Advances in Liver Disease

Vivek Mendiratta, MD
Assistant Professor - Clinical
Transplant Hepatology
The Ohio State University Wexner Medical Center

MedNet21
Center for Continuing Medical Education

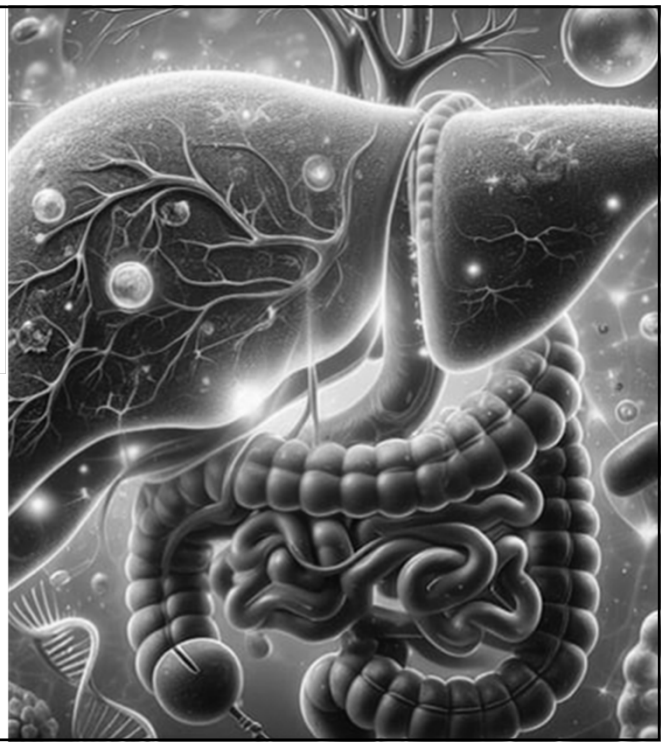
The Ohio State University
Wexner Medical Center

Disclosures

- No financial disclosures

Goals and Objectives

- Updates in steatotic liver disease
- Novel treatments for hepatocellular carcinoma
- Autoimmune liver disease, a changing of the guard?



Case Presentation

52 y/o male with PMHx significant for Type II DM, Hypertension, Obesity (BMI: 38), and Hyperlipidemia presents to clinic for elevated LFTs.

- Patient is new to clinic from another state
- Has two tattoos, professionally done
- Drinks approximately three to four drinks per week
- No history of blood transfusions
- Physical exam notable for obesity

- Liver profile:
  - AST: 34
  - ALT: 55
  - Alk Phos: 78
  - Total Bilirubin: 0.7
  - Direct Bilirubin: 0.1
  - Total Protein: 7.9
  - Albumin: 4.1

- Hepatitis panel negative
- PETH negative
- A1AT negative
- Iron studies normal
- US Abdomen showed hepatic steatosis without overt nodularity

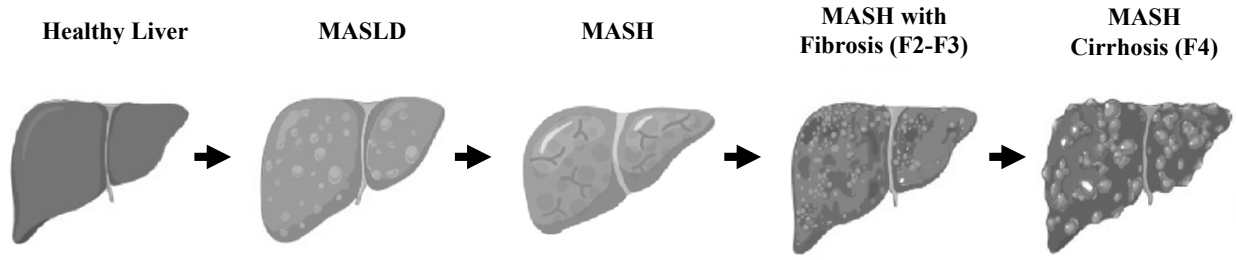
Steatotic Liver Disease: Scope of the Problem

Second most common cause of HCC and Liver Transplantation in the United States	Disease awareness remains limited	Early detection is critical to preventing fibrosis progression

Nomenclature Change

- Metabolic dysfunction-associated steatotic liver disease (MASLD) replaces non-alcoholic fatty liver disease (NAFLD)
- Metabolic dysfunction-associated steatohepatitis (MASH) replaces non-alcoholic steatohepatitis (NASH)
- Metabolic and alcohol-related liver disease (MetALD)
  - SLD for people with MASLD who drink more than 140g/week (≥10 drinks/week) for females or 210g/week (≥14 drinks/week) for males

MASLD Spectrum



Fat in <5% of hepatocytes	Steatosis (fat in ≥5% of hepatocytes)	Steatosis with inflammation and cell damage	Scarring in an inflamed liver	Nodule formation surrounding scar tissue

