–2.67) needs further evaluation
NFS	NAFLD	Age, BMI, Diabetes, AST/ALT, Platelets, Albumin	❌ (needs multiple labs and clinical data)	NAFLD	Highly specific for advanced fibrosis in NAFLD	Complex to calculate; intermediate zone (–1.455 to 0.675) includes many
BARD	NAFLD	BMI, AST/ALT ratio, Diabetes	✅✅ (very simple)	NAFLD	Easy bedside screening tool	Low specificity; many false positives; cannot distinguish intermediate from advanced fibrosis
APRI	HCV, NAFLD	AST, Platelets	✅	HCV (and NAFLD)	Simple, widely used, validated	Influenced by causes of thrombocytopenia unrelated to fibrosis; less accurate in NAFLD and early fibrosis



McPherson S Am J Gastroentrol2017; Shah et al, CGH 2009; Angulo Hepatology2007

What about complex "WET tests"?

- Incorporate direct markers of liver fibrosis
- Highly accurate for advanced fibrosis / cirrhosis
- Measures of fibrogenesis or fibrinolysis
  - hyaluronic acid,
  - procollagen N-terminal peptide III (P3NP),
  - tissue inhibitor of matrix metalloproteinase-1 (TIMP)
- But
  - Costly
  - Need specialised labs
  - Not widely available
  - Some require licencing

Test/Panel	Type	Components	Advantages	Limitations
ELF (Enhanced Liver Fibrosis)	Proprietary biomarker panel	Hyaluronic acid, PIIINP, TIMP-1	High accuracy, reflects ECM remodeling	Not widely available; expensive
FibroTest (FibroSure)	Proprietary panel	Alpha-2-macroglobulin, haptoglobin, apolipoprotein A1, bilirubin, GGT	Good for various etiologies	Costly; influenced by haemolysis and inflammation
Hepascore	Composite index	Age, bilirubin, GGT, hyaluronic acid, alpha-2-macroglobulin	Reasonably accurate	Less accessible; complex
FibroMeter	Proprietary index	Varies by disease (e.g., ALT, AST, INR, platelets, etc.)	Tailored to disease type	Requires licensing; cost and complexity

What are image based " Dry Tests"?

Standard imaging **only** detects advanced steatosis and fibrosis

BUT Elastography methods quantify liver stiffness

Increased liver stiffness typically correlates with fibrosis progression.

No serum requirement !

More accurate than simple serum NITs

2 Commonly used tests:

FibroScan

(Vibration controlled Transient Elastography)

- quick, validated in many liver diseases,
- most reliable in ruling out advanced disease,
- predicts decompensation and complications

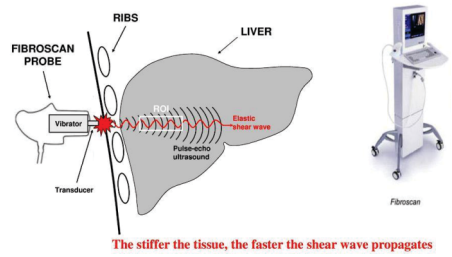
MR Elastography (MRE)

- Costly but highest accuracy,
- not operator-dependent,
- best for Obese, complex patients

Test	Modality	How it Works	Advantages	Disadvantages	Use
FibroScan (TE)	Ultrasound-based	Measures liver stiffness via low-frequency vibrations	Non-invasive, quick, reproducible, bedside tool	Limited in obesity, ascites; may overestimate fibrosis in inflammation or congestion	1st LINE imaging in NAFLD, HCV, HBV
MR Elastography (MRE)	MRI-based	Combines MRI with mechanical waves to map stiffness	Most accurate, assesses entire liver, works in obesity	Expensive, limited availability, slower	Gold standard in research or complex cases
Point Shear Wave Elastography (pSWE)	Ultrasound (conventional)	Measures stiffness using acoustic radiation force	Integrated into standard ultrasound machines	Operator-dependent; limited comparative data	Alternative to TE in standard imaging setup
2D Shear Wave Elastography (2D-SWE)	Advanced ultrasound	Measures stiffness in a larger region than pSWE	Better reproducibility than pSWE; visual map	More expensive, less available than TE	2nd line or specialist centres
Conventional Ultrasound	Imaging	Assesses size, echotexture, nodularity, splenomegaly	Widely available, cheap	Low sensitivity; changes appear late	Useful for cirrhosis signs, not early fibrosis
CT Scan (non-contrast or contrast)	Imaging	Evaluates liver morphology and indirect signs	Available in many settings	Radiation, poor sensitivity for fibrosis	Not recommended for fibrosis staging alone

Vibration Controlled Transient Elastography (VCTE)

FibroScan (Echosens, Paris, France, FDA approved): kilopascals (kPa)



The stiffer the tissue, the faster the shear wave propagates

Liver stiffness is measured via a mechanically induced, controlled 50 Hz frequency shear wave

The propagation speed of the shear wave is measured with pulse echo ultrasound, presented as kilopascals (kPa)

Measures liver stiffness over an area estimated to be **100x greater than that of liver biopsy**

Controlled Attenuation Parameter (CAP): measures liver steatosis

CAP Score	Steatosis Grade	Amount of Liver with Fatty Change
238 to 260 dB/m	S1	11% to 33%
260 to 290 dB/m	S2	34% to 66%
Higher than 290 dB/m	S3	67% or higher

E score: measures liver stiffness

	F0-F1 No or Mild Liver Scarring	F2 Moderate Liver Scarring	F3 Severe Liver Scarring	F4 Cirrhosis
Hepatitis B	2 - 7 kPa	8 - 9 kPa	8 - 11 kPa	18 kPa or higher
Hepatitis C	2 - 7 kPa	8 - 9 kPa	9 - 14 kPa	14 kPa or higher
HIV/HCV Coinfection	2 - 7 kPa	7 - 11 kPa	11 - 14 kPa	14 kPa or higher
Cholestatic Disease	2 - 7 kPa	7 - 9 kPa	9 - 17 kPa	17 kPa or higher
Nonalcoholic Fatty Liver Disease (NAFLD or NASH)	2 - 7 kPa	7.5 - 10 kPa	10 - 14 kPa	14 kPa or higher
Alcohol Related Liver Disease	2 - 7 kPa	7 - 11 kPa	11 - 19 kPa	19 kPa or higher

LIMITATIONS OF NITs

TECHNICAL LIMITATIONS
- Serum tests may not be liver specific
- Image based need experience and training

NO DISCRIMINATION OF ADJACENT FIBROSIS STAGES

COST & AVAILABILITY

POOR PERFORMANCE / LACK DATA FOR INTERMEDIATE STAGES

FALSE POSITIVITY / FALSE NEGATIVITY WITH CONFOUNDING FACTORS
- inflammation, cholestasis, congestion, obesity, and hepatic steatosis

FAILURE
- Image based tests can have higher failure rates due to pt / operator factors

THRESHOLD
- Vary across different aetiologies

UNABLE TO DIFFERENTIATE BETWEEN SIMPLE STEOTOSIS AND NASH

FOLLOW UP OF DYNAMIC FIBROSIS CHANGES

Fibrosis marker	Failure rate	Factors related to failure	Invalid/unreliable result rate	Confounders
Indirect blood-based biomarkers	Negligible	–	30% Indeterminate (FIB-4, NAFLD Fibrosis Score)	Acute hepatitis, cholestasis, systemic inflammation, Gilberts/hemolysis (scores with bilirubin)
Direct blood-based biomarkers	Negligible	–	?	Acute hepatitis, systemic inflammation
VCTE	3%–14%	Obesity (less with XL probe), ascites	1%–9%	Acute hepatitis, cholestasis, beta-blockers, food ingestion, obesity, cardiac congestion.
pSWE	0%–1%	Obesity	16%–24%	Acute hepatitis, food ingestion, obesity*
2D-SWE	1%–13%	Obesity	0%	Acute hepatitis, food ingestion*
2D-MRE	<5%	Claustraphobia, inability to fit in MRI or breath hold,	Negligible	Iron overload, acute hepatitis, massive ascites

*Additional confounding factors for VCTE also likely to impact SWE.
2D-MRE, 2-dimensional MR elastography; 2D-SWE, 2-dimensional shear wave elastography; FIB-4, Fibrosis Score 4; NAFLD, non-alcoholic fatty liver disease; pSWE, point shear wave elastography; VCTE, Vibration-controlled transient elastography.

NO TEST IS PERFECT –
THERE IS ALWAYS ROOM FOR IMPROVEMENT!

Loomba R, Gut 2020

Are NITs as good as Liver biopsy?

Studies have evaluated the diagnostic accuracy of NITs compared to liver biopsy:

- **FIB-4**:
  - AUROC values: Approximately 0.71–0.82 for detecting advanced fibrosis and cirrhosis.
  - Effective in ruling out advanced fibrosis at low cut-off values, reducing the need for biopsy in low-risk patients
- **TE (FibroScan)**:
  - Offers a quick, non-invasive assessment of liver stiffness, correlating with fibrosis stages.
  - AUROC values ranging from 0.74 to 0.92 for significant fibrosis

El-Kassas, M *et al.* *Sci Rep* **14**, 29544 (2024)
Lai JC, et al. Gastroenterol Rep (Oxf). 2024 Apr 11;12:goae024

What is the evidence on combining NITs?

Enhanced Diagnostic Accuracy: Combining FIB-4 & TE or ELF or MRE improves the sensitivity and specificity for detecting advanced fibrosis

Reduction in Liver Biopsies: Sequential NITs can significantly decrease the number of unnecessary liver biopsies

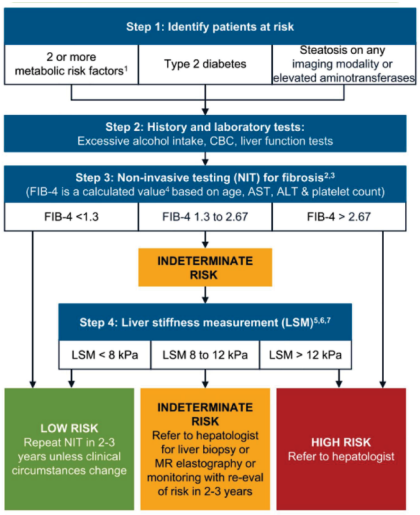
Combination of FIB-4 ≤1.73 and LSM ≤12.2 kPa **avoided liver biopsy** in 66 patients, with a false-negative rate of 3%

Efficient Resource Utilization: Implementing these algorithms in primary care settings/ low resource setting can optimize referrals and reduce healthcare costs.

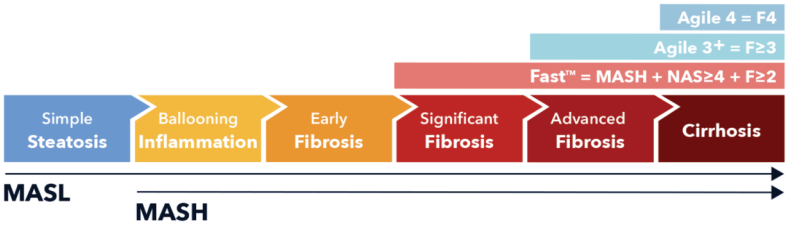
Sequential use of FIB-4 and ELF, **reduced unnecessary referrals from primary care to secondary care by 81%.**

Zoncape M, Liguori A, Tsochatzis EA. Eur J Intern Med 2024.
Srivastava A, et al. J Hepatol 2019;71:371–378.

FIB-4 & Fibroscan

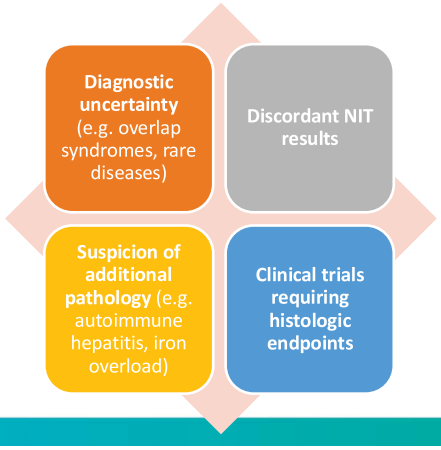


Kanwal F. Gastro 2021



- **FAST (FibroScan-AST)** = A predictive model **combining LSM, CAP, and AST**, **FAST** The FAST score provides an **efficient way to non-invasively identify patients at risk of progressive NASH**
- **Agile 3+** = combining LSM by VCTE, plt , ALT, AST, T2DM, age and sex, and has **high diagnostic performance for F3**;
- **Agile 4** = combining LSM, by VCTE, plt , ALT, AST, sex and presence of T2DM, and has **high diagnostic performance for cirrhosis**
- **MAST (MRI-AST) =** To identify **Fibro-NASH**, the score was created based on MRI

However, you may still need a liver biopsy if:



How best to use NITs in clinical practice?

- ✓NITs are useful to **exclude advanced fibrosis / cirrhosis**
- ✓NITs are **NOT** predictive when used in isolation
- ✓**Combining NITs** (serum & elastography) increases diagnostic accuracy & specificity
- ✓**Sequential use of NITs** reduces patients in intermediate zone
- ✓Can be both **screening & confirmatory**

Summary

- Rising hepatology burden worldwide with NAFLD
- Hence accurate and reliable non-invasive testing is needed
- Fibrosis stage is used to prioritize those who need treatment and identify those at risk for liver-related outcomes
- NITs include serum and imaging tests, are essential tools in modern hepatology
- NITs best used in algorithms, not in isolation
- Know their strengths & limitations
- Tailor to patient context and resource availability
- If there are doubts : liver biopsy is still there!

Q&A

Alcohol associated liver disease and Alcohol use disorder Tackling the dual burden

Dr Tharanga Liyanaarachchi

MBBS (Colombo), MD (Medicine), MRCP (UK), ESEGH

Consultant Gastroenterologist

DGH Gampaha

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Alcohol associated liver diseases and alcohol use disorder

Tackling the dual burden

Alcohol associated liver diseases (ALD) are the oldest and the most common cause of advanced liver disease worldwide. Alcohol use and Alcohol use disorder (AUD) related mortality has increased significantly due to Covid 19 pandemic. Despite two alcohol drinks a day for males and one drink for females is considered safe for the general population, people with liver disease due to any aetiology should completely abstain from alcohol.

Since the risk of developing liver disease in harmful drinkers decreases with abstinence or decreased consumption, early recognition and interventions with that goal should be implemented.Screening for harmful alcohol consumption should be done systematically and both pharmacological and psychosocial treatment modalities should be introduced at the first clinical encounter.

Besides the amount of total alcohol consumed, smoking, obesity and malnutrition, diabetes and co-existant liver diseases increase the risk of ALD. Certain genetics and coffee consumption appear to reduce the risk of developing ALD.

Spectrum of ALD includes, Alcohol associated steatosis, Alcohol associated steatohepatitis (ASH), Alcohol associated hepatitis (AH), Alcohol associated cirrhosis and hepatocellular carcinoma. Alcohol associated steatosis is a generally asymptomatic and reversible condition ASH is a histological diagnosis in which neutrophils accumulate and perivenular injury occurs with pericellular fibrosis in liver.

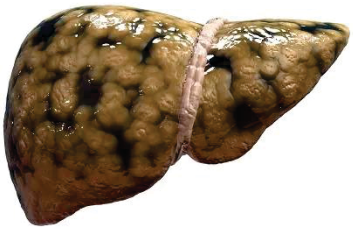
AH is a serious clinical syndrome with a high mortality characterised by the recent onset of jaundice and other signs of liver decompensation in patients with ongoing alcohol abuse or who who have ceased within last 4 weeks .Different prognostic models have been developed to identify patients at high risk of early death. The combination of MELD and the Lille model is suggested as an effective predictive algorithm of short-term mortality.

Diagnosis of AH can be made reliably with clinical, biochemical and histological testing where confounding factors are present. Treatment with steroids and intravenous N-Acetyl cysteine is beneficial whilst early liver transplant can increase the survival of patients with AH significantly.

Background and Epidemiology

- ALD is the oldest and most common cause of advanced liver disease
- ALD causes 3 million deaths (6%) annually in the world which exceeds deaths due to HT and DM combined
- Effect of Covid 19 pandemic
  - Alcohol use has risen by 14%
  - AUD-related mortality increased by 24%
- Mortality due to Alcohol related cirrhosis and Alcohol related hepatitis has increased specially in the young and in females

ALD is TWO diseases – NOT one



Chronic Liver Disease (CLD)

Alcohol Use Disorder (AUD)

How much is too much ?

(General population)

- Up to 2 drinks/day for males and up to 1 drink/day for females
- 14 grams of alcohol (One Drink)
  - 1 glass of wine
  - 12 ounces of beer
  - 1 shot of whiskey
- **Alcohol is a Carcinogen ! NO threshold for the risk of cancer**

How much is too much ?

In a patient with ALD

- Probably any amount !

- Patients with ALD, MASLD, Viral hepatitis and Haemachromatosis should be counselled that there is no safe level of drinking and they should abstain.

- Cessation of alcohol at any point reduces the disease progression

Identification of harmful alcohol use

How much do you drink ?

"I only have one drink a day"

How much do you drink ?

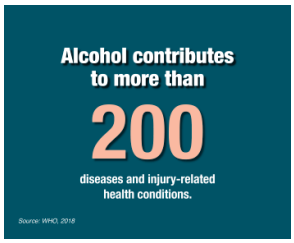
"Not much ! Four of us finish a bottle of whiskey a day"

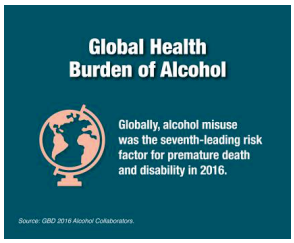
- **1 unit = 8g of alcohol=10ml of alcohol**
- 40 % Whiskey = "40 % pure alcohol by volume (ABV)
- strength (ABV) x volume (ml) ÷ 1,000 = units
- To work out the number of units in a bottle (750ml) of whiskey (ABV 40%)
  - 40 (%) x 750 (ml) ÷ 1,000 = 30 units = 240g
- One person drinks 60g or 7.5 units a day !

Alcohol use disorder

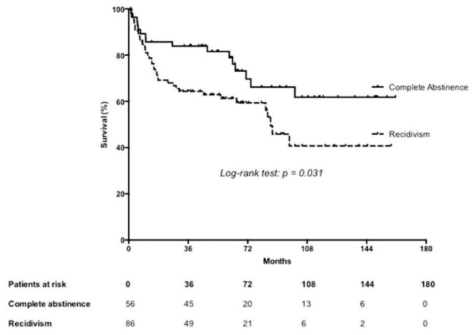
- **Alcohol use disorder (AUD)** is a **chronic relapsing and remitting syndrome**
  - in which ***excessive drinking of alcohol persists***
  - ***despite*** **causing** ***health and social problems***

- **AUD** is a **leading contributor to illness and death**
  - ***frequently overlooked, not diagnosed or treated*** in clinical settings
  - as a result, the *burden of disease remains high*





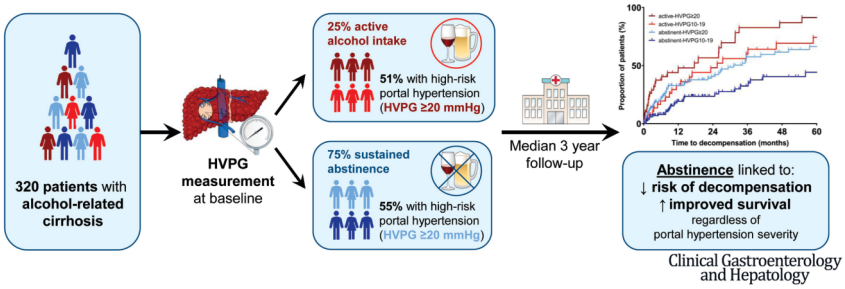
Alcohol Abstinence in Patients Surviving an Episode of Alcoholic Hepatitis: Impact on Long-Term Survival



Patients at risk	0	36	72	108	144	180
Complete abstinence	56	45	20	13	6	0
Recidivism	86	49	21	6	2	0

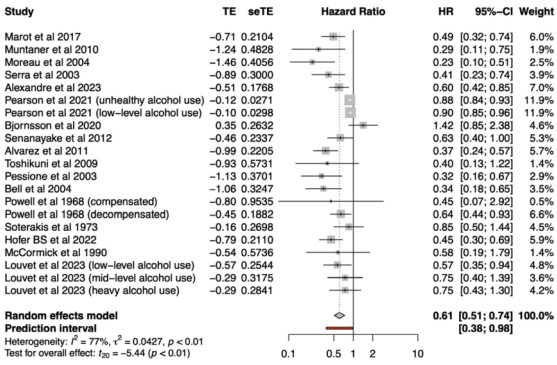
Altamirano J, et al. Hepatology. 2017

Alcohol Abstinence Improves Prognosis Across All Stages of Portal Hypertension in Alcohol-Related Cirrhosis



Hofer BS, et al. Clin Gastroenterol Hepatol. 2023

Impact of alcohol abstinence in alcohol-associated cirrhosis



Lim WH, et al. Aliment Pharmacol Ther. 2024

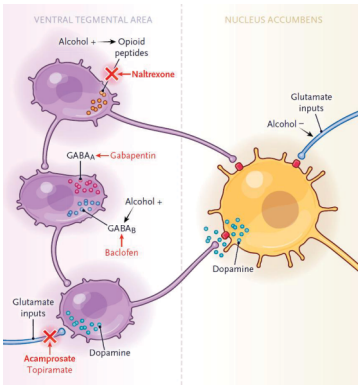
Pathophysiology

- Enduring **myth that AUD results from a moral failure**
  - continues to influence public and professional views
- An **estimated 50% of the risk is inherited**
- **Mental health disorders** are associated with a **doubled risk** of AUD
- **Adverse early life experiences and trauma in adult life** (e.g., sexual assault or trauma during military service) increase risk
- **Ready availability of alcohol at low cost and widespread outlets** are additional important risk factors

Haber PS. N Engl J Med 2025

Neurobiologics

- **Consumption of alcohol activates the reward regions of the brain**
  - increasing the release of dopamine
- The **reward system projects to the orbitofrontal cortex**
  - reduced inhibitory control
- **With repeated exposure** neurotransmitter **responses are blunted** in the severe forms of AUD
  - Increasing doses of alcohol are needed to produce the same effect (**alcohol tolerance**)
  - **Alcohol withdrawal syndrome** emerges when high levels of consumption are reduced or ceased



Haber PS. N Engl J Med 2025

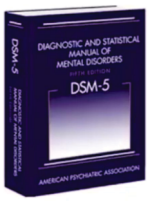
Clinical Assessment

- **Defining AUD**

Table 1. Diagnostic Criteria for Alcohol Use Disorder.*

Broad Domain	DSM-5 Diagnostic Criteria
Impaired control	Drinking larger amounts or over longer periods than intended. Desire or unsuccessful attempts to cut down or control alcohol use. Great deal of time spent obtaining or using alcohol or recovering from alcohol use. Craving or a strong desire or urge to use alcohol.
Social dysfunction and physical risk	Failure to fulfill major role obligations as a result of alcohol use. Continued drinking despite social or interpersonal problems. Diminished social, occupational, or recreational activities due to drinking. Recurrent alcohol use in physically hazardous situations. Continued drinking despite physical or psychological problems.
Physiological dependence	Tolerance, as evidenced by a markedly diminished effect of alcohol use. Withdrawal syndrome or drinking to prevent withdrawal.