Guo, International Journal of Molecular Sciences

Global Prevalence

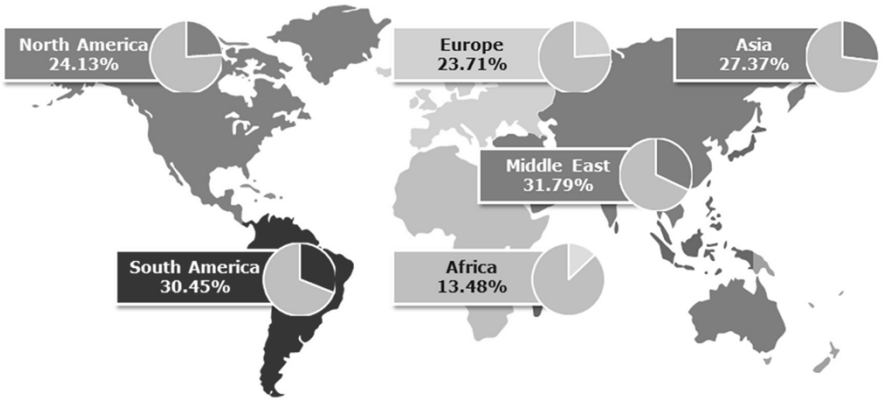
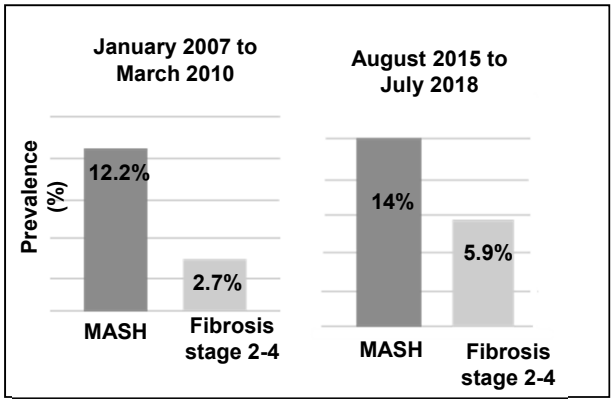
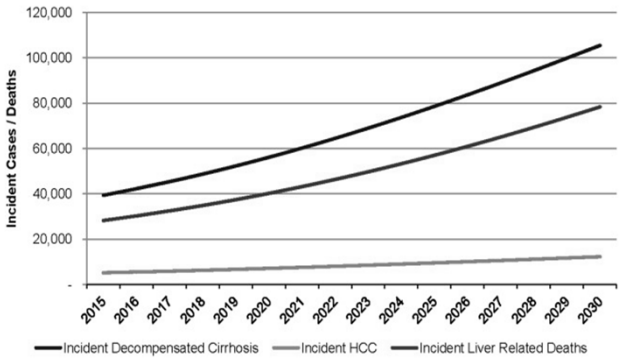


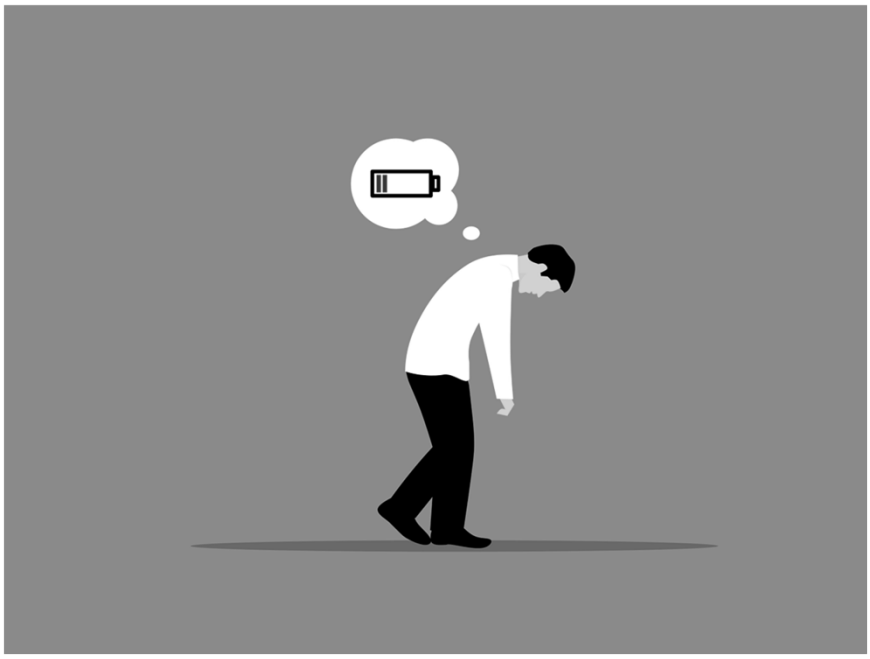
Image source: https://communityliveralliance.org/liver-health-facts/

Younossi, Hepatology, Sept 2018

Increasing Prevalence of MASH and Advanced Fibrosis







…I'm Fine

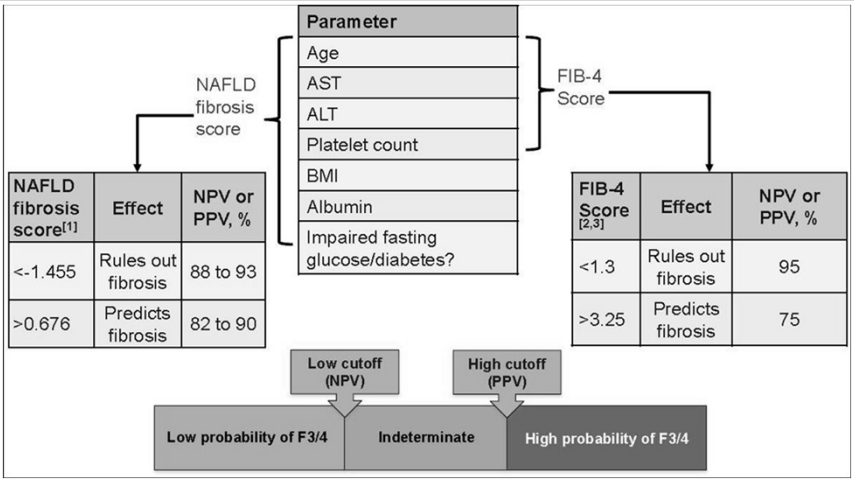
Screening Recommendations

AASLD 2022	AACE 2022	EASL 2016
• Type II DM • Medically complicated obesity • Hepatic Steatosis with moderate alcohol consumption • First-degree relatives of a patient with cirrhosis due to NAFLD/NASH	• Pre-diabetes or Type II DM • Obesity and/or ≥2 cardiometabolic risk factors • Hepatic steatosis (on imaging) or increase in AST/ALT	• Obesity, Type II DM, or Metabolic syndrome • Persistently abnormal liver enzymes

Clinical Assessment Tools

Simple Calculators	Serum Tests	Imaging	Histologic Assessment
• FIB-4 • NAFLD Fibrosis Score	• Fibrosure • Enhanced Liver Fibrosis (ELF)	• Transient elastography • MR elastography	• Liver Biopsy

Simple Calculators



Eskridge, Fatty Liver Foundation 2022

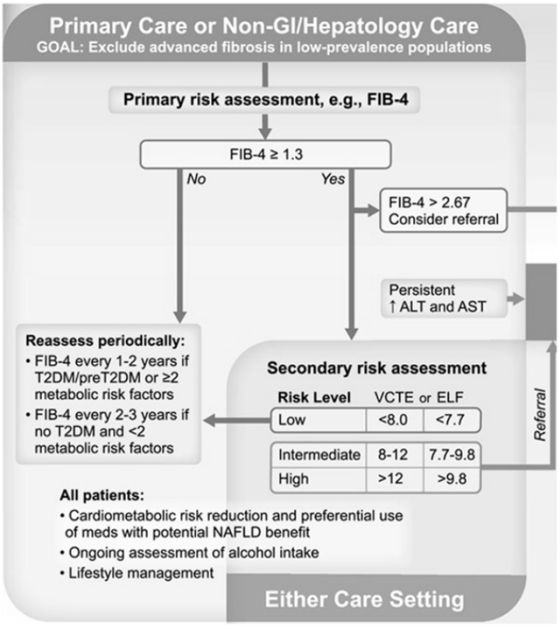
Imaging Techniques: Fibroscan

MEASURES VELOCITY OF SOUND WAVES PASSING THROUGH THE LIVER

TAKES 5-10 MINUTES

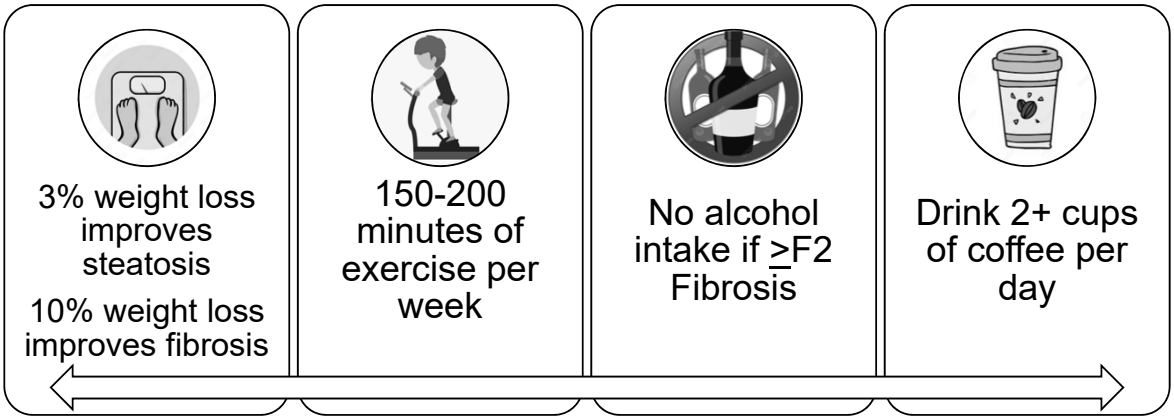
GIVES ASSESSMENT OF STEATOSIS (CAP SCORE) AND FIBROSIS

Algorithm

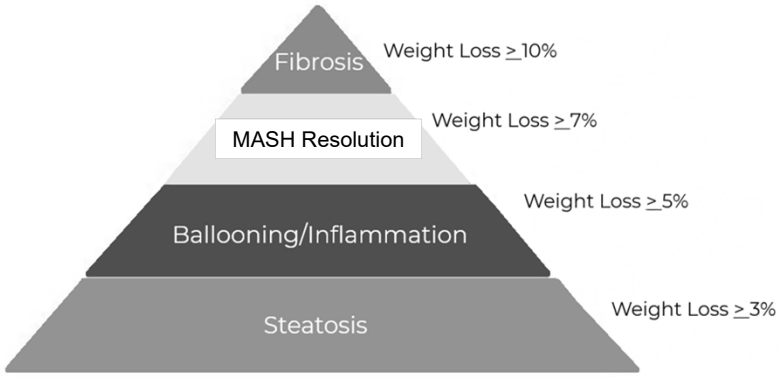


Chris Estes, Homie Razavi, Rohit Loomba, et al.. Modeling the epidemic of nonalcoholic fatty liver disease demonstrates an exponential increase in burden of disease. Hepatology 67(1):p 123-133, January 2018. | DOI: 10.1002/hep.29466