* Diagnostic criteria are from the *Diagnostic and Statistical Manual of Mental Disorders*, fifth edition (DSM-5). The diagnostic threshold is the presence of 2 of the 11 criteria during a 12-month period. The severity of the disorder is determined on the basis of the number of criteria met — mild (2 or 3 criteria), moderate (4 or 5 criteria), or severe (6 to 11 criteria). Previous versions of the DSM distinguished alcohol abuse from alcohol dependence, but there was no substantial difference in outcomes, and these two diagnoses were merged.



Clinical assessment

- A **quantitative alcohol history**
- A history of alcohol withdrawal or intoxication
- Identify common associated physical signs
- Substance Use Disorders
- Mental Health Conditions
- Social Problems

Evan Wood et al. CMAJ 2023;195:E1364-E1379

Clinical Assessment

- Alcohol Use Disorders Identification Test **(AUDIT)**
- Short versions **(AUDIT-C and AUDIT-3)**
- The four-question **CAGE** (Cut Down Drinking, Annoyed by Criticism, Guilty Feelings, and Eye-Opener) screening
- Occasionally, patients do not accurately report their alcohol use
- Occult alcohol use may also be revealed

Clinical Assessment – Biological markers

- **Elevation of γ-glutamyl transferase level (GGT)**
- **Detection of ethanol itself in blood, breath, or urine** reflects **recent exposure** but is **positive for only a limited number of hours** after drinking
  - **useful in the ED setting** to confirm recent alcohol use
- **Nonoxidative alcohol metabolites** are **emerging as clinically useful biomarkers** of alcohol consumption
  - **Phosphatidylethanol** is a conjugate of phosphatidylcholine and ethanol
  - **Carbohydrate-deficient transferrin** (expressed as a percentage) refers to isoforms of transferrin

AUD Management – Key principles

Treatment is generally effective but **underutilized**

Person-centered, nonjudgmental approach essential

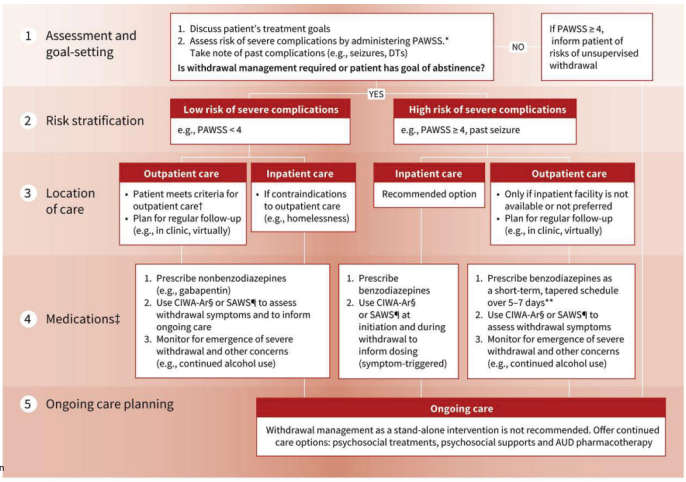
Treatment plan should be **negotiated collaboratively**

Consider cultural and racial factors in recovery support

Account for practical limitations (cost, local availability)

"Natural" recovery possible without formal intervention

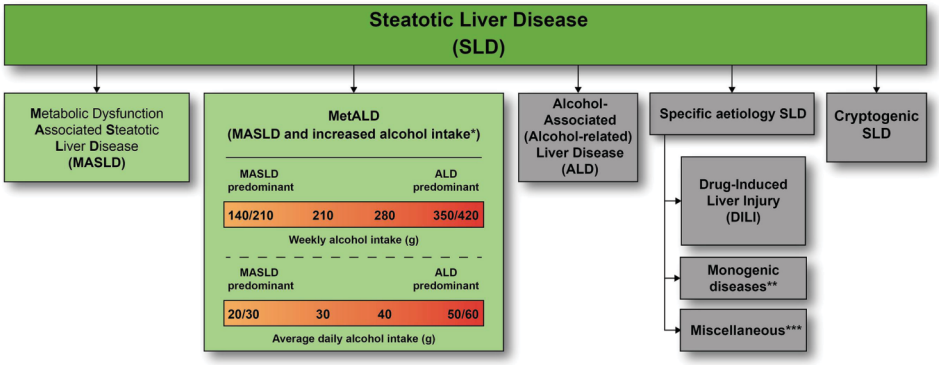
Withdrawal management pathway



Evan Wood et al. CMAJ 2023;195:E1364-E1379

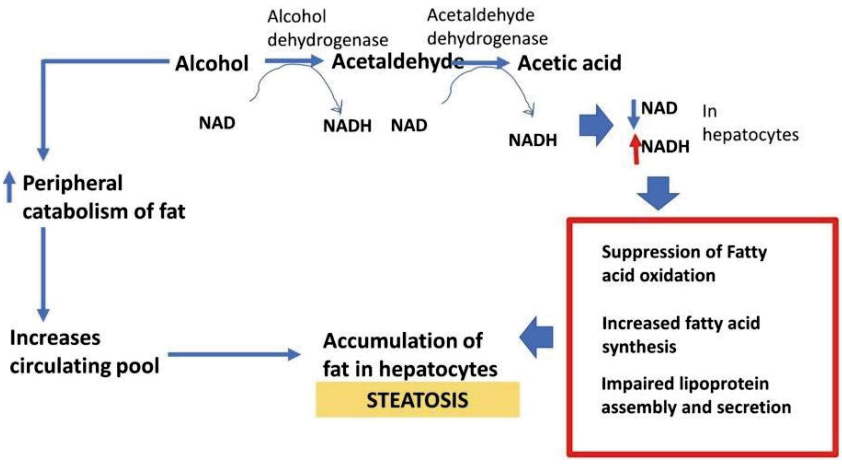
Table 3. Medications for Alcohol Use Disorder.*

Medication	Mode of Action	Typical Dose	Use in Liver Disease
Approved for the treatment of alcohol use disorder			
Disulfiram	Acetaldehyde dehydrogenase inhibitor	200 mg per day	Contraindicated
Naltrexone	Mu opioid receptor antagonist	50 mg per day 380 mg monthly intramuscular injection	Risk of hepatotoxic effects precludes use in advanced liver disease May consider in early liver disease
Acamprosate	NMDA agonist† Calcium load†	666 mg three times daily (reduce if body weight is <65 kg)	Precaution in Child–Pugh class C cirrhosis‡
Not approved in the United States for the treatment of alcohol use disorder			
Baclofen	GABA B receptor agonist	10–25 mg three times daily	Acceptable side-effect profile in patients with liver disease Minimal hepatic metabolism
Topiramate	GABA A receptor agonist AMPA–kainite glutamate receptor blocker Calcium- and sodium-channel blocker	Up to 100 mg twice daily	Risk of encephalopathy precludes use in advanced liver disease May consider in compensated liver disease
Gabapentin	GABA A receptor agonist	Up to 900 mg twice daily	Uncertain
Varenicline	Nicotinic acetylcholine receptor partial agonist	2 mg per day	Uncertain

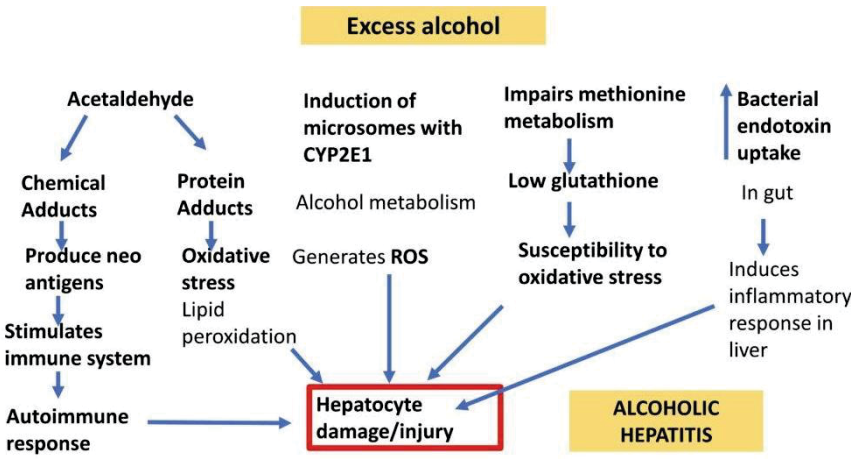


*Weekly intake 140-350g female, 210-420g male (average daily 20-50g female, 30-60g male)
**e.g. Lysosomal Acid Lipase Deficiency (LALD), Wilson disease, hypobetalipoproteinemia, inborn errors of metabolism
***e.g. Hepatitis C virus (HCV), malnutrition, celiac disease

What causes hepatocyte fat accumulation

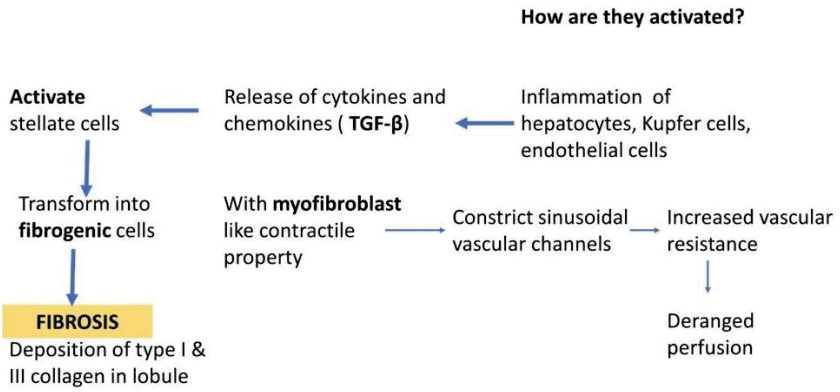


What causes hepatocyte injury



What causes hepatic fibrosis

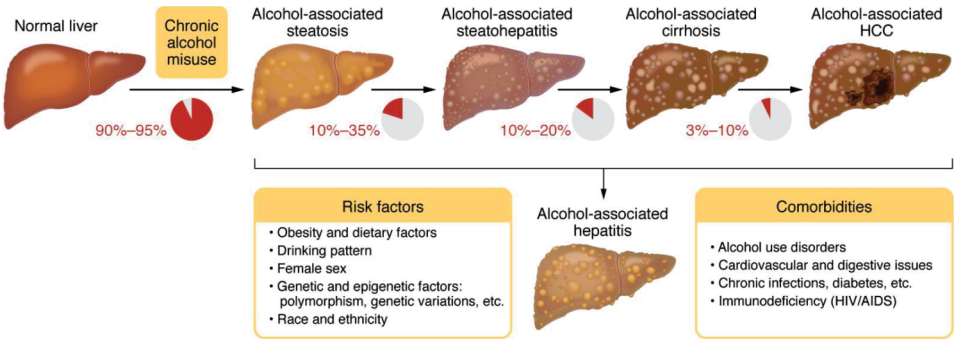
Activation of stellate cells



Risk factors for ALD

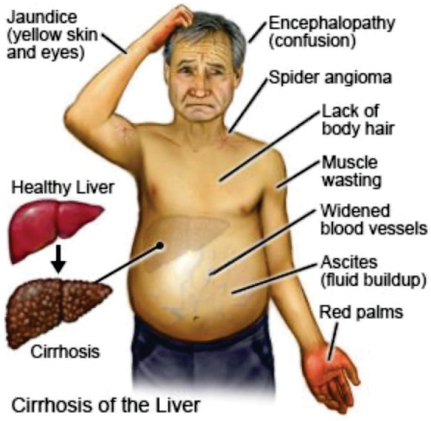
- *Amount of total alcohol use is ultimate risk factor*
- *Gender*
- Tobacco use
- *Genetics*
- Obesity and malnutrition
- Diabetes
- Co-existent liver disease (MASLD, Viral hepatitis)
- *Coffee*

Spectrum of ALD



Physical findings in ALD cirrhosis

- Jaundice
- Encephalopathy
- Muscle wasting
- Gynaecomastia, testicular atrophy
- Ascites, Leg oedema
- Splenomegally
- Spider naevi
- Hair loss, Dupyutren's contractures
- Palmer erythema



Recognise the difference

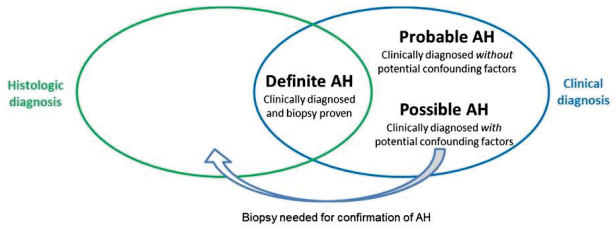
- 43 year old male
- 1/2 bottle of 33% alcohol daily
- "Feels sick"
- "A bit yellow at times"
- AST - 150, ALT - 48, GGT - 200
- Bilirubin 1.8 mg/dl
- Creatinine 0.9 mg/dl
- INR 1.2
- WBC 6000

ALD Cirrhosis
Acute mortality LOW

- 43 year old male
- 1/2 bottle of 33% alcohol daily
- "Feels sick"
- **Jaundice**
- AST - 150, ALT - 48, GGT - 200
- **Bilirubin 18 mg/dl**
- **Creatinine 0.9 mg/dl**
- **INR 3.2**
- **WBC 16000**

Alcoholic hepatitis
Acute mortality HIGH

Diagnosis of Alcoholic hepatitis



Clinical diagnosis of AH

- Onset of jaundice within prior 8 weeks
- Ongoing consumption of >40 (female) or 60 (male) g alcohol/day for ≥6 months, with <60 days of abstinence before the onset of jaundice
- AST >50, AST/ALT >1.5, and both values <400 IU/L
- Serum total bilirubin >3.0 mg/dL

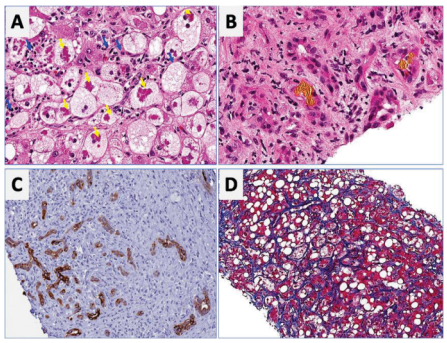
Potential confounding factors

- Possible ischemic hepatitis (e.g., severe upper gastrointestinal bleed, hypotension, or cocaine use within 7 days) or metabolic liver disease (Wilson disease, alpha 1 antitrypsin deficiency)
- Possible drug-induced liver disease (suspect drug within 30 days of onset of jaundice)
- Uncertain alcohol use assessment (e.g., patient denies excessive alcohol use)
- Presence of atypical laboratory tests (e.g., AST <50 or >400 IU/L, AST/ALT <1.5), ANA >1:160 or SMA >1:80.

HEPATOLOGY

AASLD
AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES

Liver biopsy : Alcoholic hepatitis



A. Macrovesicular steatosis
B. Hepatocellular injury is characterized by lobular infiltration of neutrophils Mallory-Denk bodies
C. Ductular reaction
D. liver fibrosis - pericellular and sinusoidal (“chicken wire” appearance)

AH Prognostic scoring indicators

TABLE 7. Characteristics of Lab-Based Prognostic Scores in Alcoholic Hepatitis

	Bili	PT/INR	Cr/BUN	Age	Alb	WBC	Stratification	Clinical Use
MDF	+	+	-	-	-	-	Severe: ≥32	Initiate corticosteroids
MELD	+	+	+	-	-	-	Severe: ≥21, but a continuous scale	Prognosis only
ABIC	+	+	+	+	-	-	Low: <6.71	Prognosis only
GAHS	+	+	+	+	-	+	Poor prognosis: ≥9	Initiate corticosteroids if ≥9 and MDF ≥32
Lille	+	+	+	+	+	-	≥0.45: Nonresponse <0.45: Response	Day 7 cessation or continuation of corticosteroids

Abbreviations: Alb, serum albumin; Bili, serum total bilirubin; Cr/BUN, creatinine/blood urea nitrogen; PT/INR, prothrombin time/international normalized ratio; and WBC, white blood cell count.

Prognostic scores: mDF out and MELD in

ARTICLE

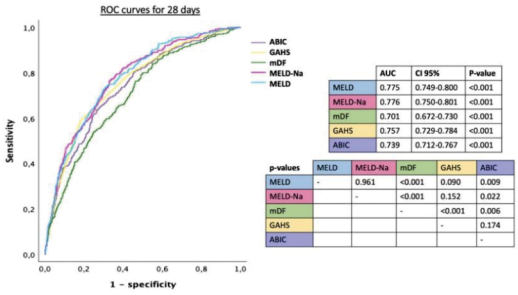
The MELD Score Is Superior to the Maddrey Discriminant Function Score to Predict Short-Term Mortality in Alcohol-Associated Hepatitis: A Global Study

D. Morales-Arráez, MD, PhD[1,2], M. Ventura-Cots, MD, PhD[1], J. Altamirano, MD, PhD[1], J.G. Abraldes, MD, PhD[3], M. Cruz-Lemini, MD[1], M.R. Thursz, MD, PhD[4], S.R. Atkinson, MD, PhD[4,5], S.K. Sarin, MD, PhD[6], W. Kim, MD, PhD[7], R. Chavez-Araujo, MD[8], M.F. Higuera-de la Tijera, MD, PhD[9], A.K. Singal, MD[10], V.H. Shah, MD[11], P.S. Kamath, MD[12], A. Duarte-Rojo, MD, PhD[13], E.A. Charles, RN[1], V. Vargas, MD, PhD[14], M. Jager, MD[15], P.E. Rautou, MD, PhD[15,16], D. Rincon, MD[17], F. Zamarripa, MD[18], J.C. Restrepo-Gutiérrez, MD, PhD[19], A. Tone, MD[20], M.R. Lucey, MD[21], J.P. Arab, MD[22], P. Mathurin, MD, PhD[23,24], A. Louvet, MD, PhD[23], G. García-Tsao, MD[25], J.A. González, MD[26], E.C. Verna, MD[27], R.S. Brown Jr, MD[28], J. Argemi, MD, PhD[1,29], C. Fernández-Carrillo, MD, PhD[1], A. Clemente, MD[1,24,30], E. Alvarado-Tapias, MD, PhD[1], E. Forrest, MD[31], M. Allison, MD, PhD[32] and R. Bataller, MD, PhD[1]

INTRODUCTION: **Several scoring systems predict mortality in alcohol-associated hepatitis (AH), including the Maddrey discriminant function (mDF) and model for end-stage liver disease (MELD) score developed in the United States, Glasgow alcoholic hepatitis score in the United Kingdom, and age, bilirubin, international normalized ratio, and creatinine score in Spain. To date, no global studies have examined the utility of these scores, nor has the MELD-sodium been evaluated for outcome prediction in AH. In this study, we assessed the accuracy of different scores to predict short-term mortality in AH and investigated additional factors to improve mortality prediction.**

METHODS: **Patients admitted to hospital with a definite or probable AH were recruited by 85 tertiary centers in 11 countries and across 3 continents. Baseline demographic and laboratory variables were obtained. The primary outcome was all-cause mortality at 28 and 90 days.**

RESULTS: **In total, 3,101 patients were eligible for inclusion. After exclusions (n = 520), 2,581 patients were enrolled (74.4% male, median age 48 years, interquartile range 40.9–55.0 years). The median MELD score was 23.5 (interquartile range 20.5–27.8). Mortality at 28 and 90 days was 20% and 30.9%, respectively. The area under the receiver operating characteristic curve for 28-day mortality ranged from 0.776 for MELD-sodium to 0.701 for mDF, and for 90-day mortality, it ranged from 0.773 for MELD to 0.709 for mDF. The area under the receiver operating characteristic curve for mDF to predict death was significantly lower than all other scores. Age added to MELD obtained only a small improvement of AUC.**



	AUC	CI 95%	P-value
MELD	0.775	0.749-0.800	<0.001
MELD-Na	0.776	0.750-0.801	<0.001
mDF	0.701	0.672-0.730	<0.001
GAHS	0.757	0.729-0.784	<0.001
ABIC	0.739	0.712-0.767	<0.001

p-values	MELD	MELD-Na	mDF	GAHS	ABIC
MELD	-	0.961	<0.001	0.090	0.009
MELD-Na		-	<0.001	0.152	0.022
mDF			-	<0.001	0.006
GAHS				-	0.174
ABIC					-

Figure 2. Receiver operating characteristic curves of the different prognostic scores for alcohol-associated hepatitis calculated baseline, used to predict mortality at 28 days, and *P* values comparing scores. ABIC, age, bilirubin, international normalized ratio, and creatinine score; AUC, area under the curve; CI, confidence interval; GAHS, Glasgow alcoholic hepatitis score; mDF, Maddrey discriminant function; MELD, model for end-stage liver disease.

Lille Model

- Predicts mortality in those on steroids
- Age, renal insufficiency, PT, Albumin, Bilirubin at D0 and D7
- Score of >0.45 indicates lack of response to steroids
  - Predicts 25% survival at 6 months
- Tells us whether to stop steroids at day 7

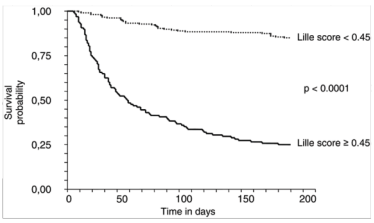
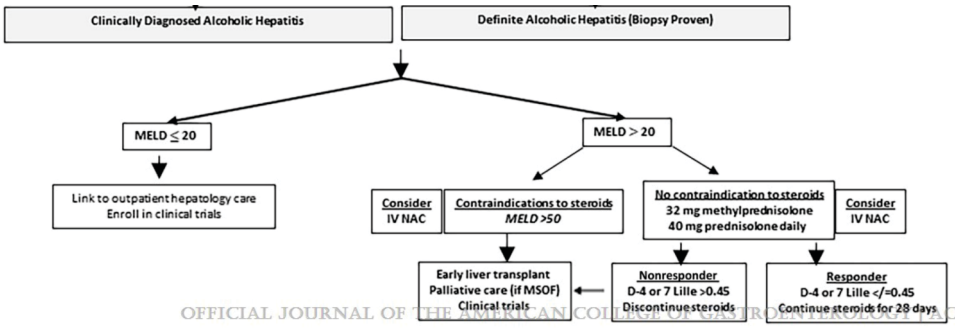


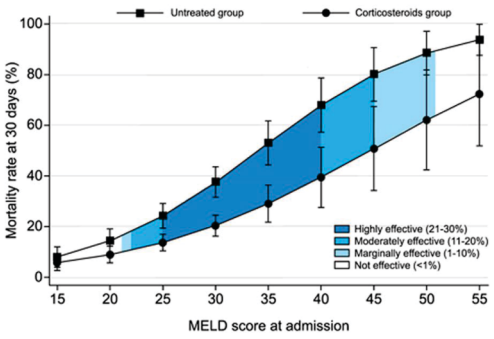
Fig. 4. Kaplan-Meier survival analysis according to 0.45 cutoff of the Lille model.

Evaluation and management of AH



The therapeutic window for corticosteroids in alcohol-associated hepatitis

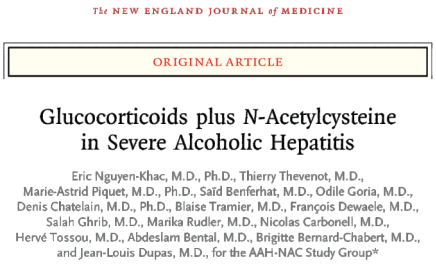
- We validated the use of steroids in severe alcohol-related hepatitis (MELD score >20)
- Corticosteroids decreased mortality at 30 days (HR=0.59)
- The most significant benefit was MELD range 25-39
- Futility of treatment could not be demonstrated in this study
- Survival benefit was not sustained at 90 or 180 days



Arab JP, J Hepatol. 2021 Nov;75(5):1026-1033

Steroids +/- N -Acetylcysteine

- 174 patients with severe AAH
  - 40mg oral prednisone for 28 days +/- IV NAC 5 days
- Mortality
  - 1 month 8% vs 24% (p=0.006)
  - 3 months 22% vs 34% (p=0.06)
  - 6 months 27% vs 38% (p=0.07)

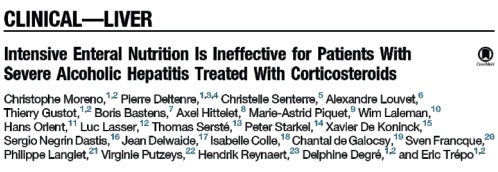

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Glucocorticoids plus *N*-Acetylcysteine in Severe Alcoholic Hepatitis

Eric Nguyen-Khac, M.D., Ph.D., Thierry Thevenot, M.D., Marie-Astrid Piquet, M.D., Ph.D., Saïd Benferhat, M.D., Odile Goria, M.D., Denis Chatelain, M.D., Ph.D., Blaise Tramier, M.D., François Dewaele, M.D., Salah Ghrib, M.D., Marika Rudler, M.D., Nicolas Carbonell, M.D., Hervé Tossou, M.D., Abdeslam Bental, M.D., Brigitte Bernard-Chabert, M.D., and Jean-Louis Dupas, M.D., for the AAH-NAC Study Group*

Nutritional therapy


CLINICAL—LIVER

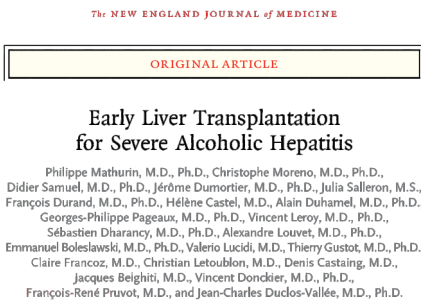
Intensive Enteral Nutrition Is Ineffective for Patients With Severe Alcoholic Hepatitis Treated With Corticosteroids

Christophe Moreno,[1,2] Pierre Deltenre,[1,3,4] Christelle Senterre,[5] Alexandre Louvet,[6] Thierry Gustot,[1,2] Boris Bastens,[7] Axel Hittelet,[8] Marie-Astrid Piquet,[9] Wim Laleman,[10] Hans Orlent,[11] Luc Lasser,[12] Thomas Sersté,[13] Peter Starkel,[14] Xavier De Koninck,[15] Sergio Negrin Dastis,[16] Jean Delwaide,[17] Isabelle Colle,[18] Chantal de Galocsy,[19] Sven Francque,[20] Philippe Langlet,[21] Virginie Putzeys,[22] Hendrik Reynaert,[23] Delphine Degré,[1,2] and Eric Trépo[1,2]

- Several studies have highlighted that protein energy malnutrition is present in almost every patient with severe AH, and is associated with poor prognosis
- ESPEN recommend a daily energy intake of 35–40 kcal/kg of body weight and a daily protein intake of 1.2–1.5 g/kg of BW in patients with AH
- Anabolic steroids trial did not alter mortality
- Intensive enteral nutrition and prednisone vs prednisolone alone in AH
  - No difference in mortality

Liver transplantation for Alcoholic Hepatitis

- Select group (n=26) of AH patients (2%)
  - No prior episodes of AH
  - Supportive families
  - No severe coexisting conditions
  - Voiced commitment to Alcohol abstinence
- 6 month survival period (p<0.001)
  - Early transplant group (n=26) 77%
  - Severe AH controls 23%
- 3 resumed alcohol use post LT



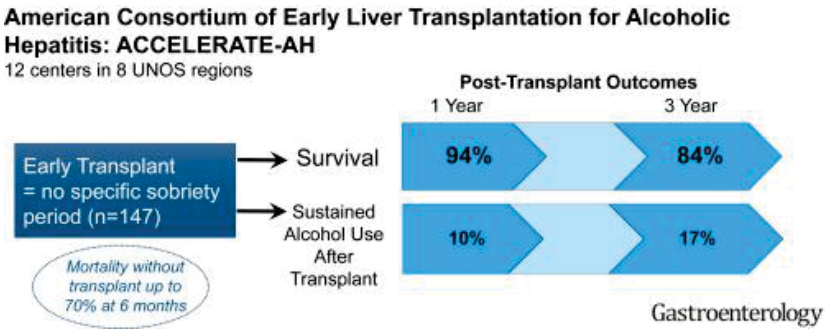
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Early Liver Transplantation for Severe Alcoholic Hepatitis

Philippe Mathurin, M.D., Ph.D., Christophe Moreno, M.D., Ph.D., Didier Samuel, M.D., Ph.D., Jérôme Dumortier, M.D., Ph.D., Julia Salleron, M.S., François Durand, M.D., Ph.D., Hélène Castel, M.D., Alain Duhamel, M.D., Ph.D. Georges-Philippe Pageaux, M.D., Ph.D., Vincent Leroy, M.D., Ph.D., Sébastien Dharancy, M.D., Ph.D., Alexandre Louvet, M.D., Ph.D., Emmanuel Boleslawski, M.D., Ph.D., Valerio Lucidi, M.D., Thierry Gustot, M.D., Ph.D. Claire Francoz, M.D., Christian Letoublon, M.D., Denis Castaing, M.D., Jacques Belghiti, M.D., Vincent Donckier, M.D., Ph.D., François-René Pruvot, M.D., and Jean-Charles Duclos-Vallée, M.D., Ph.D.

ACCELERATE - AH



Summary

- Incidence AUD, ALD and AH are increasing
- A qualitative alcohol history should be recorded
- In treatment of AUD, patient centered non judgmental approach is essential
- Pharmacological treatments are effective for withdrawals and abstinence
- Need to recognise severe AH treat the selected patients with steroids and NAC
- Mild to moderate AH without HE should be monitored but should not receive medications
- Assess for nutritional deficiencies and treat with enteral nutritional therapy
- Early liver transplant in AH improves survival

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What is new in Hepatitis B and C?

Dr. Chinthaka De Silva

Consultant Gastroenterologist & Hepatologist

Teaching Hospital Anuradhapura

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Hepatitis B and C what is new

Hepatitis B virus (HBV) and hepatitis C virus (HCV) remain significant global health threats due to their potential to cause chronic liver disease, cirrhosis, and hepatocellular carcinoma. Recent updates in the classification and management of chronic HBV have refined the nomenclature of disease phases, replacing the traditional terminology with a more clinically and virologically aligned classification: hepatitis B e antigen positive chronic HBV infection, hepatitis B e antigen positive chronic HBV, hepatitis B e antigen negative chronic HBV infection and hepatitis B e antigen negative chronic HBV[1]. Novel biomarkers such as hepatitis B core-related antigen (HBcrAg), quantitative HBsAg, and HBV RNA are enhancing disease monitoring and treatment decision-making [2]. The World Health Organization (WHO) updated its HBV treatment guidelines in 2024, promoting simplified criteria to broaden treatment eligibility, while the European Association for the Study of the Liver (EASL) issued new guideline in 2025 [3]. In parallel, novel direct-acting antivirals and immunomodulatory agents are under development, targeting a functional cure.

For HCV, the hepatitis C core antigen (HCVcAg) has emerged as a low-cost alternative to RNA-based diagnostics, particularly beneficial in resource-limited settings [4]. Pangenotypic direct-acting antiviral regimens have achieved high sustained virologic response (SVR) rates across genotypes; however, treatment resistance has been reported. In such cases, sofosbuvir–velpatasvir–voxilaprevir remains effective for retreatment [5]. Together, these developments mark a significant advancement in the global effort to eliminate viral hepatitis as a public health threat.

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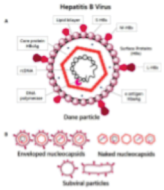
Outline

- Hepatitis B
  - Introduction
  - Natural history and Phases
  - Investigations and treatment
  - Novel antiviral therapies
- Hepatitis C
  - Introduction
  - Natural history and phases
  - Investigations and treatment
  - Novel antiviral therapies

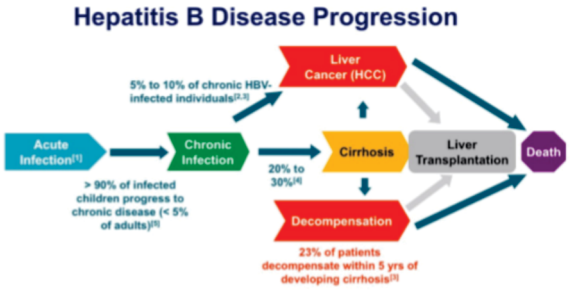
Hepatitis B

Introduction



- HBV belongs to the *Hepadnaviridae* family and is classified into ten genotypes (A to J)
- Transmitted by exposure to infectious blood or other body fluids (e.g. saliva, semen, vaginal secretions) and perinatally from infected mothers to infants.
- Global burden:
  - 240 million people with chronic hepatitis B in 2022(WHO)
  - 1.1 million deaths in 2022(WHO)

Natural history of Hepatitis B



Phases of hepatitis B

Acute hepatitis B infection

- New onset hepatitis B infection
- Recovery is accompanied by clearance of HBsAg with seroconversion to anti-HBs usually within 3 months

Chronic hepatitis B

- Persistence of HBsAg for 6 months or more after acute infection

New nomenclature for chronic phases

- The natural history of chronic HBV infection has been schematically divided into five phases

Chronic hepatitis B / Chronic HBV infection	HBeAg positive		HBeAg negative		
	Phase 1	Phase 2	Phase 3	Phase 4	Phase 5
	Chronic HBV infection	Chronic hepatitis B	Chronic HBV infection	Chronic hepatitis B	Resolved HBV infection
HBsAg	High	High/ intermediate	Low	Intermediate	Negative
HBeAg	Positive	Positive	Negative	Negative	Negative
HBV DNA	$>10^7$ IU/mL	10^4–10^7 IU/mL	<2,000 IU/mL*	>2,000 IU/mL	<10 IU/mL‡
ALT	Normal	Elevated	Normal	Elevated†	Normal
Liver disease	None/minimal	Moderate/ severe	None	Moderate/ severe	None§
Old terminology	Immune tolerant	Immune reactive HBeAg positive	Inactive carrier	HBeAg negative chronic hepatitis	HBsAg negative /anti-HBc positive

*HBV DNA levels can be between 2,000 and 20,000 IU/mL in some patients without signs of chronic hepatitis;
†Persistently or intermittently, based on traditional ULN (~40 IU/L). ‡cccDNA can frequently be detected in the liver;
§Residual HCC risk only if cirrhosis has developed before HBsAg loss.
EASL CPG HBV. J Hepatol 2017;67:370–98

EASL

Investigations in hepatitis B

- Hepatitis B surface antigen (HBsAg)
- Hepatitis B surface antibody (anti-HBs)
- Hepatitis B e antigen (HBeAg)
- Antibody to hepatitis B e antigen (anti-HBe)
- Hepatitis B core antibody (total anti-HBc)
- IgM antibodies to hepatitis B core antigen (IgM anti-HBc)
- Hepatitis B DNA levels

Newer biomarkers

- Quantitative HBsAg
- Hepatitis B core-related antigen (HBcrAg)
- HBV RNA

Quantitative HBsAg


Journal of Hepatology

The role of quantitative hepatitis B surface antigen revisited

- Can assist the differentiation of immune tolerance and immune clearance in HBeAg positive patients
- Helps to individualize pegylated interferon (PegIFN) treatment (helps to decide early termination of PegIFN among non-responders)


The Lancet Gastroenterology & Hepatology

Hepatitis B core-related antigen rapid diagnostic test for point-of-care identification of women at high risk of hepatitis B vertical transmission: a multicountry diagnostic accuracy study

- Hepatitis B core-related antigen (HBcrAg) rapid diagnostic test (RDT) to identify women at high risk of vertical transmission.
- In this study, the HBcrAg-RDT accurately identified
  - 93·1% of women who were HBsAg-positive and had high HBV DNA concentrations (≥200 000 IU/mL)
  - 94·3% of those with lower concentrations
- HBcrAg-RDT is a valid option for identifying highly viraemic individuals in resource-limited settings

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HEPATOLOGY

Serum Hepatitis B Virus RNA: A New Potential Biomarker for Chronic Hepatitis B Virus Infection

Serum HBV RNA

- May serve as a better surrogate marker for cccDNA activity in virally suppressed patients receiving NA therapy

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Treatment of hepatitis B

- Hepatitis B treatment goals are categorized into functional and complete cure
  - Functional cure is defined as sustained undetectable levels of HBsAg and HBV DNA in serum, with or without seroconversion to hepatitis B surface antibodies (anti-HBs)
  - Complete cure is considered as the total eradication of HBV DNA, including covalently closed circular DNA (cccDNA) and integrated HBV DNA, from the liver and serum
- The goal of the current therapeutic development is a functional cure

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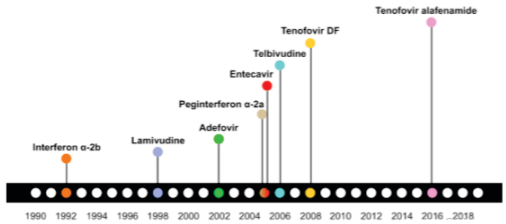
Two major categories of antiviral drugs for hepatitis B

- Interferon alpha (IFN-α)
- Nucleos(t)ide analogues (NAs)



HBV resistance for DAA

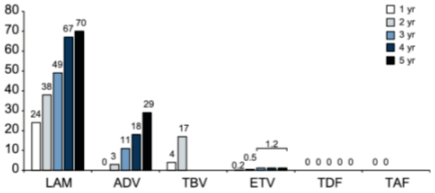


Fig. 3. Cumulative incidence of HBV resistance for lamivudine (LAM), adefovir (ADV), entecavir (ETV), telbivudine (TBV), tenofovir (TDF) and tenofovir alafenamide (TAF) in pivotal trials in nucleos(t)ide-naïve patients with chronic hepatitis B. (Collation of currently available data – not from head-to-head studies). No evidence of resistance has been shown after 8 years of TDF treatment.[69]

Treatment of chronic hepatitis B

Which patients with chronic HBV should be treated

- Treat all patients with HBV DNA >2000 IU/mL (previously >20000 IU/mL) and ALT above the upper limit of normal (30U/L for men and 19U/L for women)
- Treat all patients with significant fibrosis(>=F2) regardless of HBV DNA or ALT levels (previously only cirrhosis)
  - APRI >0.5 (aspartate amino transferase to platelet ratio index)
  - Transient elastography >7KPa
  - Cirrhosis
- Treat all patients with (regardless of HBV DNA or ALT levels)
  - Coinfections (HIV, hepatitis D and hepatitis C)
  - Family history of liver cancer or cirrhosis
  - Immune supression(such as long term steroid use, solid organ or stem cell transplant)
  - Comorbiditeis (such as diabetes or MASLD)
  - Extra hepatic manifestation (such as glomerulonephritis or vasculitis)

Recommended treatment options for chronic HBV

- First-line antiviral therapy for CHB
  - Tenofovir disoproxil fumarate(TDF) or Entacavir(ETV) - updated recommendation
  - Tenofovir+lamivudine or tenofovir + emtricitabine if no access to tenofovir monothearpy-updated recommendation
  - Tenofovir alafenamide fumarate(TAF) or ETV for patients with established renal impairment or osteoporosis - new recommendation
- Lamivudine, adefovir or telbivudine not recommended as these lead to drug resistance

- STOP-NUC and FINITE trials found that stopping nucleos(t)ide analogs substantially increased the rate of HBsAg loss (10.1% vs 0%; 19% vs 0%, respectively),
- But data from other trials do not suggest such favorable outcomes.
- A significant proportion of patients suffer clinical relapse and hepatic flares after stopping treatment

Treatment duration

- Lifelong antiviral therapy for people with cirrhosis
- Discontinuation may be considered for people
  - without cirrhosis
  - And can be followed up carefully for reactivation
  - And HBeAg loss and seroconversion to anti-HBe after completion of one additional year of treatment
  - And persistently normal ALT and undetectable HBV DNA
- If HBV DNA not available- persistent HBsAg loss and after completion of one additional year of treatment

Surveillance for HCC with abdominal ultrasound and AFP 6monthly

- People with cirrhosis
- People with family history of HCC
- Age above 40 yrs and HBV DNA level >20000 IU/mL

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Antiviral prophylaxis for HBsAg positive pregnant women

- TDF prophylaxis for HBsAg positive pregnant women with (from second trimester until at least delivery or completion of the infant HBV vaccination)- updated recommendation
  - HBV DNA >= 200000 IU/mL

    Or
  - Positive HBeAg

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Treatment of acute hepatitis B

- Antiviral therapy is not necessary if synthetic liver function is not impaired
- Patients with impaired synthetic liver function should be treated with NAs
  - Duration not yet established but generally till HBsAg loss

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- Combination therapy using PEG-IFN-2α and TDF achieves higher rates of HBsAg seroclearance, with approximately 10% of patients achieving this outcome*.
- However, the use of interferon (IFN) is frequently associated with severe adverse effects

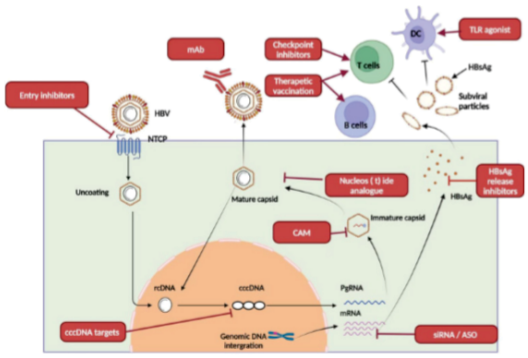
JOURNAL OF HEPATOLOGY EASL

Articles Publish Topics About Contact

EASL Clinical Practice Guidelines on the management of hepatitis B virus infection

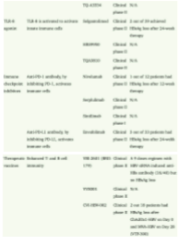
De novo combination therapy with PEG-IFNα and NAs cannot be generally recommended. PEG-IFNα as an add-on therapy can be considered in selected HBeAg-negative patients undergoing NA therapy with low HBsAg levels **(LoE 2, weak recommendation, consensus).***

Novel antiviral treatments



Novel antivirals

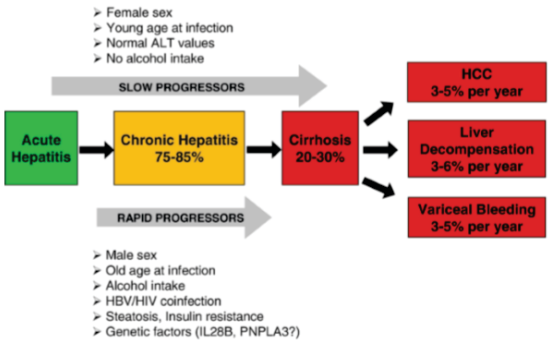
- Direct-acting antiviral agents
  - Entry inhibitors
  - Capsid assembly modulators
  - Subviral particle release inhibitors
  - cccDNA silencers
  - RNA interference molecules
- Immunomodulatory agents
  - Toll-like receptor agonists
  - Therapeutic vaccines
  - Checkpoint inhibitors
  - Monoclonal antibodies



Hepatitis C

- HCV is a bloodborne virus classified in the Flaviviridae family and Hepacivirus genus.
- Globally an estimated 50 million people have chronic hepatitis C virus infection, with about 1.0 million new infections occurring per year.
- WHO estimated that in 2022, approximately 242 000 people died from hepatitis C.

Phases of hepatitis C



Investigations in HCV

- HCV antibody
  - Can be detected in the blood usually within two or three months of HCV infection or exposure
  - A positive HCV-antibody test indicates
    - Current (active) HCV infection (acute or chronic)
    - Past infection that has resolved
    - Rare false positive
- HCV RNA
  - Can be detected and quantified in serum by nucleic acid testing (NAT).
- HCV core antigen (HCVcAg).
  - Released into plasma during viral assembly and can be detected from early on and throughout the course of infection.

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Annals of Internal Medicine

Hepatitis C Core Antigen Testing for Diagnosis of Hepatitis C Virus Infection: A Systematic Review and Meta-analysis

- This systematic review showed that there are several HCVcAg assays with high sensitivity (>90%) and specificity (>98%).
- But, even those with the highest performance do not reach the sensitivity of NAT
- Well-performing HCVcAg tests could serve as a replacement for NAT for HCV detection, particularly if a lower cost per test allows reaching more patients.

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AASLD HCV Guidance: Recommendations for Testing, Managing, and Treating Hepatitis C IDSA Infectious Diseases Society of America

- Because the sensitivity of HCV core antigen is less than that of HCV-RNA , test negative for HCV core antigen should have a confirmatory HCV-RNA test to exclude a false negative core antigen result

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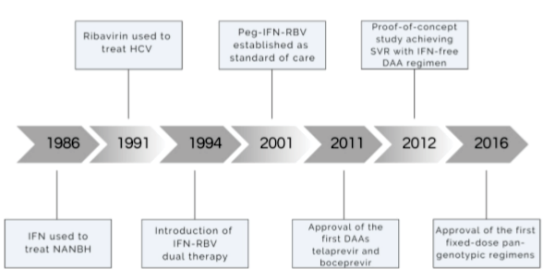
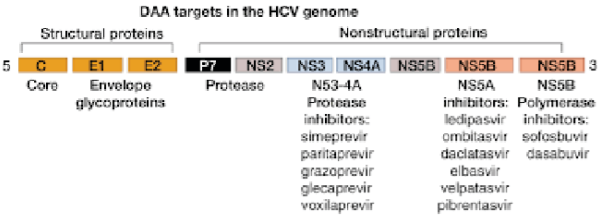
- Treatment

PHARMACOLOGICAL ADVANCEMENTS IN HCV HISTORY



Direct-acting antivirals



Treatment of acute hepatitis C

AASLD HCV Guidance: Recommendations for Testing, Managing, and Treating Hepatitis C — IDSA Infectious Diseases Society of America

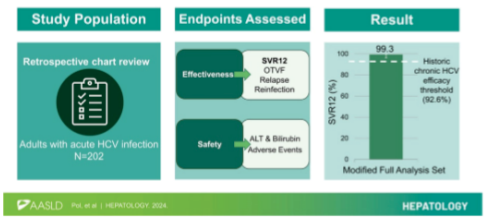
Recommendation for When and in Whom to Initiate Treatment	
RECOMMENDED	RATING
Treatment is recommended for all patients with acute or chronic HCV infection, except those with a short life expectancy that cannot be remediated by HCV therapy, liver transplantation, or another directed therapy. Patients with a short life expectancy owing to liver disease should be managed in consultation with an expert.	I, A

Recommended Regimens for Patients With Acute HCV Infection	
RECOMMENDED	RATING
Owing to high efficacy and safety, the same regimens that are recommended for chronic HCV infection are recommended for acute infection.	IIa, C

HEPATOLOGY

Effectiveness and safety of glecaprevir/pibrentasvir for 8 weeks in the treatment of patients with acute hepatitis C: A single-arm retrospective study

Effectiveness and Safety of G/P in Acute HCV Infection



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Treatment of chronic hepatitis C

- The goal of HCV therapy is sustained virologic response (virologic cure), defined as undetectable HCV RNA for 12 weeks (SVR12) after the end of treatment
- Cure of HCV infection also reduces symptoms and mortality from severe extrahepatic manifestations including cryoglobulinemic vasculitis
- HCV-infected persons with non-Hodgkin lymphoma and other lymphoproliferative disorders achieve complete or partial remission in up to 75% of cases following successful therapy for HCV infection

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AASLD HCV Guidance: Recommendations for Testing, Managing, and Treating Hepatitis C IDSA Infectious Diseases Society of America

Simplified HCV treatment (except for decompensated cirrhosis)

Recommended Regimens*

- Glecaprevir (300 mg) / pibrentasvir (120 mg) to be taken with food for a duration of 8 weeks
- Sofosbuvir (400 mg) / velpatasvir (100 mg) for a duration of 12 weeks

Patients with decompensated cirrhosis

- Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for 24 weeks
- Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) with weight-based ribavirin for 12 weeks

Regimens not recommended for:
Patients With Decompensated Cirrhosis (Moderate or Severe Hepatic Impairment; Child-Turcotte-Pugh Class B or C)

NOT RECOMMENDED	RATING
Any protease inhibitor-containing regimen (eg, glecaprevir, grazoprevir, and voxilaprevir).	III, B
Interferon-based regimens	III, B

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AASLD HCV Guidance: Recommendations for Testing, Managing, and Treating Hepatitis C IDSA Infectious Diseases Society

Pregnancy

- Currently no available data on the use of pangenotypic regimens during pregnancy
- Treatment can be considered during pregnancy on an individual basis after a patient-physician discussion about the potential risks and benefits.