Treatment: Lifestyle Modification



Weight Loss Pyramid



Pharmacologic Treatments

A Placebo-Controlled Trial of Subcutaneous Semaglutide in Nonalcoholic Steatohepatitis

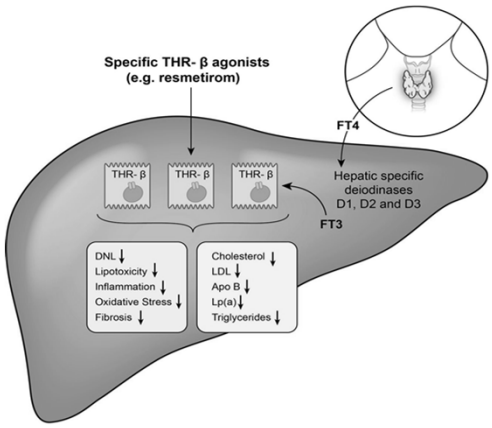
Philip N. Newsome, M.B., Ch.B., Ph.D., Kristine Buchholtz, M.D., Ph.D., Kenneth Cusi, M.D., Martin Linder, M.Sc., Takeshi Okanoue, M.D., Ph.D., Vlad Ratziu, M.D., Ph.D., Arun J. Sanyal, M.D., Anne-Sophie Sejling, M.D., Ph.D., and Stephen A. Harrison, M.D. for the NN9931-4296 Investigators*

- 72-week, double-blind trial involving patients with biopsy-confirmed MASH (F1, F2, or F3 fibrosis)
- 320 patients were randomly assigned to receive semaglutide at a dose of 0.1 mg, 0.2 mg, 0.4 mg or to receive placebo
- MASH resolution occurred in 40% in the 0.1-mg group, 36% in the 0.2-mg group, 59% in the 0.4-mg group, and 17% in the placebo group ($P<0.001$ for semaglutide 0.4 mg vs. placebo)
- Trend towards improvement in fibrosis stage occurred in 43% of the patients in the 0.4-mg group and in 33% of the patients in the placebo group ($P=0.48$)

Newsom NEJM 2020

Resmetirom

- Drug that acts as an agonist on thyroid hormone receptor-β
  - THR-β pathway is active primarily in the liver
  - Regulates de novo lipogenesis
  - Reduces LDL and improves metabolic control
- Originally developed to treat dyslipidemia
- Patients with hypothyroidism have higher rates of MASLD



https://gut.bmj.com/content/73/4/573

A Phase 3, Randomized, Controlled Trial of Resmetirom in NASH with Liver Fibrosis

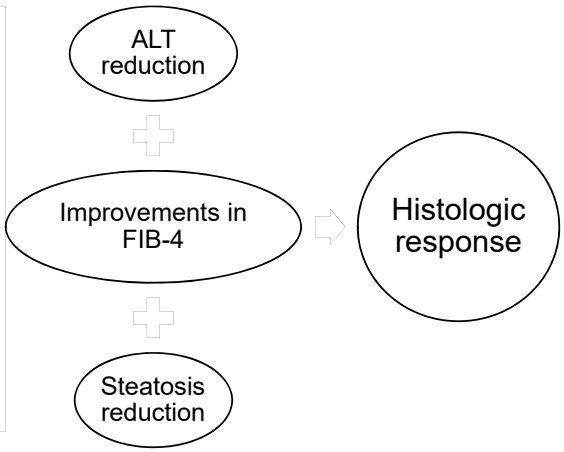
S.A. Harrison, P. Bedossa, C.D. Guy, J.M. Schattenberg, R. Loomba, R. Taub, D. Labriola, S.E. Moussa, G.W. Neff, M.E. Rinella, Q.M. Anstee, M.F. Abdelmalek, Z. Younossi, S.J. Baum, S. Francque, M.R. Charlton, P.N. Newsome, N. Lanthier, I. Schiefke, A. Mangia, J.M. Pericàs, R. Patil, A.J. Sanyal, M. Noureddin, M.B. Bansal, N. Alkhouri, L. Castera, M. Rudraraju, and V. Ratziu, for the MAESTRO-NASH Investigators*

- 52-week, double-blind trial involving patients with biopsy-confirmed MASH (F1, F2, or F3 fibrosis)
- 966 patients randomly assigned in a 1:1:1 ratio to receive once-daily resmetirom at a dose of 80 mg or 100 mg or placebo
- MASH resolution achieved in 25.9% in the 80-mg resmetirom group, 29.9% in the 100-mg resmetirom group, and 9.7% in the placebo group (P<0.001 for both comparisons with placebo)
- Fibrosis improvement by at least one stage achieved in 24.2% in the 80-mg resmetirom group, 25.9% in the 100-mg resmetirom group, and 14.2% in the placebo group (P<0.001 for both comparisons with placebo)
- Change in LDL from baseline to week 24 was -13.6% in the 80-mg resmetirom group, -16.3% in the 100-mg resmetirom group, and 0.1% in the placebo group (P<0.001 for both comparisons with placebo)
- Incidence of serious adverse events was similar across trial groups: 10.9% in the 80-mg resmetirom group, 12.7% in the 100-mg resmetirom group, and 11.5% in the placebo group