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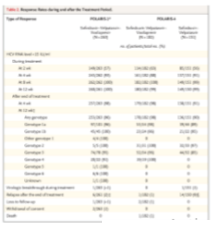
The NEW ENGLAND JOURNAL of MEDICINE

Sofosbuvir, Velpatasvir, and Voxilaprevir for Previously Treated HCV Infection

Authors: Marc Bourlière, M.D., Stuart C. Gordon, M.D., Steven L. Flamm, M.D., Curtis L. Cooper, M.D., Alnoor Ramji, M.D., Myron Tong, M.D., Natarajan Ravendhran, M.D., +35, for the POLARIS-1 and POLARIS-4 Investigators* Author Info & Affiliations

Published June 1, 2017 | N Engl J Med 2017;376:2134-2146 | DOI: 10.1056/NEJMoa1613512
VOL. 376 NO. 22 | Copyright © 2017

- Daily sofosbuvir–velpatasvir–voxilaprevir for 12 weeks is highly effective for patients infected with HCV of any genotype, with or without compensated cirrhosis, who did not have a sustained virologic response after treatment with DAA-based regimens.



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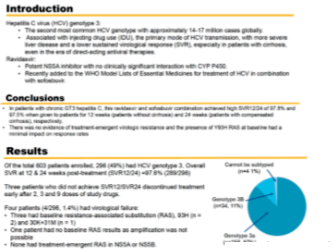
ARTICLES · Volume 6, Issue 6, P448-458, June 2021 · Open Access Download Full Issue

Efficacy and safety of ravidasvir plus sofosbuvir in patients with chronic hepatitis C infection without cirrhosis or with compensated cirrhosis (STORM-C-1): interim analysis of a two-stage, open-label, multicentre, single arm, phase 2/3 trial

MD Isabelle Andrieux-Meyer [1,a] ✉ · MRCP Soek-Siam Tan [1,b] · MD Sombat Thanprasertsuk [1,c] · PhD Nicolas Salvadori [d] · BSc Caroline Menétrey [e] · BSc François Simon [e] · et al. Show more



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Thank you

Autoimmune Hepatitis: From A to Z

Dr. Hasitha Wijewantha

MBBS (Col), MD (Col), MRCP (UK), FRCP (London), FCCP (SL)

Consultant Gastroenterologist and Hepatologist

National Hospital - Kandy

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Autoimmune Hepatitis –from A to Z

Autoimmune Hepatitis (AIH) is a relatively rare autoimmune disease that primarily affects the hepatocytes, occurs more commonlyin females. It typically presents as a slowly progressive chronic hepatitis but may also manifest as asymptomatic elevation of transaminases in 25–30% of patients, or, rarely, as acute liver failure. Without appropriate treatment, AIH can progress to cirrhosis and liver failure.

AIH arises from a combination of genetic susceptibility, gut microbiome factors, and environmental triggers such as infections or medications.

Diagnosis is based on clinical suspicion, hepatocellular type liver enzyme elevation, presence of autoantibodies, and characteristic liver biopsy findings.

Corticosteroids, particularly prednisolone (alone or with azathioprine), are the cornerstone of treatment. In cirrhosis and acute liver failure, monotherapy with prednisolone is preferred. Budesonide can be considered for patients who experience steroid-related side effects, but should be avoided in decompensated cirrhosis. Mycophenolatemofetil (MMF) can be used as an alternative to azathioprine, however, it is contraindicated in pregnancy.

Immunisation should be up-to-date in all patients. Vitamin D deficiency is a poor prognostic marker and should be promptly detected and treated.

Patients with AIH require non-invasive assessment of fibrosis every 2-3 years. In adults, treatment can be withdrawn after 3-4 years of complete biochemical remission without a liver biopsy. Lifelong monitoring for relapse and fibrosis is required with prompt re-initiation of therapyupon relapse.

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4. Snijders RJALM, Alfen JS van, Zelinkova Z, van Gerven NMF, van Erpecum KJ, van Hoek B, et al. An open-label randomised-controlled trial of azathioprine vs. mycophenolatemofetil for the induction of remission in treatment-naive autoimmune hepatitis. *J Hepatol*. 2024;80:576–585.
5. Gleeson D, Mells G, Hirschfield G, Jones DEJ, Heneghan MA, Webb GJ, et al. British Society of Gastroenterology guidelines for diagnosis and management of autoimmune hepatitis. *Gut*. 2025;0:1–46. doi:10.1136/gutjnl-2024-333171.

Autoimmune Liver Diseases

- Immune mediated injury to the hepatocytes and/or biliary epithelium and bile ducts
- Autoimmune Liver Diseases are classified according to
  - Clinical Phenotype
  - The main target of immune mediated injury
    - Hepatocytes
      - Autoimmune Hepatitis
    - Biliary epithelium and bile ducts
      - Primary Biliary Cholangitis – Small interlobular bile ducts
      - Primary Sclerosing Cholangitis – Medium sized intra and extra hepatic bile ducts
      - IgG 4 Associated Cholangitis – Medium size itra and extra hepatic bile ducts. Affects bile duct walls and surrounding tissues

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Autoimmune Hepatitis (AIH)

Meeting of the German Society for Digestive and Metabolic Disorders – 1950
Jan Gösta Waldenström

*"Six patients, five **females**, affected by a peculiar form of hepatitis ('hepatitis sui generis') with marked **elevation of serum gamma globulins** and amenorrhea, who had a **striking improvement** of symptoms and a dramatic fall of the erythrocyte sedimentation rate after administration of **adrenocorticotropic hormone**"*

Journal of Clinical Investigations 1951 - **Henry G. Kunkel**

***Extreme hypergammaglobulinemia** in young women with liver disease and a remarkable degree of **plasma cell infiltration in the liver**"*

Epidemiology of AIH

- Affect all ages and all populations, regardless of race and ethnicity.
- Pooled annual incidence per 100,000
  - Asians – 1.31
  - Europeans – 1.37
  - Americans – 1
- Pooled prevalence per 100,000
  - Asians - 12.99
  - Europeans - 19.44
  - Americans - 22.80
- Incidence of AIH is on the rise
  - In England from 1.27 to 2.56 /100,000 during the 1997-2015 period

Muratori L et al. BMJ 2023;380:e070201

Pathogenesis of AIH

- Genetics and Epigenetics
- Abnormal Immune Regulation
- Environmental trigger factors
- Microbiome

Muratori L et al. BMJ 2023;380:e070201

Clinical Presentation of AIH

- Extremely heterogeneous
  - Asymptomatic
  - Insidious onset – Fatigue is the commonest symptom
  - Acute onset – Transaminases 5 – 10 times the upper limit
- Nearly 75 % are females
- Two peaks – 2nd decade and 5th/6th decade of life
- Co – existing other autoimmune disorders
  - Type 1 diabetes
  - Autoimmune thyroid disease
  - Rheumatoid arthritis
  - Autoimmune Skin Diseases
  - IBD
  - Celiac disease

Autoimmune Hepatitis (AIH)

"AIH must be considered in <u>all patients</u> presenting with acute or chronic liver disease, including patients with asymptomatic liver test abnormalities, ALF, and autoantibody-negative hepatitis"

AASLD Clinical Practice Guideline on Diagnosis and Management of Autoimmune Hepatitis in Adults and Children 2019 – Hepatology Aug 2020

Diagnosis of AIH

- Autoimmune hepatitis lacks a signature diagnostic marker
- Clinical diagnosis based on
  - Suggestive history
  - Laboratory findings - Liver functions, Autoantibodies
  - Characteristic histological findings
- Need to exclude competing etiologies – DILI, Viral hepatitis, Wilsons

Autoantibodies in AIH

Presence of auto antibodies is not diagnostic of autoimmune liver diseases

Autoantibodies in AIH

Anti Nuclear Antibody

- With indirect immunofluorescence technique
- Can be positive in
  - PSC – 29%
  - Chronic Hepatitis C – 26 %
  - Chronic Hepatitis B – 32 %
  - MASLD – 34 %
  - Alcohol Associated Liver Disease – 21 %

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Autoantibodies in AIH

Anti Smooth Muscle Antibody (SMA)

Can be positive in

- PSC -6%
- Chronic Hepatitis C – 6%
- Chronic Alcohol Associated Liver Disease – 4%

ANA and SMA are concurrent in <10 % of liver diseases outside AIH

Better diagnostic accuracy if both antibodies are detected at presentation

AASLD Clinical Practice Guideline on Diagnosis and Management of Autoimmune Hepatitis in Adults and Children 2019 – Hepatology Aug 2020

Autoantibodies in AIH

Liver Kidney Microsomal Antibody – 1 (LKM 1)

- Low sensitivity for AIH
- Positive in Type 2 AIH
- Commonly detected when ANA and SMA are absent

Anti Soluble Liver Antigen (Anti SLA)

- Present in 7 -22 % patients with type 1 AIH
- 99 % specificity

AASLD Clinical Practice Guideline on Diagnosis and Management of Autoimmune Hepatitis in Adults and Children 2019 – Hepatology Aug 2020

Autoantibodies in AIH

Atypical Perinuclear Antineutrophil Cytoplasmic Antibodies (pANCA)

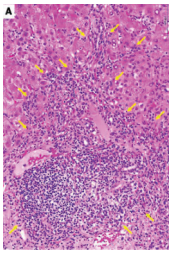
- Low specificity
- Present in 50 – 92 % patients with type 1 AIH
- Present in
  - PSC
  - PSC –AIH overlap
  - Ulcerative Colitis
  - Minocycline related liver injury

AASLD Clinical Practice Guideline on Diagnosis and Management of Autoimmune Hepatitis in Adults and Children 2019 – Hepatology Aug 2020

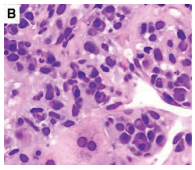
Diagnosis of AIH

Diagnosis of Autoimmune Hepatitis is **can not** be made without suggestive histopathological findings

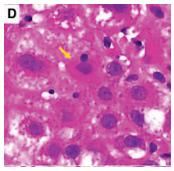
Characteristic histological features of AIH



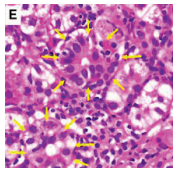
Lymphoplasmacytic infiltration of the portal tract and **interface hepatitis** involving >50% of the portal tract circumference



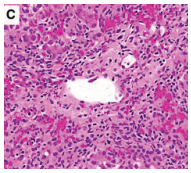
Plasma cell predominant **portal inflammatory** infiltrate



Emperipolesis (Presence of an intact cell within the cytoplasm of another cell)



Rosettes of regenerating hepatocytes



Perivenulitis of a central vein

IAIHG Diagnostic scoring systems

Revised scoring system for diagnosis of autoimmune hepatitis

Parameters/Features	Score	Notes*
Female sex	+2	
ALP:AST (or ALT) ratio:		
<1.5	+2	1
1.5-3.0	0	
>3.0	−2	
Serum globulins or IgG above normal		
>2.0	+3	
1.5-2.0	+2	
1.0-1.5	+1	
<1.0	0	
ANA, SMA or LKM-1		
>1:80	+3	7
1:80	+2	
1:40	+1	
<1:40	0	
AMA positive	−4	
Hepatitis viral markers:		
Positive	−3	3
Negative	+3	
Drug history:		
Positive	−4	4
Negative	+1	
Average alcohol intake		
<25 g/day	+2	
>60 g/day	−2	
Liver histology:		
Interface hepatitis	+3	
Predominantly lymphoplasmacytic infiltrate	+1	
Rosetting of liver cells	+1	
None of the above	−5	
Biliary changes	−3	5
Other changes	−3	6
Other autoimmune disease(s)	+2	7
Optional additional parameters:		8
Seropositivity for other *defined* autoantibodies	+2	9
HLA DR3 or DR4	+1	10
Response to therapy:		
Complete	+2	11
Relapse	+3	
Interpretation of aggregate scores.		
Pre-treatment:		
Definite AIH	>15	
Probable AIH	10-15	
Post-treatment:		
Definite AIH	>17	12
Probable AIH	12-17	

Table 2. Simplified Diagnostic Criteria for Autoimmune Hepatitis

Variable	Cutoff	Points
ANA or SMA	≥1:40	1
ANA or SMA	≥1:80	
or LKM	≥1:40	2*
or SLA	Positive	
IgG	>Upper normal limit	1
	>1.10 times upper normal limit	2
Liver histology (evidence of hepatitis is a necessary condition)	Compatible with AIH	1
	Typical AIH	2
Absence of viral hepatitis	Yes	2
		≥6: probable AIH
		≥7: definite AIH

*Addition of points achieved for all autoantibodies (maximum, 2 points).

Auto antibody titres determined by indirect immunofluorescence on rodent tissues or, for ANA, on HEp-2 cells

Alvarez F et al. J Hepatol. 1999 Nov;31(5):929-38.
Hennes EM et al. Hpatology, Vol. 48, No. 1, 2008

Diagnosis of AIH

Compatible histological findings

Supported by

- Elevated transaminases, no evidence of cholestasis
- Elevated serum Ig G and/or positive serological markers
  - ANA and SMA in adults
  - ANA, SMA and LKM1 in children
- Exclusion of viral, hereditary, metabolic, cholestatic, and drug-induced diseases that may resemble AIH.

AASLD Clinical Practice Guideline on Diagnosis and Management of Autoimmune Hepatitis in Adults and Children 2019 – Hepatology Aug 2020

Type 1 and Type 2 AIH

TABLE 3. Characteristic Features of Type 1 and Type 2 AIH

Features	Type 1 AIH	Type 2 AIH
Frequency	US adults, 96%[61,554]	US children, 9%-12%[14-16]
		UK children, 38%[13]
Age at presentation	Peripubertal and adults	Usually under 14 years[153]
Mode of presentation	Chronic symptoms common	Acute onset (~40%)
	Ascites or GI bleeding rare	Acute liver failure possible[555,556]
	Asymptomatic in 25%-34%	Relapse frequent[108]
	Acute in 25%-75%	
	Acute severe in 2%-6%	
Laboratory features	Hypergammaglobulinemia	IgA levels may be reduced[153]
Autoantibodies	ANA	Anti-LKM1
	SMA, anti-actin	[Anti-LC1, Anti-LKM3]
	SLA	
Concurrent immune diseases	Autoimmune thyroiditis	Autoimmune thyroiditis
	Rheumatic diseases	Diabetes mellitus
	IBD	Vitiligo
Autoimmune overlap with PSC (ASC in children)	Common in children	Rare
	Atypical pANCA-positive	Atypical pANCA-negative
Overlap with PBC	Seen in adults (not children)	Not reported
Cirrhosis at presentation	Adults, 28%-33% (especially elderly)	Rare
	Children, ≤33%	
Remission after drug withdrawal	Possible	Rare, usually need long-term immunosuppression

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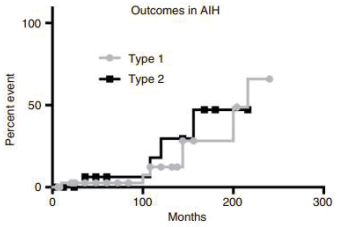
Type 1 and Type 2 AIH

	ANA/SMA+ve (52)	Anti-LKM1/ anti-LC1+ve (26)	P
Age (years)	27 (17–53)*	25 (17–53)*	0.238*
Female Sex	83%	92%	0.490
Onset			
Acute	50%	31%	0.106
Insidious	21%	19%	0.843
Asymptomatic	29%	50%	0.066
Associated autoimmune disorders	37%	35%	0.820
Severe liver histology	59%	45%	0.294
Cirrhosis	12%	19%	0.456
Albumin (g/L)	40 (18–62)*	43 (19–46)*	0.318*
Gamma globulin (g/L)	22 (9–60)*	23 (9–63)*	0.659*
AST (× UNL)	10 (1.2–61)*	6 (1.2–51)*	0.554*
ALT (× UNL)	13 (1.6–60)*	12 (1.7–80)*	0.655*
Bilirubin (mg/dL)	1.39 (0.16–50)*	1.6 (0.57–21)*	0.802*
Alkaline Phosphatase (× UNL)	1.2 (0.44–8.4)*	1.1 (0.5–6)*	0.925*
gammaGT (× UNL)	2.38 (0.17–21)*	1.32 (0.3–8.4)*	0.073*
IgG (× UNL)	1.54 (0.7–3.8)*	1.12 (0.7–2)*	0.062*
IgA (× UNL)	0.68 (0.1–2)*	0.62 (0.07–1.4)*	0.739*
IgM (× UNL)	0.7 (0.13–2.3)*	0.7 (0.35–1.9)*	0.976*
INR	1.1 (1–3)*	1.05 (1–2.5)*	0.486*
Cholesterol (mg/dL)	140 (85–271)*	179 (93–278)*	0.022*
Treatment response			
Complete	50%	60%	0.464
Partial	37.5%	25%	0.333
No response	12.5%	15%	0.788
Relapse	81%	78%	0.961
Progression	18%	15%	0.633
Disease duration (mo.)	78 (13–280)*	70 (12–280)*	0.591*



Clinical, biochemical, genetic and histological profiles are similar

Muratori P et al. Aliment Pharmacol Ther 2015; A41: 1281–1287

Type 1 and Type 2 AIH

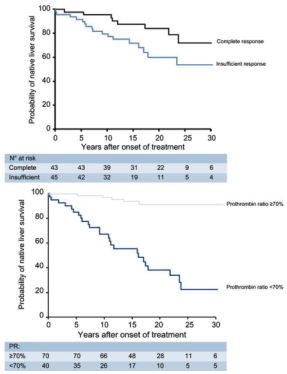
117 children with autoimmune hepatitis type 1 = 65 type 2 = 52
immunosuppressive therapy
Median follow-up 20 years in survivors

Normalization of transaminase and prothrombin ratio in 93% and 84% of children
Sustained remission after treatment withdrawal in 24% (median follow-up 7 years)
Treatment-free remission in 11 of 24 children (follow-up 4-22 years)

Liver transplant = 23

Deaths = 17

No differences in outcomes between types 1 and 2 hepatitis
Withdrawal of treatment is possible without liver histology
Persistent abnormal prothrombin predicts the need for liver transplantation

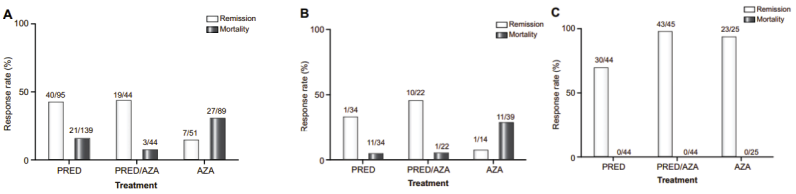


Maggiore G et al. Journal Hepatology:78 (5) May 2023

Treatment of AIH

- Untreated AIH leads to liver failure and death within 5 years in most patients
- The main aim - induction of full biochemical remission with normal transaminases and IgG
- Complete biochemical remission allows regression of fibrosis
- Response to steroids is universal in AIH
- Measurement of bone density at the start of steroids and Calcium and vitamin D supplementation for all patients on steroids
- Up to date immunisation – Hep A & B, COVID, Influenza, Pneumococcus, HPV in females < 25yrs/ GBMSM men <45 yrs

Treatment options for AIH



Induction - Naïve AIH patients | Induction – Relapse patients | Maintenance therapy

- **Prednisolone mono therapy and Pred +Aza combination are options for induction**
- **Pred +Aza combination and Aza mono therapy are superior to Pred mono therapy for maintenance**

Lamers MMH et al. Journal of Hepatology 2010 vol. 53 :191–198

First-Line Treatment of AIH

	AIH	AIH with Cirrhosis	Acute Severe AIH
Induction	**STEROIDS** Adults: Prednisone (20-40 mg/d) Pediatrics: Prednisone (1-2 mg/kg/d) Or budesonide (9mg daily) **AZATHIOPRINE (AZA)** Check TPMT. After 2 weeks add AZA (50-150 mg/d) Laboratory testing every 1-2 weeks	**STEROIDS** *Do not use budesonide* Adults: Prednisone (20-40 mg/d) Pediatrics: Prednisone (1-2 mg/kg/d) **AZATHIOPRINE (AZA)** Do not use in decompensated cirrhosis Compensated cirrhosis: Check TPMT. After 2 weeks add AZA (50-150 mg/d) Laboratory testing every 1-2 weeks	**STEROIDS** *Do not use budesonide* *Do not use azathioprine (AZA)* Adults: Prednisone (60 mg/d) Pediatrics: Prednisone (2 mg/kg/d) OR I.V. steroids Laboratory testing every 12-24 hours
	Assess Response by 4-8 weeks: (+) Biochemical response • Taper prednisone to 5-10 mg daily (budesonide 3 mg daily) over the next 6 months • Maintain AZA • Laboratory testing every 2-4 weeks (-) Biochemical response • Re-evaluate diagnosis • Consider second-line drugs	**Assess Response by 4-8 weeks:** (+) Biochemical response • Taper prednisone to 5-10 mg daily over the next 6 months • If started, maintain AZA • Laboratory testing every 2-4 weeks (-) Biochemical response • Re-evaluate diagnosis • Consider second-line drugs	**Assess Response by 7-14 days:** (+) Biochemical response • Cautiously reduce prednisone • Consider AZA after cholestasis is resolved (check TPMT first) • Laboratory testing every 1-2 weeks (-) Biochemical response • Re-evaluate diagnosis • Consider second-line drugs • Initiate transplant evaluation If hepatic encephalopathy develops • Urgent transplant evaluation
Maintenance	**Once Biochemical Remission is acheived:** • Laboratory testing every 3-4 months • May attempt a steroid withdrawal while continuing AZA After prolonged biochemical remission (24 months): • Laboratory testing every 4-6 months • Consider immunosuppression withdrawal if appropriate (+/- biopsy)		**Once Biochemical Remission is acheived:** • Laboratory testing every 3-4 months • Use lowest immunosuppression doses to maintain remission • *Do not withdraw immunosuppression*

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First Line Treatment of AIH

- Mild AIH (ALT <50, mild inflammation and fibrosis) – weigh risks and benefits of treatment
- Initial dose of steroids 0.5 -1 mg/kg/day – not exceeding 40mg/d
- Prednisolone monotherapy in decompensated CLD, Hx of malignancy, uncertain diagnosis or suspected precipitant (Viral/DILI induced)
- Azathioprine can be started whenever bilirubin is < 6mg/dl, ideally two weeks after starting steroids

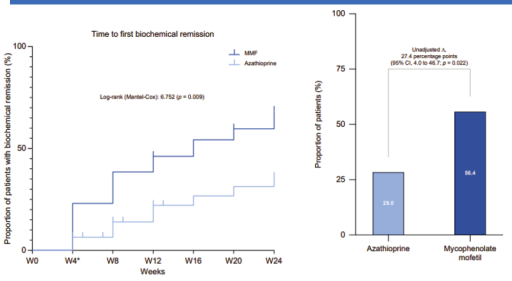
Gleeson D et al. BSG guidelines for diagnosis and management of autoimmune hepatitis. *Gut*. 2025;0:1–46. doi:10.1136/gutjnl-2024-333171.