Harrison, NEJM, 2024

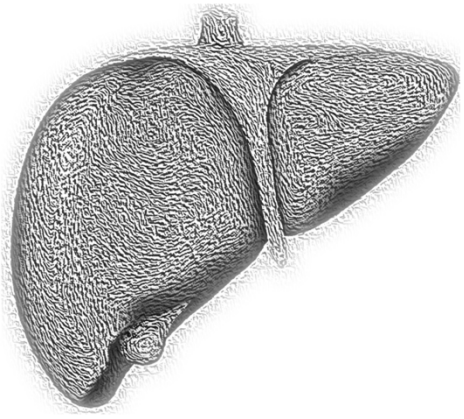
How should we use it?

- Consider it in patients with F2 or F3 Fibrosis
  - Has not yet been studied in patients with compensated cirrhosis (F4 fibrosis) though studies ongoing
  - Dosing: 80mg per day if <100kg, 100mg per day if >100kg
- Does not replace lifestyle modifications and should be used in conjunction to nutrition/exercise counseling
- Consider combination therapy with GLP-1 in diabetic or obese patients
- How do we know that it is working?
- How long does the patient need to be on this?



Case Presentation

- 52 y/o male with MASLD, T2DM, Hypertension, Obesity (BMI: 38) and Hyperlipidemia who presented with elevated LFT's and hepatic steatosis on imaging. What test should we order next?
- Fibroscan showing F2 Fibrosis and S3 Steatosis
- What type of treatment options should we consider in this patient?
- Patient presents years later with abdominal pain. He undergoes an MRI showing a cirrhotic appearing liver, as well as a 4.2cm right hepatic lobe LR-5 observation with tumor thrombus. His AFP is 450 ng/ml.



What's New?

PRACTICE GUIDANCE

AASLD Practice Guidance on prevention, diagnosis, and treatment of hepatocellular carcinoma

Singal, Amit G.[1]; Llovet, Josep M.[2,3,4]; Yarchoan, Mark[5]; Mehta, Neil[6]; Heimbach, Julie K.[7]; Dawson, Laura A.[8]; Jou, Janice H.[9]; Kulik, Laura M.[10]; Agopian, Vatche G.[11]; Marrero, Jorge A.[12]; Mendiratta-Lala, Mishal[13]; Brown, Daniel B.[14]; Rilling, William S.[15]; Goyal, Lipika[16]; Wei, Alice C.[17]; Taddei, Tamar H.[18,19]

Author Information

Hepatology 78(6):p 1922-1965, December 2023. | **DOI:** 10.1097/HEP.0000000000000466

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Hepatocellular Carcinoma

Version 2.2023 — September 14, 2023

Hepatocellular Carcinoma: Why is it important?

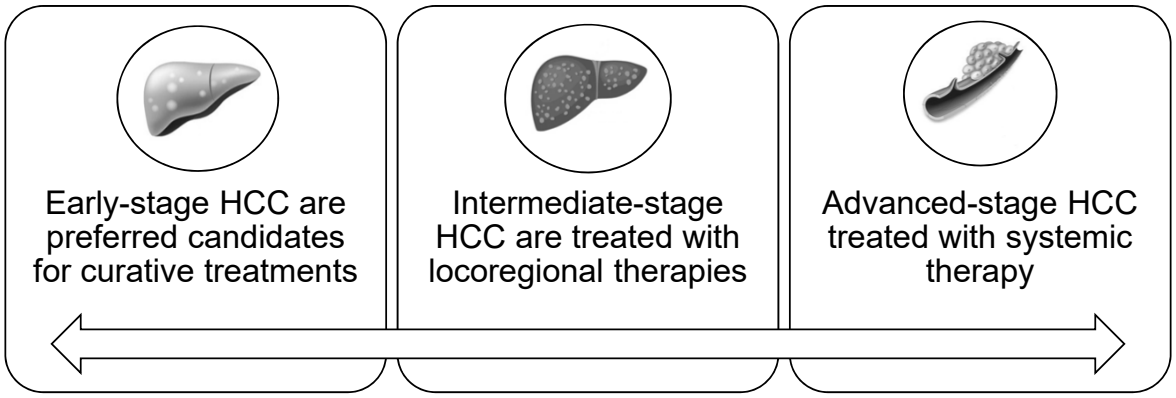
Liver cancer is the 2nd most frequent cause of cancer-related deaths