First Line Treatment of AIH

- Budesonide is considered in **adults** without cirrhosis when cosmetic side effects of steroids are a concern – starting dose 9mg/d
- Reduce Prednisolone in 5-10 mg/d increments every 2 weeks over 3 months
- Reduce Prednisolone to < 20mg/d as soon as possible
- Initial dose of Azathioprine is 50 mg, increased until 1-2mg/kg depending on toxicity and response to therapy

Gleeson D et al. BSG guidelines for diagnosis and management of autoimmune hepatitis. *Gut*. 2025;0:1–46. doi:10.1136/gutjnl-2024-333171.

Azathioprine Vs MMF for induction therapy



- Significantly higher rate of biochemical remission at 24 weeks with MMF and Prednisolone compared to Azathioprine and prednisolone
- MMF showed superior tolerability compared to Azathioprine

MMF is Contraindicated in pregnancy – FDA category D

Snijders RJALM et al. Journal of Hepatology. April 2024. vol. 80:576–585

Response Criteria of Treatment

Inadequate Response

- After 1 month - < 50% decrease in ALT/AST
- After 6 months – Failure of normalization of ALT/AST and IgG

Endpoint	Definition
Complete biochemical response	Normalisation of serum transaminases and IgG below the ULN. Should be achieved no later than 6 months after initiation of treatment.
Insufficient response	Lack of complete biochemical response. Should be determined no later than 6 months after initiation of treatment.
Non-response	<50% decrease of serum transaminases within 4 weeks after initiation of treatment.
Remission	Hepatitis activity index <4/18.
Intolerance to treatment	Any adverse event possibly related to treatment as assessed by the treating physician leading to potential discontinuation of the drug.

Gleeson D et al. BSG guidelines for diagnosis and management of autoimmune hepatitis. *Gut*. 2025;0:1–46. doi:10.1136/gutjnl-2024-333171.

Pape S et al. Journal of Hepatology 2022 vol. 76:841–849

Negative Prognostic Markers of AIH

- Cirrhosis at onset
- Young age at onset
- Repeated relapses of active disease on drug withdrawal
- Variant syndromes (autoimmune hepatitis-PSC, autoimmune hepatitis-PBC)
- Concomitant liver disease (NASH/NAFLD)
- Ethnicity (black race)
- Vitamin D deficiency

Muratori L et al. BMJ 2023;380:e070201

Treatment of AIH

Second Line treatment

- Calcineurin Inhibitors
  - Tacrolimus
  - Cyclosporin

Evolving Salvage therapies

- Anti-TNF alpha antibodies – Infliximab, Adalimumab
- Anti CD 20 Antibodies – Rituximab
- Thioguanine

Long term management of AIH

- Non invasive assessment for liver fibrosis every 2-3 years
- In adults who achieve complete biochemical remission after 6 months, steroids can be withdrawn over 3 months
- After 3- 4 years of sustained biochemical remission treatment withdrawal can be considered
- Liver biopsy is not mandatory in adults
- Life long monitoring for relapse and fibrosis required after treatment withdrawal
- Relapse require urgent reinstitution of original treatment and subsequent maintenance therapy

Long term management of AIH

- Monitor long term adverse effects of Azathioprine
  - Women - regular cervical screening
  - Avoid sun light, medical advice on newly developing skin lesions
- In Cirrhotics
  - 6 monthly ultra sound surveillance for HCC
  - Endoscopic surveillance of varices
  - Early referral to transplant centre if persistent impairment of synthetic function or symptoms of decompensation

Gleeson D et al. BSG guidelines for diagnosis and management of autoimmune hepatitis. *Gut*. 2025;0:1–46. doi:10.1136/gutjnl-2024-333171.

MASLD and AIH

- Older
- Higher BMI
- No female preponderance
- Lower AST,ALT,ALP and Bilirubin values
- Higher prevalence of
  - Diabetes
  - Hypertension
  - Hypertriglyceridemia

- Induction therapy
  - With usual doses steroid and rapid tail off
  - With lower initial doses <0.5mg/kg/d
- Budesonide for non cirrhotics
- Early addition of Aza/6-MP/MMF, up to safe highest doses
- Strict control of components of MetS
- Withdraw steroids completely in 6-8/12

Dalekos et al. European Journal of Internal Medicine Jan 2020

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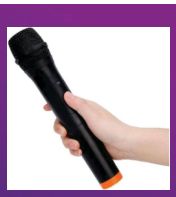
Dalekos et al. European Journal of Internal Medicine Jan 2020

Autoimmune Hepatitis – Take Home Messages

1. Relatively rare autoimmune disease affecting hepatocytes
2. Female preponderance but can affect anyone
3. Extremely heterogeneous presentation
4. Diagnosed clinically and confirmed with histopathology
5. Elevated serum IgG and specific auto antibodies supports the diagnosis
6. Rapid steroid responsiveness is a universal feature
7. Achieving full biochemical remission with normal transaminases and IgG is the main aim of therapy
8. Non invasive testing for liver fibrosis every 2-3 years
9. Effective management of adverse effects of therapy improves the outcome
10. Excellent prognosis when properly treated

GRH 2025
Grand Rounds in Hepatology
Sri Lanka Society of Gastroenterology



Questions ?

GRH 2025
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Sri Lanka Society of Gastroenterology

Assessment & management of nutritional issues in advanced chronic liver disease

Dr. Vadivel Vijitharan

Consultant Gastroenterologist

TH - Batticaloa

GRH 2025

Grand Rounds in Hepatology

Sri Lanka Society of Gastroenterology

Assessment and Management of Nutritional Issues in Advanced Chronic Liver Disease.

Malnutrition and sarcopaenia are highly prevalent and under recognised in advanced chronic liver disease (ACLD). With the epidemic of obesity, sarcopaenic obesity in ACLD patients is increasingly recognised. The severity of malnutrition correlates with the progression of the liver disease. Malnutrition and sarcopaenia and strongly linked to morbidity, mortality and poor transplant outcomes in ACLD patients.

Malnutrition in ACLD is multifactorial, including poor dietary intake, gastrointestinal dysfunction and disease related adaptive and maladaptive changes in metabolism. Important mechanism of sarcopaenia involves accelerated fasting state and dysregulated protein homeostasis.

Early and routine screening for malnutrition, sarcopaenia and frailty is essential in all patients with ACLD. However, assessment of malnutrition in patients with ACLD using traditional methods is challenging due influence by liver disease related changes (e.g: ascites). Assessing for muscle mass and strength are important recognised indicators correlate with outcomes. Management of malnutrition in ACLD include adequate, balanced caloric intake, late evening carbohydrate snacks, plant-based or branched chain amino acid enriched protein sources and avoidance of unnecessary protein restriction and fructose consumption. Micronutrient replacements and regular coffee consumption are also suggested. When sufficient, enteral nutrition is preferred over parenteral.

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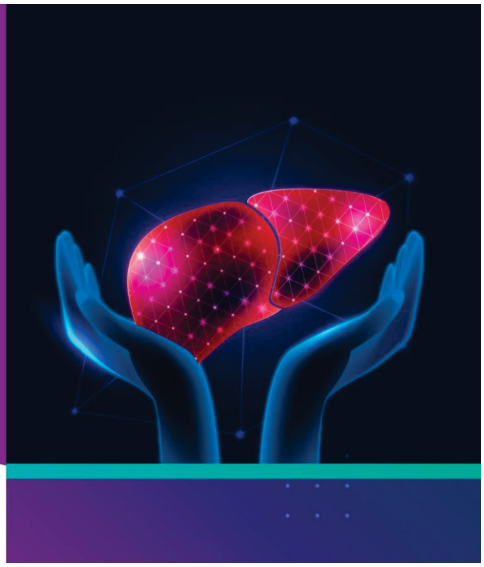

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Assessment and management of Nutritional issues in Advanced Chronic Liver Disease

Dr. Vadivel Vijitharan
Consultant Gastroenterologist
Teaching Hospital, Batticaloa

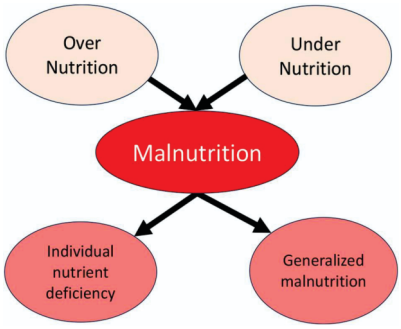
Outline

Introduction: why it is important
Definitions
Causes of malnutrition
Pathophysiology
How malnutrition affects the prognosis
Assessment of malnutrition
Nutritional interventions
Nutritional aspects in special scenarios

Introduction

- Liver is the largest and metabolically most complex organ in human body
- Portal blood supply exposes liver to nutrients and gut-derived metabolites
- Malnutrition is highly prevalent in compensated (20%) and decompensated (60%) patients with Advanced chronic liver disease, but under-recognised
- Malnutrition is strongly linked to morbidity, mortality and poor transplant outcomes

Definitions



Definitions

Malnutrition: Nutrition-related disorder resulting from lack of intake or uptake of nutrition that leads to altered body composition (decreased fat free mass) and body cell mass, leading to diminished physical and mental function and impaired clinical outcome from disease.

Sarcopenia: A generalised reduction in muscle mass and function due to aging (primary sarcopenia), acute or chronic illness (secondary sarcopenia), including chronic liver disease
The most frequent phenotype of the “undernourished” patient.

Frailty: Loss of functional, cognitive, and physiologic reserve leading to a vulnerable state. Frailty may be considered a form of nutrition-related disorder

Causes of malnutrition in ACLD

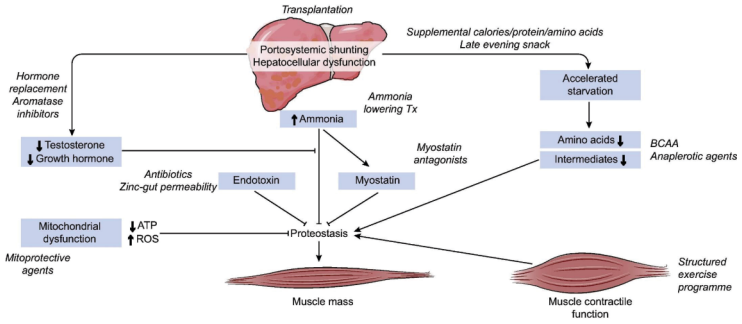
Inadequate dietary intake	Malabsorption	Metabolic disturbances
Nausea and early satiety: ascites and impaired gut motility	Porto-systemic shunting	Hypermetabolic state: Increased sympathetic activity Bacterial translocation
Loss of appetite: Upregulation of leptin and TNF-alfa	Chronic pancreatitis	Physical inactivity: Obesity and endocrine factors
Altered taste: Zinc deficiency	Bile acid deficiency Reduced production Porto-systemic shunting	Sepsis and cytokine strome
Dietary restriction and unpalatable diet: Salt and protein Fasting for investigations	Small bowel bacterial overgrowth	Increased luconeogenesis: Loss of fat and muscle
Alcohol dependence: Irregular and poor eating	GI bleeding: Bowel hypermobility Protein loss	

How it happens: Pathophysiology

- Loss of glycogen storage
- State of accelerated starvation
- Dysregulated protein homeostasis
- Gut dysbiosis: alteration in the gut flora
- Gut dysfunction and loss of intestinal barrier function
- Effects of portal hypertension
- Micronutrient deficiency related cellular metabolic dysfunction
- Endocrine abnrmalities

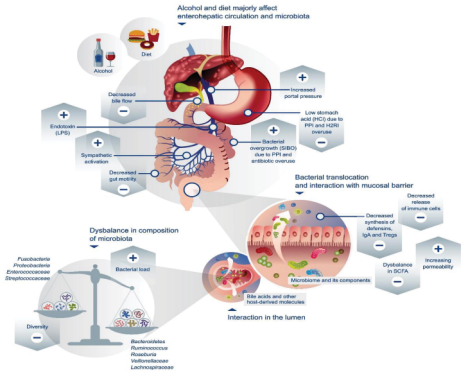
Pathophysiology:

patients with advanced liver disease to enter a accelerated starvation state within a few hours of fasting.



Pathophysiology: the gut-liver axis

Portal hypertension, Gut dysfunction, dysbiosis and leaky gut



How alcohol use disorder (AUD) adversely affects nutrition

- Approximately, 50 % of the calories are derived from alcohol in AUD
- Alcohol provides ‘empty calories’ devoid of critical nutrients
- Associated with reduce intake of adequate proteins
- Gut dysbiosis and epithelial dysfunction occur in long term alcohol use

How fructose consumption affects the patients with ACLD

- potent inducers of hepatic de novo lipogenesis (DNL) and insulin resistance.
- Associated with chronic liver disease and fibrosis in a dose-dependent manner.
- Low-fructose diets are recommended in all patients with chronic liver disease across the entire spectrum of disease severity.

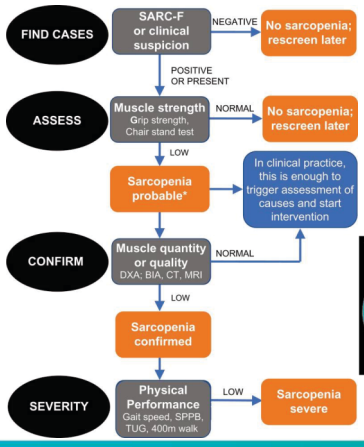
Assessment of malnutrition: Screening tool for malnutrition in ACLD

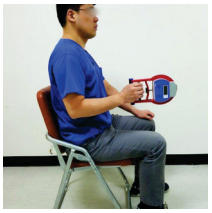
All patients with ACLD should be offered screening for malnutrition at diagnosis and subsequently.

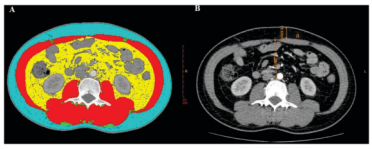
The Royal Free Hospital-nutritional prioritizing tool (RFH-NPT) score

- Correlates with clinical deterioration, severity of disease, and clinical complications
- Improvement in RFH-NPT score was associated with improved Survival

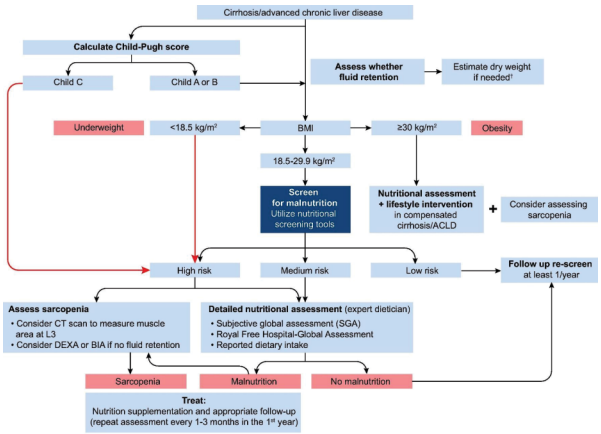
Assessment and diagnosis of sarcopaenia







Assessment and diagnosis of malnutrition



Assessment and diagnosis of malnutrition in ACLD

Table 4. Clinically available methods for assessing malnutrition

Method	Advantages	Disadvantages
Anthropometry (triceps skinfold, mid arm circumference, body weight, body mass index, waist circumference, waist/hip ratio)	Easily measured, little or no cost	Many potential confounders (e.g., height, muscle mass, fluid retention, and bone density)
Biological parameters (e.g., prealbumin)	Inexpensive	Proteins, such as albumin and prealbumin, are made in the liver
Assessment of muscle strength (e.g., hand grip strength)	Inexpensive, easy	Some are time-consuming, such as 6-min walk
Bioelectrical impedance	Easily performed	Instrumentation availability; cannot identify fat compartments
Imaging (dual-energy X-ray absorptiometry, CT, MRI, ultrasound)	Accurate and reproducible measure of fat mass and fat-free mass	Cost; instrument availability; personnel training; radiation exposure for some tests
Subjective global assessment	Inexpensive	Subjective; requires training

CT, computed tomography; MRI, magnetic resonance imaging.

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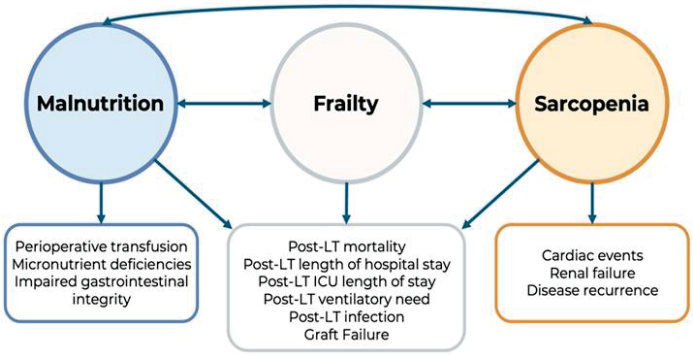
The impact of malnutrition, frailty and sarcopaenia in end-stage liver disease.



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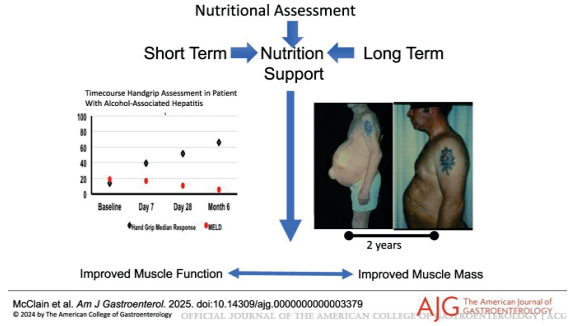
Can malnutrition and sarcopaenia be improved in ACLD?

Both sarcopaenia and malnutrition are dynamic processes and effect of interventions on muscle mass has been appreciated in 3-6 months time



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AJG The American Journal of GASTROENTEROLOGY
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Mineral and vitamin deficiencies in ACLD

Table 8. Mineral and vitamin clinical signs and symptoms in patients with liver disease

Mineral/vitamin	Complications
Iron	Anemia, fatigue
Magnesium	Muscular cramps, weakness, insulin resistance, decreased bone density
Calcium	Decreased bone density, tetany
Zinc	Skin lesions, anorexia, decreased wound healing, hypogonadism, decreased immune function, diarrhea, depressed mental function
Copper	Anemia, neutropenia, neuropathy, fatty liver
Chromium	Glucose intolerance
Selenium	Myopathy, cardiomyopathy
Vitamin B12	Megaloblastic anemia, neuropathy
Folate	Macrocytic anemia, increased cancer risk, increased homocysteine
Thiamine	Ataxia, encephalopathy
Niacin	Dermatitis, diarrhea, dementia
Vitamin A	Decreased night vision, skin lesions
Vitamin D	Bone disease, immune and gut barrier dysfunction
Vitamin E	Oxidative stress
Vitamin K	Bruising, impaired clotting

Nutritional requirements in ACLD

- Total energy expenditure (TEE) varies between 28 to 37.5 kcal/kg.BW/day
- Resting energy expenditure is relatively high severe ACLD
- The actual body weight, corrected for ascites is considered safe for estimates
- Recommended protein intake is 1.2–1.5 g/kg.BW/day
- Recommended energy intake is 30-35 kcal/kg/d

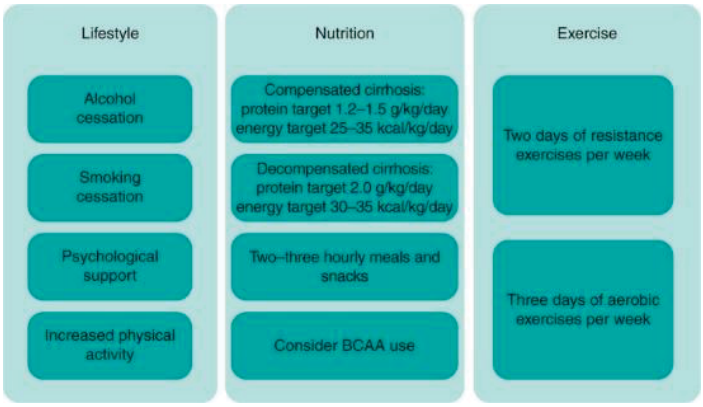
Routs of nutrition administration in ACLD

- Oral nutrition is encouraged in general
- Enteral nutrition should be provided during prolonged periods of poor oral intake including encephalopathy, gastrointestinal bleeding and impaired gut motility or ileus
- Naso-gastroenteric tubes are not contraindicated in patients with non-bleeding oesophageal varices
- It is best to avoid PEG insertion in cirrhotic patients because of the risk of bleeding.
- If oral diet or enteral nutrition are not tolerated or contraindicated parenteral nutrition should be provided.