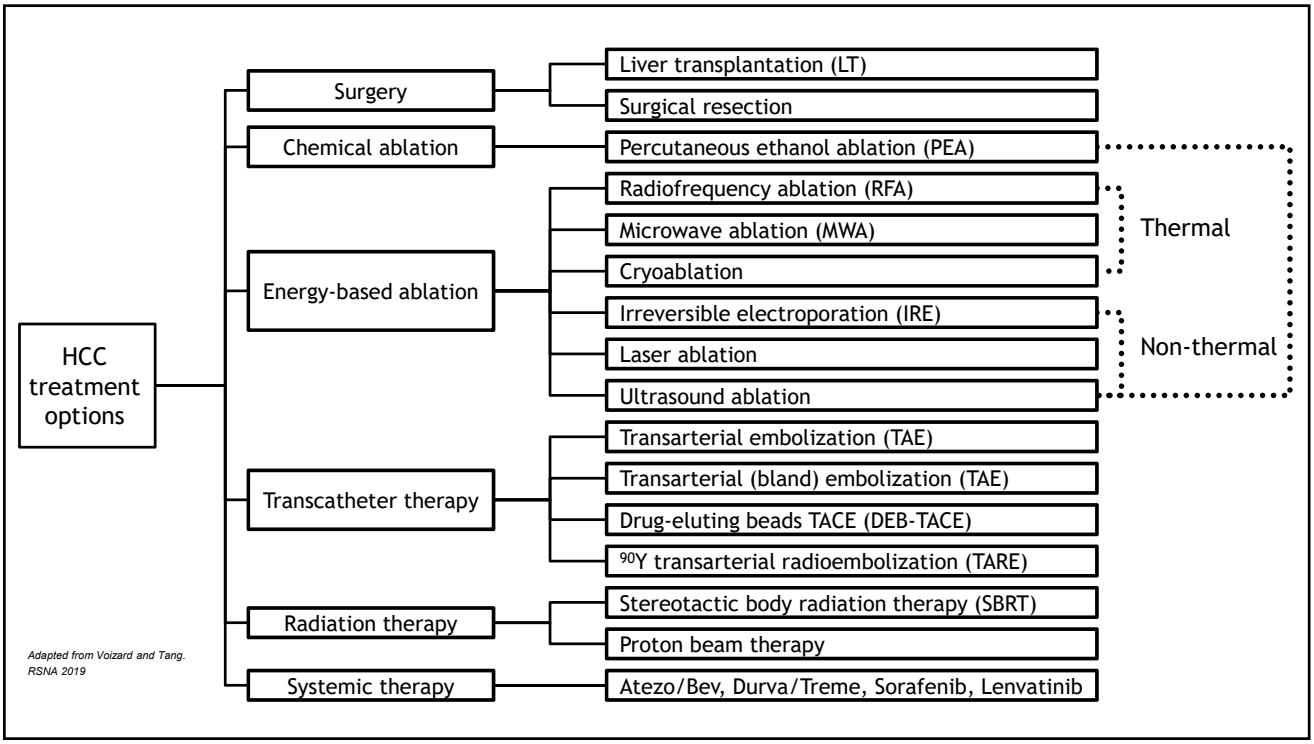
Incidence rates estimated to exceed 1 million by 2025

Screen with US and AFP every six months

2-5% per year risk of HCC in cirrhotic patients

Management


Early-stage HCC are preferred candidates for curative treatments
Intermediate-stage HCC are treated with locoregional therapies
Advanced-stage HCC treated with systemic therapy


HCC treatment options
Surgery
Liver transplantation (LT)
Surgical resection
Chemical ablation
Percutaneous ethanol ablation (PEA)
Energy-based ablation
Radiofrequency ablation (RFA)
Microwave ablation (MWA)
Cryoablation
Irreversible electroporation (IRE)
Laser ablation
Ultrasound ablation
Thermal
Non-thermal
Transcatheter therapy
Transarterial embolization (TAE)
Transarterial (bland) embolization (TAE)
Drug-eluting beads TACE (DEB-TACE)
90Y transarterial radioembolization (TARE)
Radiation therapy
Stereotactic body radiation therapy (SBRT)
Proton beam therapy
Systemic therapy
Atezo/Bev, Durva/Treme, Sorafenib, Lenvatinib
Adapted from Voizard and Tang. RSNA 2019

IMbrave150: Atezolizumab plus Bevacizumab for Unresectable HCC

- 501 patients with unresectable HCC were randomly assigned in a 2:1 ratio to receive either atezolizumab plus bevacizumab or sorafenib
- Overall survival at 12 months was 67.2% (95% CI, 61.3 to 73.1) with atezolizumab–bevacizumab and 54.6% (95% CI, 45.2 to 64.0) with sorafenib
- Median progression-free survival was 6.8 months (95% CI, 5.7 to 8.3) and 4.3 months (95% CI, 4.0 to 5.6) in the respective groups

Cheng, Journal of Hepatology, 2022

Finnm, NEJM, 2020

Himalaya: Tremelimumab plus Durvalumab in Unresectable HCC

Tremelimumab/Durvalumab (n=393) vs. Durvalumab (n=389) vs. Sorafenib (n=389)

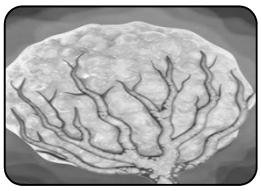
OR for STRIDE was 20.1%, 17.0% with Durvalumab alone, 5.1% for Sorafenib

Median Survival: 16.43 months with STRIDE, 16.5 months with Durvalumab, and 13.7 months with Sorafenib

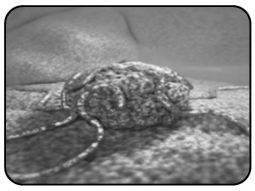
Time to QOL deterioration: 7.5 months for STRIDE, 7.4 months for Durvalumab, 5.7 months for Sorafenib

About-Alfa, July 2022, NEJM

Transarterial Radioembolization



- Microspheres embedded with Yttrium-90 (Y-90)
  - Intra-arterial delivery
  - High radiation doses to the target tumor



- Performs better than cTACE
  - Longer TTP (26 vs. 6.8 months)
  - Improved pathologic necrosis (87% vs. 74%)
  - Better side effect profile

Combination Therapies: Is more better?