Nutritional interventions in ACLD: goals and impact

- Prevent and treat malnutrition
- Preserve liver function
- Prevent and manage complications
- Optimise immune function
- Improve quality of life
- Support pre and post transplant

Management of sarcopaenia



Late evening snacks and frequent meals

- Prevents activation of accelerated starvation cascade overnight
- Composition: high complex carbohydrate (200 kcal) and 20-30g of protein
  - Reduces muscle protein breakdown
  - Improve BMI and lean muscle tissue
  - Reduce the risk of ascites and hepatic encephalopathy
- Frequent daytime small meals or snacks also reported to maintain nutrition
- An adequate breakfast was associated with improved cognitive function in ACLD

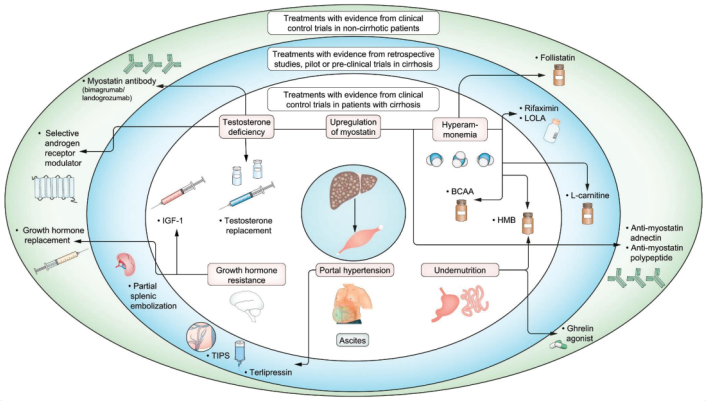
Exercise

- Encourage patients to avoid hypomobility
- Increased physical activity and exercise are anabolic stimuli that can improve muscle mass and function
- Physical activity should be progressively increased to prevent and/or ameliorate sarcopaenia
- Moderate intensity, endurance and aerobic activities and 3 days a week

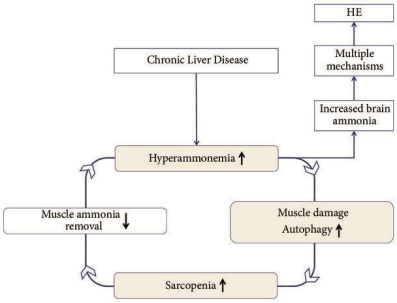
Testosterone replacement therapy for sarcopaenia

- Lower levels of anabolic hormones, IGF-1 and testosterone were observed in male cirrhotic patients
- Intramuscular testosterone administration to men with cirrhosis and low serum testosterone levels has shown a significant improvement in muscle mass

Pharmacotherapies for sarcopaenia in ACLD



Protein intake in hepatic encephalopathy : Not to restrict



Muscle plays a major role in the removal of ammonia by its conversion to glutamine by glutamine synthase.

Nutrition in hepatic encephalopathy

Impact of vegetable vs animal source of protein

- Recommend diet enriched in vegetarian sources of protein in patients with HE who require nutritional supplementation
- Vegetable sources of protein compared with animal sources have:
  - higher arginine content: increases urea production
  - higher fiber content: creates an acidic environment in the colon, mediating excretion of ammonia in the stools
  - lower content of methionine and tryptophan.
  - lower circulating blood levels of ammonia and mercaptans

Nutrition in hepatic encephalopathy (HE)

Use of Branched Chain Amino Acids (BCAA)

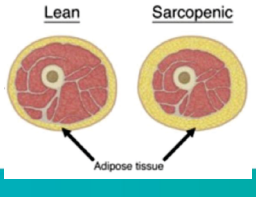
- BCAA can be supplemented in addition to standard-of-care treatment in HE.
  - Reduced BCAA/AAA ratio observed in HE
  - BCAA are important to generate glutamate which is necessary for detoxification of ammonia.
  - BCAA reduce protein breakdown and improve muscle mass which eventually clears ammonia

Salt and free water consumption

- Active sodium and passive fluid retention occurs in ACLD
- Emerging evidence contradicting beneficial effect of salt restriction in ascites management
- Salt restriction reduces palatability of diet
- Moderate salt should be allowed
- free water restriction may be needed when serum sodium is below 126 mEq/L in patients with cirrhosis and evidence of fluid retention.

Management of obesity in ACLD

- Sarcopaenic obesity: muscle loss and excess fat, either in absolute terms or the muscle-to-fat ratio.
- Increasingly seen with epidemic of obesity and MASLD and leads to poor prognosis.
- A hypokaloric diet without compromising protein intake is suggested to achieve desired effect

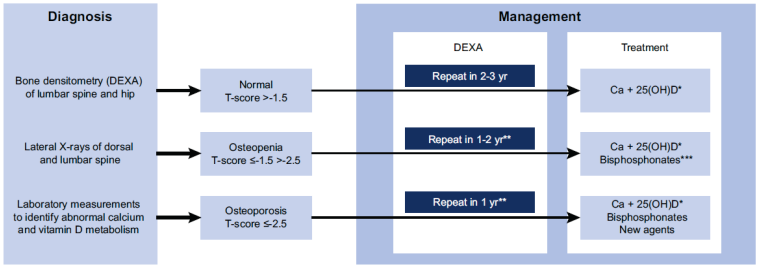


Coffee consumption

- Coffee consumption has shown to reduce:
  - The risk of hepatic fibrosis progression
  - Development of HCC
- Coffee consumption, preferably more than 2 cups per day is beneficial
- Coffee is associated with epigenetic effects that may confer liver health
- Potential mechanism or responsible molecules of these benefits are not clear

Vitamin D and bone health in ACLD

Vitamin D deficiency is common in patients with cirrhosis
Associated with osteoporosis, infections, mortality and hepatocellular cancer
Evidence for supplementation of vitamin D is limited if levels are normal
When low levels present, supplementation may benefit bone and liver



Vitamin E

- In patients with MASH without cirrhosis, treatment with natural vitamin E 800 IU daily is suggested
- vitamin E treatment reduces ALT and AST levels and improves most features of liver histology except fibrosis
- The potential risks of long-term high-dose (e.g., 800 IU daily) use of vitamin E should be discussed with patients

Zinc deficiency

Table 9. Clinical manifestations of zinc deficiency

Skin lesions
Depressed mental function, encephalopathy
Impaired night vision; altered vitamin A metabolism
Anorexia
Alterations in taste and smell acuity
Hypogonadism
Depressed wound healing
Altered immune function

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- Zinc deficiency or altered metabolism is associated with abnormal ammonia metabolism, infections, encephalopathy and malnutrition
- Supplementation improve gut barrier function, endotoxemia and oxidative stress

Nutrition in special scenarios in ACLD

- Alcoholic liver disease and alcoholic hepatitis
- Gastrointestinal bleeding
- Critically ill patients
- Pre and post transplant patients
- Pre and post surgical patients

Oral or enteral nutrition started within 48 hours associated with reduced leangth of stay and in-hospital mortality.

Summary of nutritional interventions:

1. We suggest early administration of oral or enteral nutrition supplementation therapy in hospitalized patients with cirrhosis (conditional recommendation, low quality of evidence)
2. In patients with cirrhosis or alcohol-associated hepatitis, we suggest implementation of nutritional supplementation therapy (conditional recommendation, very low quality of evidence)
3. In patients with MASH without cirrhosis, we suggest treatment with natural vitamin E 800 IU daily (conditional recommendation, low quality of evidence)
4. We suggest coffee consumption, preferably ≥2 cups per day, in patients with chronic liver disease to reduce risk of hepatic fibrosis progression or HCC development (conditional recommendation, low quality of evidence)
5. In patients with cirrhosis and ascites who are managed with diuretic therapies, we cannot recommend for or against strict sodium restricted diets (insufficient evidence, no recommendation)
6. We suggest not restricting dietary protein in patients with decompensated cirrhosis and hepatic encephalopathy (conditional recommendation, very low quality of evidence)
7. We suggest a diet enriched in vegetarian sources of protein in patients with cirrhosis and hepatic encephalopathy who require nutritional supplementation (conditional recommendations, low quality of evidence)
8. We recommend the use of branched chain amino acids (when available) in addition to standard-of-care treatment in patients with cirrhosis and hepatic encephalopathy (strong recommendation, moderate quality of evidence)
9. We recommend incorporating late evening snacks in patients with cirrhosis to improve body mass index, lean muscle tissue, and reduce the risk of ascites and hepatic encephalopathy (strong recommendation, moderate quality of evidence)
HCC, hepatocellular carcinoma; MASH, metabolic dysfunction-associated steatohepatitis. OFFICIAL JOURNAL OF THE AMERICAN COLLEGE OF GASTROENTEROLOGY | ACG

What NOT to do when managing nutrition in ACLD

- Approach malnutrition as inevitable consequence of the disease (”Nothing can be done”)
- Overload the patient with numerous unjustified dietary or lifestyle restrictions.
- Prescribe low protein diets to prevent or treat hepatic encephalopathy.
- Disregard the detrimental effect of long fasting periods.
- Overlook the relevance of muscle mass depletion on the prognosis in patients with liver ACLD

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Clinically Significant Portal Hypertension (CSPH)

Dr Dhanushi Abeynayake

MBBS MD (Col), MRCP (Lond) MRCP (UK)

Consultant Gastroenterologist and Hepatologist

DGH Embilipitiya

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Clinically Significant Portal Hypertension (CSPH)

Clinically significant portal hypertension (CSPH) is a key predictor of hepatic decompensation and hepatocellular carcinoma (HCC). The hepatic venous pressure gradient (HVPG) is the gold standard for assessing portal hypertension severity, but its invasive nature and limited availability make non-invasive alternatives essential. Transient elastography, especially when combined with platelet count, is a reliable surrogate for HVPG. Additionally, spleen stiffness measurement is emerging as a useful marker, reflecting increased splenic venous pressure during portal hypertension.

Management focuses on addressing the underlying cause—such as alcohol cessation, antiviral therapy, immunosuppression or weight loss in metabolic liver disease—alongside encouraging a healthy lifestyle. Non-selective beta-blockers (NSBBs) are used to prevent decompensation, with carvedilol being the most effective in lowering HVPG. Statins, beyond their lipid-lowering effects, offer antifibrotic and vascular benefits in cirrhosis and are recommended in Child-Pugh A/B patients. Aspirin use has been associated with reduced risk of HCC, liver-related complications, and mortality, although bleeding risks must be considered. Albumin and antibiotics are reserved for specific clinical settings.

Overall, CSPH management combines etiological treatment, lifestyle modification, and evidence-based pharmacotherapy to delay progression and reduce complications.

Outline

•Clinically Significant Portal Hypertension (CSPH) as a predictor of prognosis

•Pathophysiology

•Assessment of portal hypertension

•Importance of Noninvasive assessment tools for CSPH

•Management of CSPH for disease modification
-Life style modifications
-Pharmacotherapy

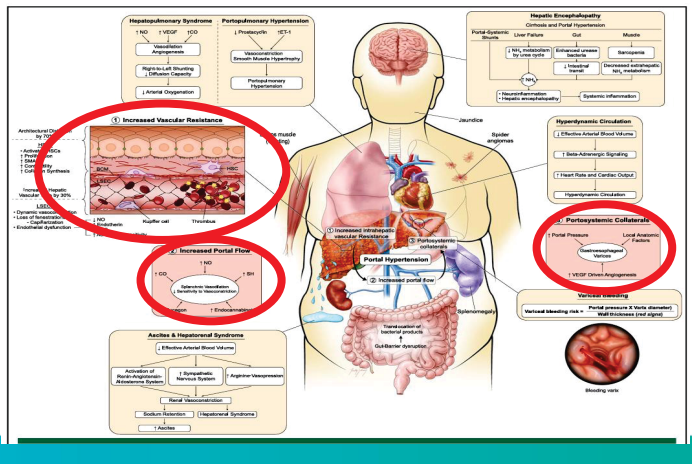
Portal Hypertension - Clinical importance

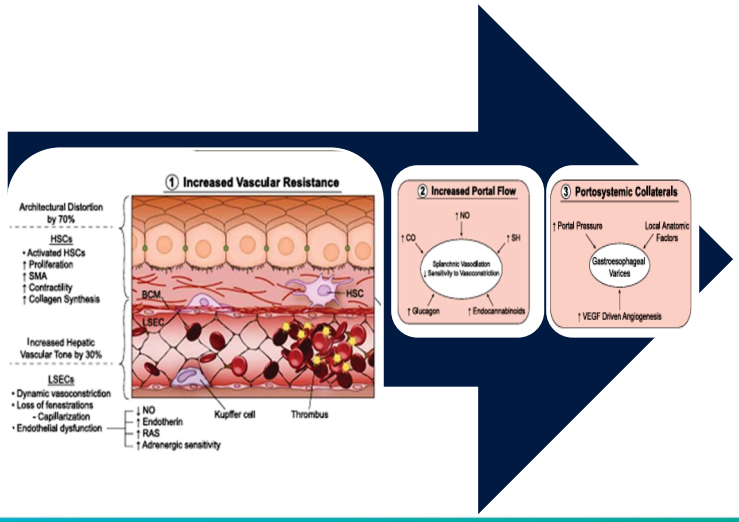
Major determinant of disease progression

- compensated → decompensated advanced chronic liver disease (ACLD)

Strong prognostic value

Pathophysiology





Portal Hypertension-Assessment

Gold standard- hepatic venous pressure gradient (HVPG)	Normal- 1 - 5 mmHg Pre clinical portal hypertension 6-10mmHg	**Clinically Significant Portal Hypertension (CSPH) - >10mmHg**
Esophageal varices, ascites, hepatic encephalopathy, HCC	Invasive, costly, only performed in specialist centres	Reduction in HVPG **below 12 mm Hg or by >20%** -significant reduction in complications and death

Clinically significant portal hypertension

The development of **clinically significant portal hypertension (CSPH)** (>10mmHg) is a key event that alters the **prognosis** of a patient with liver cirrhosis

HVPG	Prognosis
<10mmHg	Predicts patients that do not decompensate (Median survival 4 years)
>10mmHg	Predicts the development of varices
Reducing <12mmHg or >20%	Prevents re-bleeding (secondary prophylaxis)
>20mmHg	Predicts ITU stay, hospital stay, short term and long-term mortality in acute variceal bleed

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Stages of chronic liver disease	No cirrhosis	Compensated cirrhosis		Decompensated cirrhosis	
		Lower risk of decompensation	Higher risk of decompensation	First decompensation	Further decompensation
Clinical features (ascites, VH or HE)	None	None	None	One event	>1 event or complication of event*
Histological diagnosis	F0-F2	F3/F4 (thin septa)	F4 (thick septa)	Clinical	Clinical
Hemodynamic features (HVPG mmHg)	3-5	5-10	>10 (CSPH)	>20 worse outcomes in VH	>20 worse outcomes in VH
Endoscopic features	None	No varices	± Varices	± Varices	± Varices

Risk of death

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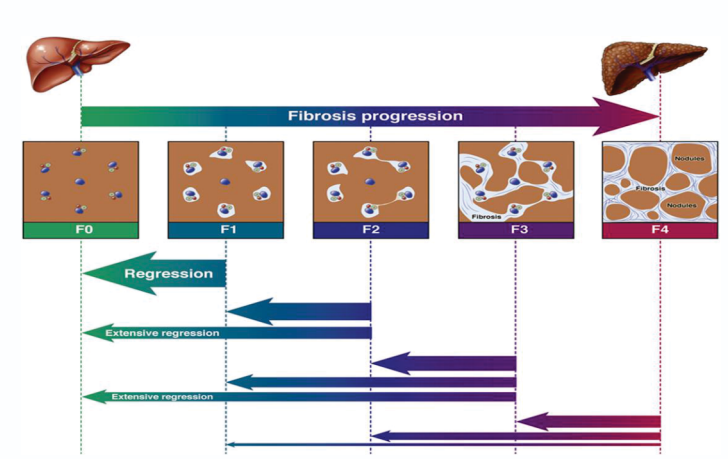


Dynamic

Bidirectional

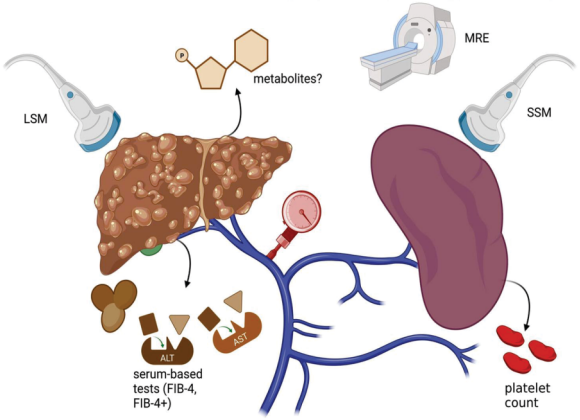
Treatment shift

Bleeding-centric view (prevention of bleeding and rebleeding)

CSPH should be **treated as soon as it can be proven**

Surrogate for HVPG- **Non invasive tests**

Non-invasive assessment of clinically significant portal hypertension (CSPH)



Transient Elastography

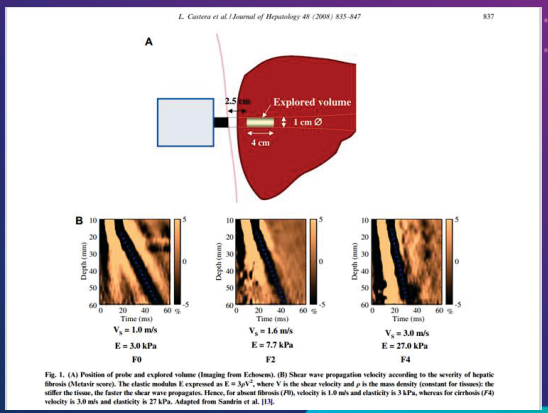


Fig. 1. (A) Position of probe and explored volume (Imaging from Echosens). (B) Shear wave propagation velocity according to the severity of hepatic fibrosis (Metavir score). The elastic modulus E expressed as $E = 3\rho V^2$, where V is the shear velocity and ρ is the mass density (constant for tissues): the stiffer the tissue, the faster the shear wave propagates. Hence, for absent fibrosis (*F0*), velocity is 1.0 m/s and elasticity is 3 kPa, whereas for cirrhosis (*F4*) velocity is 3.0 m/s and elasticity is 27 kPa. Adapted from Sandrin et al. [13].

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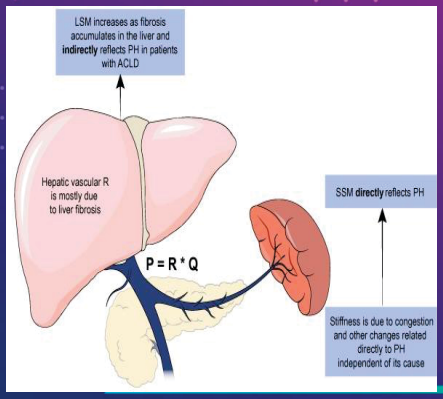
Splenic stiffness measurement

Splenic vein pressure →Splenic blood congestion

→**increased spleen size and stiffness** good surrogate parameter for CSPH.



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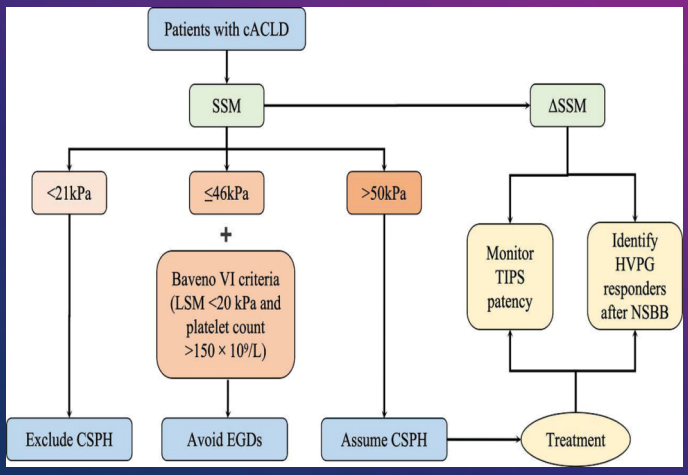

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Liver Stiffness Measurement

- Compensated Advanced Chronic liver disease (CACLD)
- Clinically Significant Portal Hypertension(CSPH)

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Complications of Cirrhosis

What- cACLD & CSPH→ New Paradigm **"Rule of 5"**

Non-invasive staging of chronic liver disease	No cACLD	Possible cACLD	Highly suggestive of cACLD	cACLD	
Liver stiffness (kPa)	<10	10-15	15-20	20-25	>25
Platelet count (K/mm³)	NR	NR	If <110 = CSPH	If <150 = CSPH	CSPH**

Risk of decompensation

ANTICIPATE model -predict the risk of CSPH. LSM 20- 25 kPa +platelet count <150 or LSM 15-20kPa + Plt <110 has a risk of CSPH 60%

AGG 2024 October 25-30, Philadelphia, PA

Kaplan, Hep 2024- AASLD PG
De Franchis, J Hep 202

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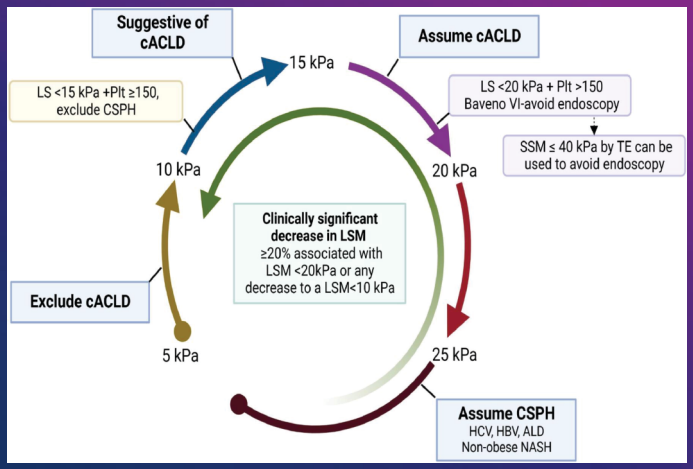

D. Segna, Y.P. Mendoza, N.F. Lange et al.

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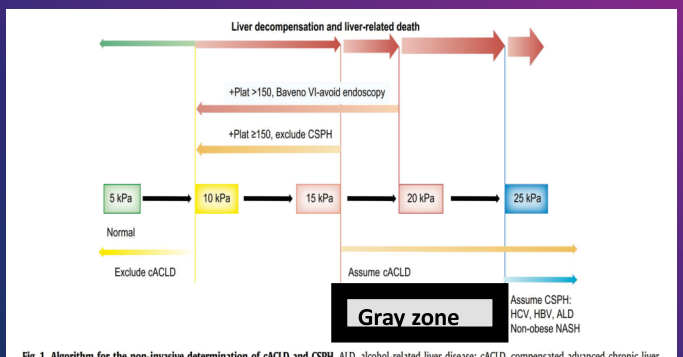

Fig. 1. Algorithm for the non-invasive determination of cACLD and CSPH. ALD, alcohol-related liver disease; cACLD, compensated advanced chronic liver disease; CSPH, clinically significant portal hypertension; NASH, non-alcoholic steatohepatitis.

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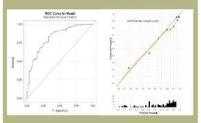
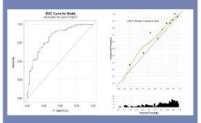
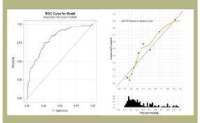
Predicting Clinically Significant Portal Hypertension in NASH Cirrhosis

ANTICIPATE model	ANTICIPATE-NASH model	FIB4+ model
Abraldes, et al. 2016 (Liver stiffness, platelet)	*Pons, et al. 2021* (Liver stiffness, platelet , BMI)	*Rabiee, et al. 2022* (Age, AST, ALT, platelet, albumin)
Formula developed in 229 patients with compensated hepatitis C and alcohol cirrhosis by Abraldes et al	*Formula developed in training cohort of 248 patients with compensated NASH cirrhosis by Pons et al*	*Formula developed in training cohort of 309 patients with compensated NASH cirrhosis*
		
Performance in validation cohort of 222 patients with compensated NASH cirrhosis AUC: 0.8	Performance in validation cohort of 222 patients with compensated NASH cirrhosis AUC: 0.8	Performance in validation cohort of 245 patients with compensated NASH cirrhosis after update AUC: 0.8

Rabiee, et al. *Hepatol Commun.* 2022.

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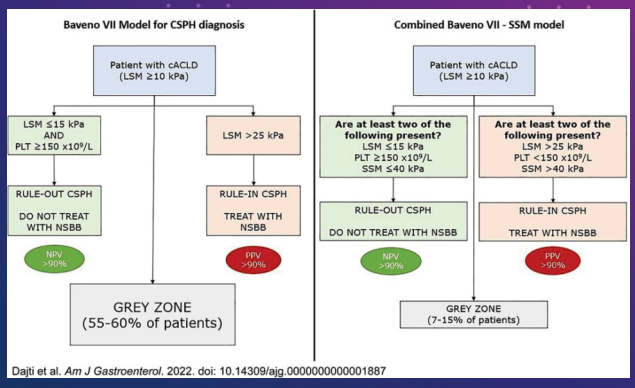
Liver Stiffness Measurement +Platelet count +Splenic stiffness Measurement



Dajti et al. *Am J Gastroenterol.* 2022. doi: 10.14309/ajg.0000000000001887

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Liver Stiffness Measurement + Platelet + endoscopy

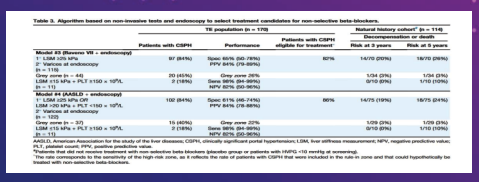

Table 3. Algorithm based on non-invasive tests and endoscopy to select treatment candidates for non-selective beta-blockers.

	TR population (n = 178)			Natural history cohort* (n = 114)	
	Patients with CSPH	Performance	Patients with CSPH eligible for treatment†	Decompensation or death	
				Risk at 3 years	Risk at 5 years
Model #3 (Baveno VII + endoscopy)					
1° LSM ≤25 kPa	97 (84%)	Spec 66% (60-78%)	82%	14/70 (20%)	18/70 (26%)
2° Varices at endoscopy		PPV 84% (79-89%)			
(n = 116)					
Grey zone (n = 44)	20 (45%)	Grey zone 26%		1/34 (3%)	1/34 (3%)
LSM ≤15 kPa + PLT ≥150 × 10^9/L	2 (18%)	Sens 96% (94-99%)		0/10 (0%)	1/10 (10%)
(n = 11)		NPV 82% (50-96%)			
Model #4 (AASLD + endoscopy)					
1° LSM ≤25 kPa OR					
LSM >20 kPa + PLT <150 × 10^9/L	102 (84%)	Spec 81% (46-74%)	86%	14/75 (19%)	18/75 (24%)
2° Varices at endoscopy		PPV 84% (78-88%)			
(n = 103)					
Grey zone (n = 37)	15 (40%)	Grey zone 22%		1/39 (3%)	1/39 (3%)
LSM ≤15 kPa + PLT ≥150 × 10^9/L	2 (18%)	Sens 96% (94-99%)		0/10 (0%)	1/10 (10%)
(n = 11)		NPV 82% (50-96%)			

AASLD, American Association for the study of the liver diseases; CSPH, clinically significant portal hypertension; LSM, liver stiffness measurement; NPV, negative predictive value; PLT, platelet count; PPV, positive predictive value.
*Natural history cohort: patients not treated with non-selective beta-blockers (placebo group or patients with HVPG <10 mmHg at screening).
†The rate corresponds to the sensitivity of the high-risk zone, as it reflects the rate of patients with CSPH that were included in the rule-in zone and that could hypothetically be treated with non-selective beta-blockers.

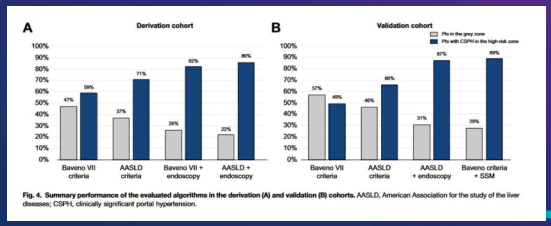

Fig. 4. Summary performance of the evaluated algorithms in the derivation (A) and validation (B) cohorts. AASLD, American Association for the study of the liver diseases; CSPH, clinically significant portal hypertension.

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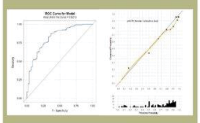	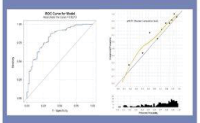	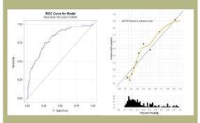
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Rabiee, et al. *Hepatol Commun.* 2022.

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Site of increased R to portal flow		Liver Stiffness	Spleen Stiffness	HVPG
Pre-hepatic PH due to Extrahepatic portal vein obstruction/thrombosis		Normal	Increased	Normal
Intra-hepatic PH	Pre-sinusoidal PH due to Portosinusoidal vascular disorder	Normal or slightly elevated (< 10 kPa)	Increased SSM ≤ 40 kPa in patients with Bilirubin < 1 exclude high risk varices	Normal or slightly elevated (< 10 mmHg) Often veno-venous communications
	Sinusoidal PH due to ACLD/cirrhosis	Increased LSM > 25 kPa: assume CSPH (except in obese MASLD)	Increased SSM > 40 kPa: assume CSPH	Increased HVPG≥10 mmHg defines CSPH
Post-hepatic PH due to Budd-Chiari syndrome		Scarce data; increased due to venous congestion	Very scarce data; increased due to PH	Normal or increased, with high free hepatic venous pressure

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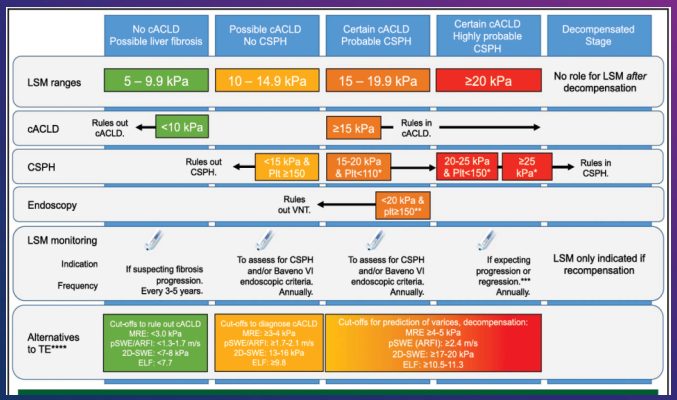
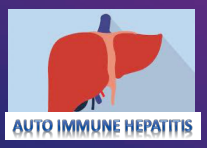
Monitoring



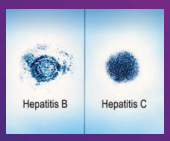
Management

Removal of the primary aetiological factor

Alcohol abstinence



Immunosuppression



Sustained virological response (SVR)

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Healthy life style

- Weight loss – 7-10% from baseline (dry weight)
- Moderate aerobic exercise
- Protein intake >1g/kg/day
- Avoid- processed food, sugar, fructose, salty food
- High protein nocturnal snack
- Stop smoking

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PREDESCI Study

Study design

- Investigator initiated, randomised, double-blind, placebo controlled, multicentre clinical trial
- All patients had a baseline HVPG measurement

Included patients

Patients with baseline CSPH (HVPG ≥10mmHg)

- Adults (18-80 years old)
- No prior decompensation
- Without high-risk varices
- Without HCC/PVT
- No severe liver disfunction or platelets below 30.000/mm3
- No HCV treatment, pregnancy, lactation
- No CI to NSBB

Acute response NSBB

20´after iv propranolol
Decrease >10% HVPG

YES → **Responders** Randomly assigned to propranolol or placebo

NO → **Non-responders** Randomly assigned to carvedilol or placebo

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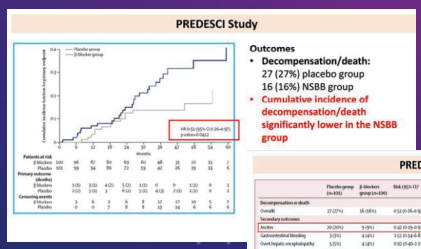

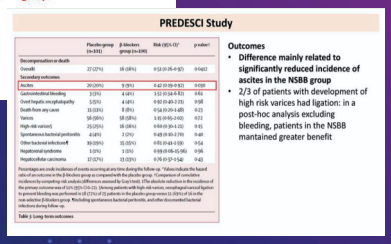

NSBB for all with CSPH

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Beta blockers

NSBBs (propranolol, nadolol or carvedilol)-prevention of decompensation in CSPH

carvedilol- anti-alpha adrenergic vasodilatory effects

Carvedilol -more effective at reducing HVPG
- prevents decompensation
- better tolerance than traditional NSBBs
- improve survival

compensated cirrhosis who are on NSBBs - do not need a screening endoscopy since endoscopy will not change management
- If BB is Contraindicated-EBL

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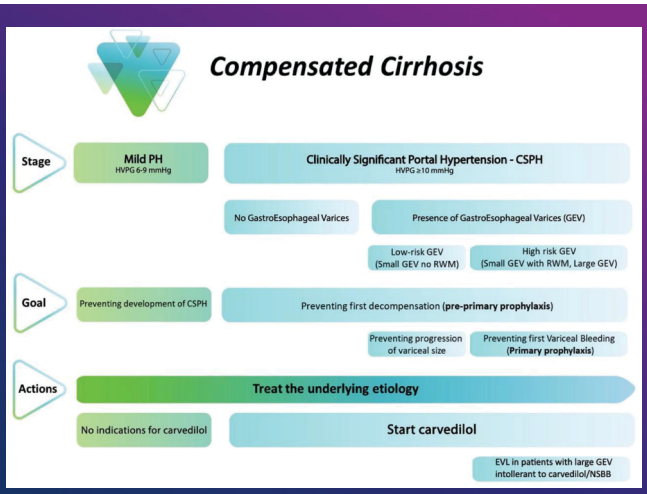

Statins

Available Data Suggest	• May lower HVPG • Improved survival after acute EV bleed with addition of statin to usual secondary PPx • Decreased rate progression to cirrhosis, decompensation, death, HCC (retrospective)
Where there is Uncertainty	• Do they add benefit to HVPG reduction provided by beta blocker therapy? • Optimal agent(s) and dosing • Safety/benefit in Child-Pugh C
What to do in Current Practice	• Encourage use in Child-Pugh A/B and another indication for use • Atorvastatin metabolism is altered in cirrhosis • Consider lower dose Simvastatin (20mg max with DC) and monitor for muscle/liver toxicity

Baveno VII - Renewing consensus in portal hypertension. J Hepatol. 2022 Apr;76(4):959-974.
AASLD Practice Guidance on risk stratification and management of portal hypertension and varices in cirrhosis. Hepatology 79(5):p 1180-1211, May 2024

Aspirin -reduce the risk of HCC, liver-related complications and death

Short-term albumin.

- spontaneous bacterial peritonitis
- acute kidney injury (AKI) >stage 1A
- large-volume paracentesis
- combined with terlipressin for hepatorenal syndrome (HRS)- AKI

Long-term albumin-improve transplant-free survival

Antibiotics

Primary prophylaxis.

- GI haemorrhage
- Child-Pugh C cirrhosis with low protein ascites - at high risk of SBP

Secondary prophylaxis

- SBP
- HE

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Summary

- CSPH- strong predictor of prognosis
- Gold standard- HVPG
- Surrogate markers are needed
- Non invasive investigations of assessment of PHT
- LSM and SSM – promising results
- Address the **primary aetiological factor**
- **BB as soon as CSPH is suspected**
- **Statins and Asprin** use is beneficial with regards to liver related outcomes

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Q&A

Managing Common Complications of Decompensated Cirrhosis: Ascites, SBP & AKI

Dr. Kuleesha Kodisinghe
Consultant Gastroenterologist
District General Hospital Matara

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Managing Common Complications of Decompensated Cirrhosis: Ascites, SBP & AKI

Ascites, spontaneous bacterial peritonitis (SBP) and acute kidney injury (AKI) are major complications that can occur in a patient with decompensated advanced chronic liver disease (dACLD).

Salt restriction, diuretics and paracentesis are the mainstay of management of ascites.In a patient with ascites and altered coagulation parameters, paracentesis should not be avoided due to fear of bleeding.

Diagnosis of SBP is based on an ascites neutrophil count >250/mm3.Empirical antibiotics suggested for community-acquired SBP are third-generation cephalosporins in areas with low antibiotic resistance and piperacillin-tazobactamin areas with high antibiotic resistance. For nosocomial SBP, piperacillin-tazobactam is recommended in areas with low antibiotic resistanceand carbapenemin areas with high antibiotic resistance.

AKI in cirrhosis should not be considered synonymous with hepatorenal syndrome (HRS).Initial management of AKI involves removing the precipitating cause, avoiding contributing medications, diuretic withdrawal and volume expansion for 24hours. In addition to this general AKI management, intravenous infusions of vasoconstrictors (terlipressin or noradrenaline) in combination with 20% albumin is recommended in the management of HRS.Liver transplant with or without concomitant renal transplant may be required in non-responders.

Ascites

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Salt restriction

Moderate restriction of sodium intake (80–120 mmol/day, corresponding to 4.6–6.9 g of salt) is recommended.
This is generally equivalent to a no added salt diet with avoidance of high salt food.

Diets with a very low sodium content (<40 mmol/day) should be avoided, as they favour diuretic-induced complications (hyponatremia, AKI) and can endanger a patient's nutritional status.

Fluid restriction is not necessary.

Diuretics

Patients with the first episode of grade 2 ascites should receive an anti-mineralocorticoid drug (spironolactone) alone with stepwise increase in dose until ascites is controlled or until the maximal dose is reached. Loop diuretic (frusemide) should be added in suboptimal response or in patients who develop hyperkalemia.

Patients with long-standing, recurrent ascites should receive combination therapy.

	Starting dose	Increment steps (every 3 days)	Maximum dose
Spironolactone	100 mg/day	100 mg	400 mg/day
Frusemide	40 mg/day	40 mg	160 mg/day

Diuretics

Eplerenone can be given in patients developing androgenic side effects of spironolactone.
Amiloride is less effective than anti-mineralocorticoids, and should only be used in patients who develop severe side effects with aldosterone antagonists.
Torasemide can be given in patients exhibiting a weak response to frusemide.

Biochemical monitoring with S.creatinine and SE is recommended during the first weeks of treatment and after dose escalation.

Diuretics

Loop diuretics should be combined with but not substituted for anti-mineralocorticoids.

Over-diuresis should be avoided. Maximum weight loss of 0.5 kg/day in patients without oedema and 1 kg/day in patients with oedema is recommended.

Diuretics should not be prescribed without regular assessment of the dose. Once ascites has largely resolved, the dose of diuretics should be reduced to the lowest effective dose.

Diuretics should be avoided in the presence of:
- GI haemorrhage
- AKI
- Hepatic encephalopathy
- Severe hyponatraemia (<125 mmol/L)
- Severe hypokalemia (<3 mmol/L) for frusemide / Severe hyperkalemia (>6 mmol/L) for spironolactone
- Incapacitating muscle cramps

Diuretics should be discontinued in patients with refractory ascites who do not excrete >30 mmol/day of sodium under diuretic treatment

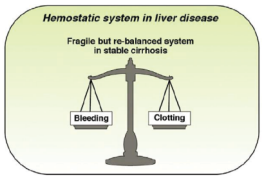
Paracentesis

Diagnostic paracentesis should be performed:
- New onset grade 2 or 3 ascites
- Worsening of ascites
- Presence of any complication of cirrhosis

Ascites fluid full report and culture should be done routinely.

When the cause of ascites is in doubt, ascites fluid should be sent for other investigations – SAAG, ADA, cytology

Paracentesis should not be avoided due to fear of bleeding.



Ascitic fluid culture should not be sent in normal sterile bottles; should be inoculated into a blood culture bottle with 10 ml fluid.

Large volume paracentesis (LVP)

LVP is the first-line therapy in patients with grade 3 ascites.

Unmonitored LVP without plasma volume expansion should be avoided. If LVP is >5L, infusing albumin 8 g/L of ascites removed is recommended.

Invasive therapies

TIPS insertion should be considered in patients with recurrent ascites (≥3 LVP within 1 year) or those with loculated ascites.

Alfapump implantation can be considered in experienced centers in patients with refractory ascites not amenable to TIPS insertion.

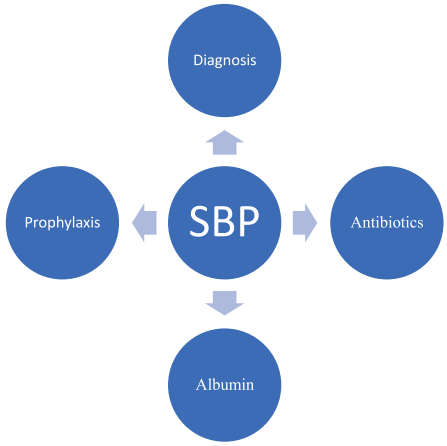
Avoiding harmful drugs

NSAIDs should not be used in patients with ascites because of the high risk of developing further sodium retention, hyponatraemia, AKI and diuretic resistance.

ACEI, ARBs and alpha 1-adrenergic receptor blockers should not generally be used in patients with ascites because of increased risk of renal impairment and hypotension.

The use of aminoglycosides is discouraged, as they are associated with an increased risk of AKI

Spontaneous Bacterial Peritonitis (SBP)



Diagnosis

Diagnostic paracentesis should be carried out in all patients with cirrhosis presenting with ascites, GI bleeding, hepatic encephalopathy, AKI, worsening of liver functions, local symptoms or signs of peritonitis or signs of systemic inflammation.

Diagnosis of SBP is based on ascites neutrophil count >250/mm^3.

Ascitic fluid and blood cultures should be performed before starting antibiotic treatment.

Diagnostic paracentesis should not be delayed after hospital admission.

All cases of neutrophilic ascites should not be considered as SBP. Secondary bacterial peritonitis should be suspected incase of localized abdominal symptoms or signs, very high ascitic neutrophil count and/or high ascitic protein concentration, multiple organisms on ascitic culture or in those patients with an inadequate response to therapy.

Antibiotics

Empirical antibiotics:
Community-acquired SBP - Third-generation cephalosporins (in areas with low resistance) / piperacillin-tazobactam (in areas with high resistance)
Nosocomial SBP – Piperacillin-tazobactam (in areas with low resistance) / carbapenem (in areas with high prevalence of ESBL producing Enterobacteriaceae) +/- vancomycin or linezolid (in areas with high prevalence of gram positive MDR bacteria)

The duration of treatment should be at least 5–7 days.

Antibiotics

A second paracentesis should be performed at 48h after starting treatment. Failure of antibiotic therapy should be suspected if there is failure of reduction in neutrophil count by at least 25% or if clinical signs / symptoms worsen.

Albumin infusion

The administration of albumin (1.5 g/kg at diagnosis and 1 g/kg on day 3) is recommended.

Prophylaxis

Primary prophylaxis:
Low ascitic protein (<15 g/l) with one of the following:
- Liver failure (Child score ≥9 + bilirubin ≥3 mg/dl)
- Renal impairment (creatinine ≥1.2 or BUN ≥25 or serum sodium ≤130 meq/l)

Secondary prophylaxis:
After an episode of SBP*

DOC - Norfloxacin (400 mg/day)
When norfloxacin is unavailable, oral ciprofloxacin is acceptable.

Primary prophylaxis should be stopped in patients with long-lasting improvement of their clinical condition and disappearance of ascites.
Same regarding secondary prophylaxis is still uncertain.

*May result in a higher risk of non-SBP infections, especially urinary tract infections

Silvey S, Patel N, O'Leary JG, Jakab SS, Patton H, Ragal S, Markley JD, Cheung R, Patel A, Morgan TR, Bajaj JS. Secondary Spontaneous Bacterial Peritonitis Prophylaxis Is Associated With a Higher Rate of Infections other than Spontaneous Bacterial Peritonitis in 2 US-Based National Cirrhosis Cohorts. Clin Transl Gastroenterol. 2025 May 1;16(5):e00837. doi: 10.14309/ctg.0000000000000837. PMID: 40062879; PMCID: PMC12101923.

AKI / HRS

Diagnosis - AKI

AKI is defined as either of:

- Increase in sCr ≥0.3 mg/dl within 48h
- Increase in sCr >50% from baseline* known or presumed to have occurred within the previous 7 days
- Urine output <0.5 ml/kg >6 h

*Baseline sCr - lowest stable SCr value obtained in the previous 3 months
If no values are available in the previous 3 months, the most recent value up to 12 months
In the absence of a known baseline SCr, lower of either SCr on admission or SCr back-calculated from an eGFR of 75 ml/min/1.73 m2

AKI can be staged as:

Stage	Serum creatinine	Urine output
1	Increase by 1.5–1.9 times baseline within 7 days OR Increase by ≥0.3 mg/dL (26.5 µmol/L) within 48 hours	Less than 0.5 mL/kg/h for 6–12 hours
2	Increase by 2–2.9 times baseline	Less than 0.5 mL/kg/h for ≥12 hours
3	Increase by ≥3 times baseline OR Increase to ≥4 mg/dL (353.6 µmol/L) OR Renal replacement therapy initiation OR In patients younger than 18 years, decrease in estimated GFR to <35 mL/min/1.73 m²	Less than 0.3 mL/kg/h for ≥24 hours OR Anuria for ≥12 hours

Address potential causes

Address potential causes:

- Nephrotoxic drugs e.g. NSAIDs, aminoglycosides, contrast agents
- UTI

Stop contributing medications:

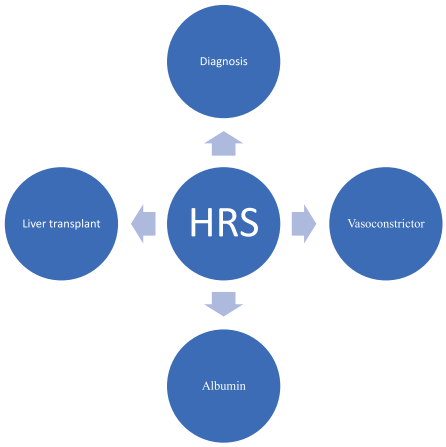
- Diuretics, NSBB
- ACEI / ARBs, alpha blockers

Judicious fluid management

In patients with AKI requiring fluid resuscitation, crystalloids preferentially balanced solutions, are recommended. In patients with AKI with volume overload discontinuation of all fluids and initiation of diuretic therapy or RRT is recommended.

RRT

RRT should be considered for the same indications as in the general population. CRRT is probably better tolerated.



Diagnosis - HRS

Diagnostic criteria for HRS-AKI:

- AKI according to KDIGO criteria
- Cirrhosis with ascites
- Absence of improvement in serum creatinine and/or urine output within 24 hours following adequate volume resuscitation (when clinically indicated)
- Absence of strong evidence for an alternative explanation as the primary cause of AKI

AKI in cirrhosis should not be considered synonymous with HRS.

Need for the administration of albumin for 48 h as a prerequisite for the diagnosis of HRS-AKI is not valid anymore.

Vasoconstrictor

Terlipressin is the first-line vasoconstrictor option.
Terlipressin as a continuous infusion is preferred than bolus doses - started at 2mg/24h and dose increased every 24h by 2mg/24 h if SCr has not decreased by 25% from baseline up to a maximum of 12 mg/day

Noradrenaline should be considered as second line agent if terlipressin is contraindicated or unavailable.
Started at 0.5 mg/h and dose increased every 4 hours by 0.5 mg/h to a maximum of 3 mg/h with the goal of increasing the MAP by ≥10 mmHg or achieve UOP ≥50ml/h

Albumin

20% albumin is started at 20-40 mg/d. Patient's volume status should be closely monitored during treatment and the dose of albumin should be adjusted daily based on patient's volume status

Treatment should be continued till:

- Complete response - SCr within 0.3 mg/dl of baseline
- Futility of treatment – no response after 48-72h of treatment with maximal tolerated doses or after 14 days treatment
- Initiation of RRT
- Liver transplant

Liver transplant

Treatment of choice regardless of the response to drug therapy.