Emerald 1: TACE+Durva+Bev

- 616 patients with HCC not amenable to curative therapy were randomized in 1:1:1 ratio to receive TACE+durvalumab+bevacizumab, TACE+durvalumab, or TACE+placebo
- Median progression free survival was improved by 6.8 months in the D+B+TACE vs. placebo+TACE arm (15 months vs 8.2 months)

Y-90 Induces Immune Response

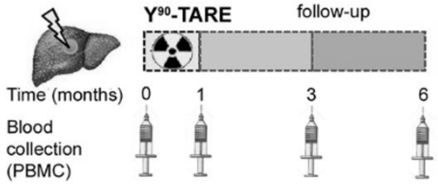
Y90 causes an altered adaptive and innate immune response, resulting in increased frequency of activated CD3+ T Cells and CD8+ regulatory T cells

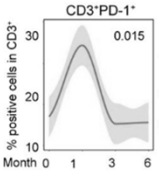
Increased inflammatory (PD-L1+ and HLA-DR+) monocyte populations

Effect peaks at 1 month after treatment and decreased significant at 3 and 6 months

Using immunotherapy within 1 month post-Y90 could have a synergistic immune response

HCC patients (n=49) with preserved hepatic function (Child Pugh ≤B7, MELD score ≤10) and no indication to liver transplantation, undergoing Y^{90}TARE (as first-line loco-regional treatment) and longitudinal blood immune monitoring.

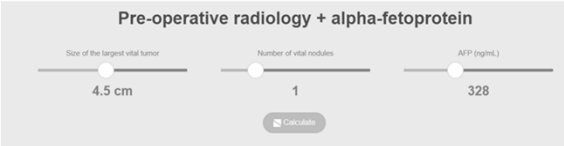




Rivoltini L, Bhoori S, Camisaschi C, *et al*. Y^{90}-radioembolisation in hepatocellular carcinoma induces immune responses calling for early treatment with multiple checkpoint blockers *Gut* 2023;72:406-407. CC BY-NC 4.0

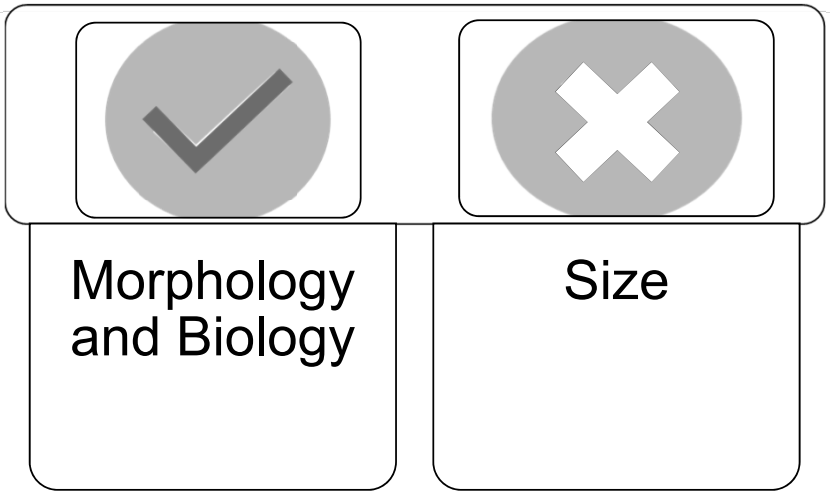
Liver Transplant for HCC

- Historically, candidacy for transplanting patients with HCC has been based off tumor size alone
- Metroticket 2.0 showed that biomarkers and size both play an important role in predicting post-transplant HCC recurrence
- Novel tumor biomarkers such as DCP and AFP-L3 have now been shown to be significantly associated with high-risk explant features

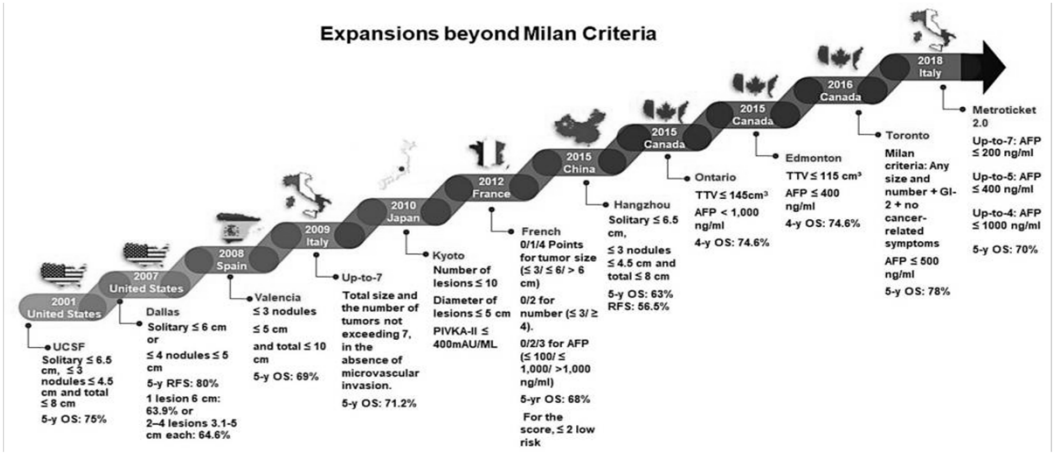


Mazzaferro, Gastroenterology, 2018

Post Transplant Recurrence



Pushing the Boundaries



Abdelrahim M, Esmail A,Transplant Oncology: An Emerging Discipline of Cancer Treatment. Cancers (Basel). 2020 Nov