Combined liver-kidney transplantation should be considered in patients with sustained AKI refractory to drug therapy.

Survival rate is lower compared to patients with cirrhosis without HRS (approximately 65%).

Summary

- Paracentesis should not be avoided due to fear of bleeding.
- Salt restriction, diuretics and LVP are the mainstay of management of ascites.
- Diagnosis of SBP is based on an ascites neutrophil count >250/mm3.
- Empirical antibiotics suggested for community-acquired SBP are third-generation cephalosporins / piperacillin-tazobactam; for nosocomial SBP Piperacillin-tazobactam / carbapenem.

Summary

- AKI in cirrhosis should not be considered synonymous with HRS.
- Initial management of AKI involves removing the precipitating cause, diuretic withdrawal and volume expansion for 24h.
- Vasoconstrictors (terlipressin / noradrenaline) + 20% albumin are recommended in the management of HRS.
- Liver +/- renal transplant may be required in non-responders.

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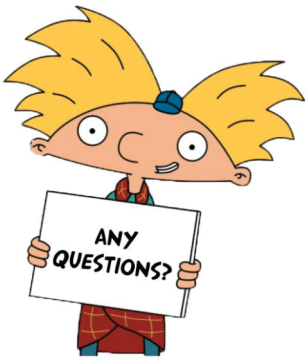

Improving outcomes in acute liver failure in non-transplant settings

Dr. Uditha Dissanayake

Senior Lecture, Faculty of Medicine, University of Kelaniya and Consultant Gastroenterologist, NCTH, Ragama

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Improving Outcomes in Acute Liver Failure in Non-Transplant Settings

Introduction

Acute liver failure (ALF) is a rare but life-threatening condition characterized by rapid hepatocellular injury, coagulopathy, and hepatic encephalopathy in patients without pre-existing liver disease. Mortality remains high, particularly in settings where liver transplantation is not immediately available. Management focuses on stabilizing patients, preventing complications, and bridging to recovery or transplant. In non-transplant settings, therapeutic strategies such as plasma exchange (PLEX) and continuous renal replacement therapy (CRRT) have emerged as key adjunctive treatments to improve outcomes.

Early Recognition and Etiology-Specific Treatment

The first step in improving outcomes is prompt recognition and treatment of the underlying cause. Paracetamol overdose should be treated immediately with N-acetylcysteine (NAC), which improves outcomes even in non-paracetamol-induced ALF due to its antioxidant properties. Viral hepatitis may require antivirals, while autoimmune hepatitis responds to corticosteroids. Early transfer to a specialized liver center is crucial for advanced care.

Management of Complications

- Hepatic Encephalopathy and Cerebral Edema

ALF-associated cerebral edema is a leading cause of mortality. Elevated ammonia levels contribute to intracranial hypertension (ICH), necessitating aggressive management.

- Coagulopathy and Bleeding Risk

While coagulopathy is common, prophylactic plasma transfusion is not routinely recommended unless bleeding occurs or invasive procedures are planned. Vitamin K should be administered to correct deficiency.

Role of Plasma Exchange (PLEX)

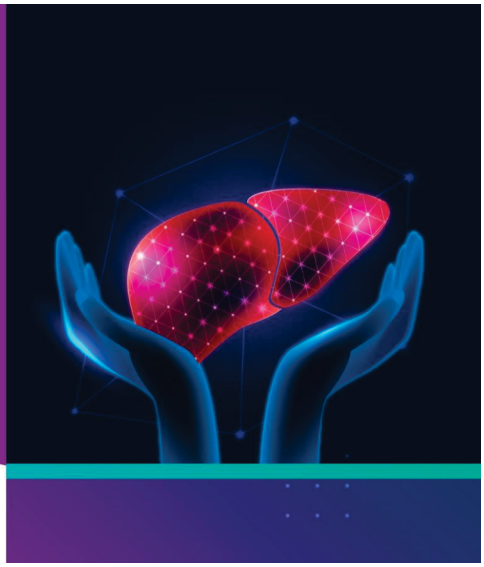
Larsen et al. in 2016 demonstrated improved survival in patients with ALF receiving high-volume PLEX compared to standard care. PLEX may serve as a bridge to transplantation or spontaneous recovery by stabilizing the patient's condition.

Continuous Renal Replacement Therapy (CRRT)

Acute kidney injury (AKI) complicates up to 50% of ALF cases, worsening prognosis. CRRT is preferred over intermittent hemodialysis due to hemodynamic stability and better ammonia clearance.

In non-transplant settings, these interventions stabilize patients, buying time for liver regeneration or bridging to transplantation. Future research should refine patient selection for these therapies to maximize survival benefits.

GRAND ROUNDS IN HEPATOLOGY



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IMPROVING OUTCOMES IN ACUTE LIVER FAILURE: WHEN TRANSPLANTATION IS NOT AN OPTION

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DEFINITIONS

Acute liver failure is a rare syndrome comprising

A coagulopathy of liver origin

Jaundice

Encephalopathy (Not essential in children)

in someone **without pre-existing liver disease**.

But don't wait for encephalopathy to refer patients!

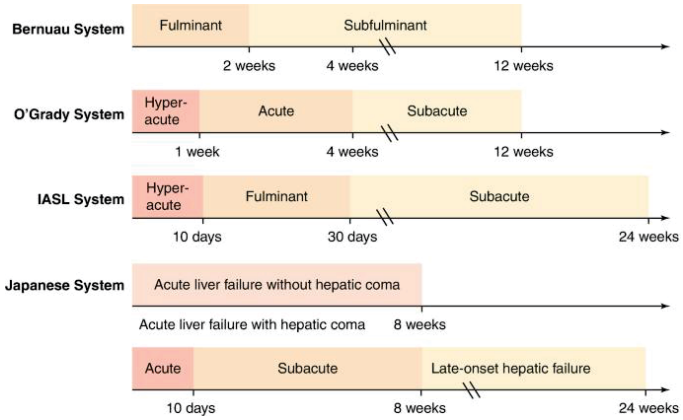
DIAGNOSIS

- Should be suspected in cases with Transaminases > 3 ULN, INR > 1.5 & Jaundice
- Hepatic encephalopathy can be very subtle. Crucial in the diagnosis, esp for liver transplant criteria.

Table 2. West Haven hepatic encephalopathy criteria

Grade	1	2	3	4
Features	Preserved consciousness, behavioural changes.	Drowsiness, disorientation, asterixis. Inappropriate behaviour.	Marked confusion. Incoherent speech. Somnolescence. Rouses to voice.	Comatose. Decerebrate or decorticate posturing.

NB There is some overlap between grades; a neat, sequential passage through grades does not always accompany progression.



Rabinowich & Bernal 2022

Table 4. ALF presentations

Type of ALF	Time frame	Examples	Risk of cerebral edema	Risk of death
Hyperacute	<7 d	Acetaminophen hepatitis A & E ischemic injury	High	Low
Acute	7–21 d	Hepatitis B	Intermediate	Intermediate
Subacute	>21 d and <26 wk	Nonacetaminophen DILI	Low	High

ALF, acute liver failure; DILI, drug-induced liver injury.

AETIOLOGY

- Developed countries: paracetamol toxicity, ischaemia, drug-induced liver injury, hepatitis B virus, and autoimmunity (nearly 80% of cases.)
- Developing countries: Viral hepatitis A, B, and E
- Outcomes are dependent on the aetiology

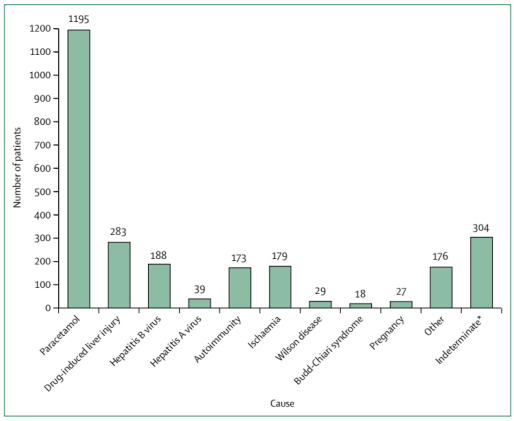


Figure 1: Causes of acute liver failure, as recorded by the site principal investigator in the US Adult Acute Liver Failure Study Group Registry

Stravitz et al 2023

	Paracetamol (n=1195)	Ischaemia (n=181)	Drug-induced liver injury (n=283)	Autoimmunity (n=173)	Hepatitis B virus (n=188)	Hepatitis A virus (n=39)	Pregnancy (n=27)	All other causes (n=528)
Age (median, years)	37	53	47	46	45	50	31	40
Women (%)	75%	58%	67%	81%	45%	44%	100%	64%
Jaundice coma (median, days)	1	2	12	16	8	4	7	7
Hepatic encephalopathy grade 3 or higher (%)	54%	56%	36%	27%	51%	54%	54%	44%
Alanine aminotransferase (median, IU/L)	3780	2311	654	404	1410	2229	43	758
Bilirubin (median, mg/dL)	4·3	3·8	19·6	22·8	19·2	12·0	9·0	16·2
Transplanted* (%)	9%							36%
Transplant-free survi	65%	57%	24%	14%	19%	51%	78%	22%
Overall survival* (%)	72%							55%

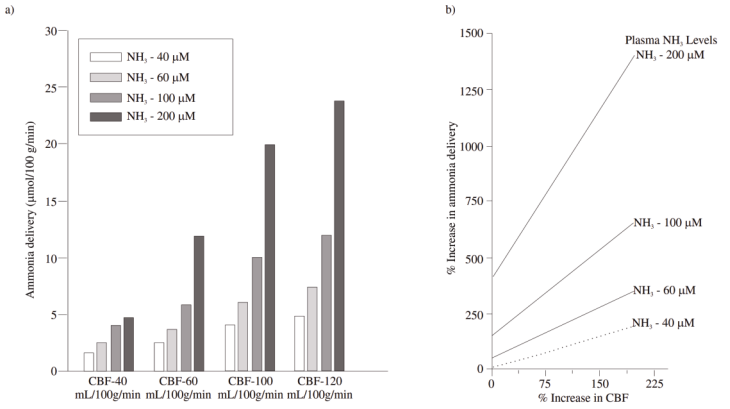
Data were collected between Jan 1, 1998, and March 31, 2019. Total number of patients=2614. *Represents outcomes 21 days after admission to the Acute Liver Failure Study Group Registry.

Table 1: Comparison of demographics, admission laboratory results, and outcome between different causes of acute liver failure in the Acute Liver Failure Study Group Registry

Stravitz et al 2023

Secondary Organ Dysfunction

- The brain is the most frequent secondary organ involved in ALF.
- Ammonia (and other neurotoxins), systemic and local inflammation leads to:
  - Neurotransmitter imbalance
  - Disruption of the blood-brain barrier
  - Neuroexcitation, agitation, seizures - worsening of cerebral oedema.
  - Loss of cerebral autoregulation



Influence of Cerebral Blood Flow on Ammonia Delivery to the Brain

Vaquero et al 2004

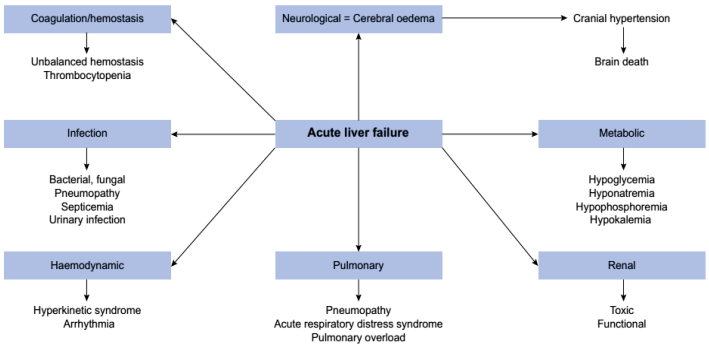


Fig. 2. Main organ specific complications in ALF.

- Commonest cause of death in ALF-MODS is sepsis

Assessment of Increased ICP

- Optic Nerve Sheath Diameter (ONSD): >6mm
- Transcranial Doppler Ultrasound: pulsatility Index of the MCA
- Continuous EEG monitoring
- Arterial ammonia levels: > 150 umol/L predicts poor outcome

MANAGEMENT

Routine monitoring:

- Oxygen saturation, blood pressure, heart rate respiratory rate, hourly urine output
- Clinical neurological status

Standard care:

- Glucose infusions (10–20%): glycemic target ± 140 mg/dl, Na 135–145 mmol/L
- Stress ulcer prophylaxis
- Restrict clotting factors unless active bleeding
- N-acetylcysteine in early stage, even in non-paracetamol cases

Preventative measures:

- Avoid sedatives
- Avoid hepatotoxic and nephrotoxic drugs

In case of hepatic encephalopathy:

- Transfer to an appropriate level of care (ideally critical care) at the first symptoms of mental alterations
- Quiet surrounding, head of bed >30°, head in neutral position and intubate, ventilate and sedate if progresses to >3 coma.
- Low threshold for empirical start of antibiotics if hemodynamic deterioration and/or increasing encephalopathy with inflammatory phenotype
- In case of evolving HE intubation and sedation prior to the transfer
- Ensure volume replete and normalize biochemical variables (Na, Mg, PO_4, K)

MANAGEMENT: Cardiovascular

Volume replacement with crystalloids +/- colloids

↓

1st line vasopressor: Noradrenaline

↓

2nd line vasopressor:Vasopressin/Terlipressin

↓

IV Hydrocortisone

- All patients with hypotension should have septic screen.

Management: Aetiology-specific

AETIOLOGY	TREATMENT
Acute Hepatitis B	Tenofovir/Entacavir
Acute Hepatitis E	Ribavirin
Acute HSV	Aciclovir
DILI	Stop the drug/ steroids?
Wilson's	PLEX/Zn
Autoimmune Hepatitis	Steroids

Management: Aetiology-specific

AETIOLOGY	TREATMENT
Acute Hepatitis B	Tenofovir/Entacavir
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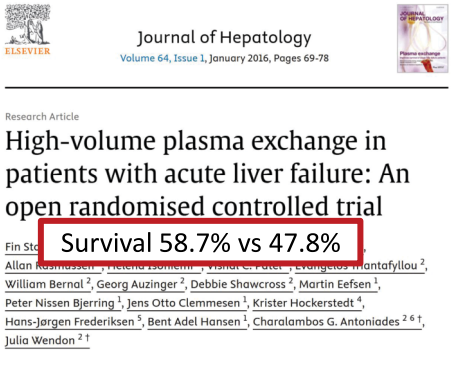
Acute HSV	Aciclovir
DILI	Stop the drug/ steroids?
Wilson's	PLEX/Zn
Autoimmune Hepatitis	Steroids

N-Acetylcysteine in Non-PCM ALF

- May improve survival in patients with grade 1-2 encephalopathy.
- Improves transplant free survival and reduces hospital stay – but does not improve overall survival.
- EASL guideline (2017) – "N-acetylcysteine in early stage, even in non paracetamol cases"
- Standard PCM dose is recommended.

Walayat et al 2021; Amjad et al 2022

Plasma Exchange



High Volume Plasma Exchange

- 15% of the ideal bodyweight or 8-12 litres; with FFP
- Frequent complications (Coirier et al 2025)
  - Severe alkalosis
  - Hypotension
  - Hypokalemia
- Corrects INR – interferes with monitoring

Standard-Volume Plasma Exchange Improves Outcomes in Patients With Acute Liver Failure: A Randomized Controlled Trial

- Patients with confirmed cerebral oedema on imaging
- 1.5-2 liters per session
- 3 sessions per patient
- Higher 21-day transplant free survival (75% vs 45%)

Maiwall et al 2022

Journal of Hepatology
Volume 82, Issue 4, April 2025, Pages 615-621

Research Article

Plasma exchange does not improve overall survival in patients with acute liver failure in a real-world cohort

Letter to the Editor

JOURNAL OF HEPATOLOGY

Late use of plasma exchange in acute liver failure: The battle is lost?

[1] Leeds Liver Unit, Leeds NHS Teaching Hospitals Trust, Leeds, UK
[2] Leeds Institute for Medical Research, University of Leeds, Leeds, UK
[3] Liver Intensive Therapy Unit, Institute of Liver Studies, Kings College Hospital, London, UK

Coirier, Artru and Camus

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Continuous renal replacement therapy is associated with reduced serum ammonia levels and mortality in acute liver failure

Filipe S. Cardoso, MD MSc[1], **Michelle Gottfried, MSc**[2], **Shannan Tujios, MD**[3], **Jody C. Olson, MD**[4], **Constantine J. Karvellas, MD SM**[5,*], and **For the US Acute Liver Failure Study Group**

Filipe S. Cardoso: filipe.cardoso@chlc.min-saude.pt; Michelle Gottfried: gottfrie@musc.edu; Shannan Tujios: Shannan.Tujios@utsouthwestern.edu; Jody C. Olson: jolson2@kumc.edu; Constantine J. Karvellas: dean.karvellas@ualberta.ca

[1]Intensive Care Unit, Curry Cabral Hospital, Central Lisbon Hospital Center, Lisbon, Portugal

[2]Department of Public Health Sciences, Medical University of South Carolina, Charleston, South Carolina, United States

[3]Division of Digestive and Liver Diseases, University of Texas Southwestern Medical Center,

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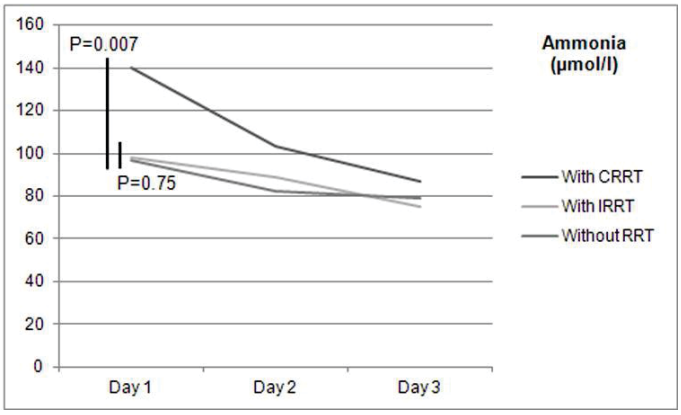

Cardoso et al 2017

CRRT

- CRRT has been shown to reduce ammonia levels.
- Improves overall survival and transplant free survival compared to SMT. (Dong et al 2024)
- High volume haemofiltration may be more beneficial than standard volume.
- Early initiation (4-6hr) and prolonged (>7hr) CRRT is more beneficial.
- No head-to-head trials with PLEX

CRRT – AGA Guidelines 2023

"In patients with ALF and grade 2 or higher encephalopathy, we suggest early CRRT for management of hyperammonemia even in the absence of conventional RRT indications."

"In patients with ALF requiring renal replacement therapy, we recommend CRRT over intermittent hemodialysis."

LIVER TRANSPLANTATION

- With advances in liver critical care, transplant free survival has increased to over 50%
- Both LDLT and DDLT have similar outcomes in ALF
- Early communication with transplant centers is crucial for management.

SUMMARY

- ALF has many aetiologies, which will affect the outcome. ∴ investigating for the aetiology is important.
- Early referral for tertiary care and EARLY INTERVENTION is crucial.
- There is evidence to suggest that IV NAC, TPE, CRRT improve survival without a liver transplant.
- Managing ALF cases without transplant facilities will always be a difficult and futile exercise.

Symposium on Metabolic Dysfunction Associated Steatotic Liver Disease

Dr Eranga Thalagala

Consultant Gastroenterologist and Hepatologist,
DGH, Chilaw

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Nomenclature Change of Steatotic Liver Disease and Identifying 'At Risk' Cases

Steatotic liver disease is the broader term used to identify the conditions characterized byabnormal lipid accumulation in the liver. Steatotic liver disease comprises of MASLD (previously known as NAFLD), Alcohol related liver disease (ALD), MetALD(Describes theindividuals with MASLD who also consume alcohol)and other rare causes of liver steatosis. Presenceof metabolic risk factors, amount of alcohol consumption and presence of other causes of hepatic steatosis are the determinants used in the new nomenclature.The previous term NAFLD was changed to MASLD recently. The new nomenclatureaims to improve clarity, represents the underlying pathophysiology,reducesstigma and highlights the relationship between metabolic health and liver disease.

Individuals with hepatic steatosis are at an increased risk for developing cirrhosis and hepatocellular carcinoma. Severity of hepatic fibrosis is an important predictor of adverse liver related outcomes. There are various risk factors responsible for the development of MASLD; which include metabolic, environmental and genetic risk factors.Cardiovascular disease and malignancies are the major causes of death among the people with MASLD. Early detection of at-risk patients is important toalter the disease course in a favorable manner. Due to the high prevalence of the condition, simple noninvasive tests to detect advance fibrosis are more feasible over invasive investigations such as liver biopsy. Non-invasive tests (NITs)consist of clinical and laboratory-based tests and imaging-based tests. National wide general population screening is not recommended. Patients with high risk factors should be screened annuallywithNITs. Patients with suspected advanced MASH or discordant NITs should be referred toa specialist.

Symposium on Metabolic Dysfunction Associated Steatotic Liver Disease

Dr. N. P. Dinamithra

Consultant Gastroenterologist and Hepatologist,
NH, Kandy

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Advances in the Management of Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD): A Multimodal Approach

Metabolic dysfunction-associated steatotic liver disease **(MASLD)**, previously known as NAFLD, has emerged as a leading global cause of chronic liver disease, demanding innovative and patient-centered management strategies. Recent advances underscore a multimodal approach, integrating lifestyle optimization, pharmacotherapy, surgical interventions, and cutting-edge diagnostics.

Lifestyle modification—anchored in the Mediterranean diet and targeted weight loss of 7–10%—remains the cornerstone, capable of reversing steatosis and early fibrosis.

Pharmacological progress is exemplified by **resmetirom (MAESTRO-NASH trial)**, now clinically approved for improving both NASH and fibrosis, and semaglutide(ESSENCE trial), which shows similar promise and is **pending approval**. Other agents, such as vitamin E and pioglitazone, offer partial benefits, while obeticholic acid and traditional agents like metformin and statins **lack comprehensive efficacy** for NASH endpoints.

Surgical solutions, notably bariatric procedures (sleeve gastrectomy, Roux-en-Y gastric bypass), yield significant histological and metabolic improvements, especially in obese patients with type 2 diabetes.

Diagnostic innovations—non-invasive tools like transient elastography, MRI-PDFF, and serum biomarker panels (FIB-4, FAST score)—are revolutionizing early detection and disease monitoring.

The future of MASLD care lies in **personalized medicine**, leveraging genomics, metabolomics, and AI-driven risk stratification to tailor therapy and predict outcomes. For advanced cases, liver transplantation remains the ultimate recourse, though challenges such as recurrence and donor scarcity persist.

In summary, MASLD management is rapidly transitioning toward a precision-based, multidisciplinary paradigm. The integration of lifestyle, pharmacological, surgical, and diagnostic advances promises to enhance long-term outcomes and transform the therapeutic landscape for this increasingly prevalent disease.

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