Autoimmune Hepatitis

PREVALENCE OF 31.2 PER 100,000 PERSONS

FEMALE PREDOMINANCE (4:1)

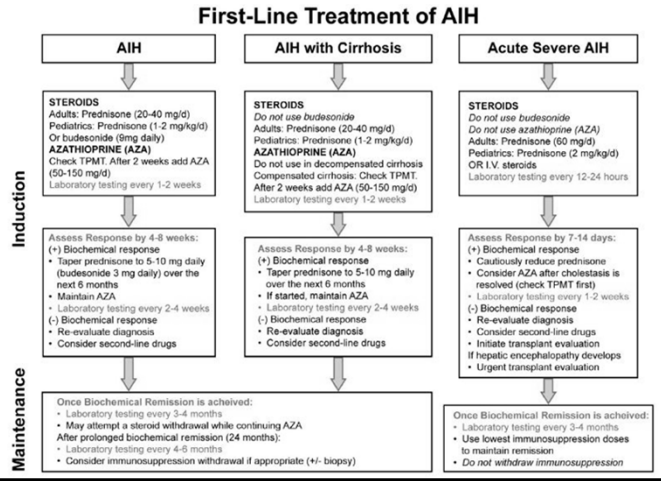
ONSET PEAKS AT AGES 1-30 AND 40-60

OCCURS FREQUENTLY WITH CONCOMITANT AUTOIMMUNE DISEASES

Clinical Presentation

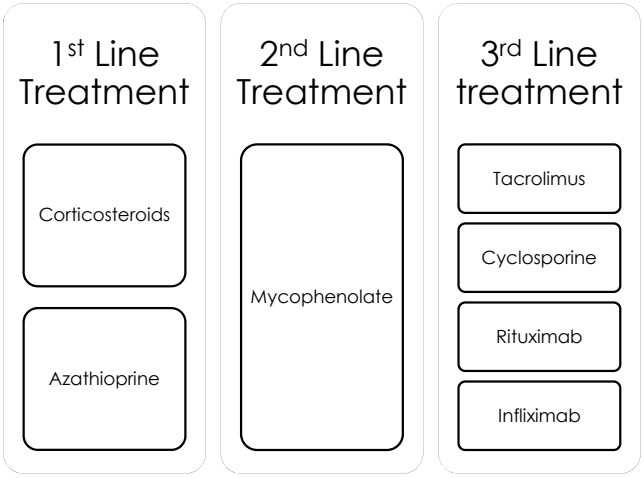
- Symptomatic
  - Most patients with AIH present after the development of chronic nonspecific symptoms (fatigue, malaise, arthralgias, or amenorrhea)
  - Easy fatigability is the main complaint in 85% of patients
- Asymptomatic
  - Asymptomatic in 25%-34% of patients
  - Asymptomatic patients infrequently achieve spontaneous laboratory improvement (12%)
  - The absence of symptoms should not discourage treatment
  - Histology similar to symptomatic patients

Management



Mack, AASLD practice guidance, August 2020

Treatment Options



Patient Perspective of Treatment

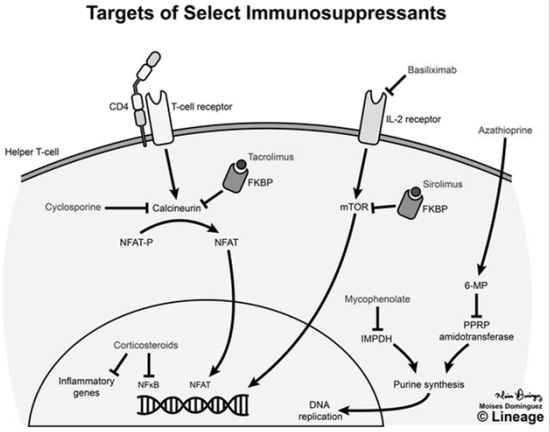
- How satisfied are you with your current AIH treatment?
  - 38% somewhat satisfied
  - 14% dissatisfied
  - 5% very dissatisfied
- What would you most like to change about your treatment of AIH?
  - 56%: Treatment should have less side effects

Medication	Number ever taken	Number discontinued (%)	Most cited reasons for stopping (n, %)
Azathioprine (AZA)	199	57 (29%)	Side effects (30/44, 68%),Toxic metabolism 5/44, 11%)
Mercaptopurine	23	11 (48%)	Toxic metabolism 5/10, 50%)
Mycophenolate mofetil (MMF)	42	7 (17%)	Side effects (4/5, 80%)

Lloyd 2023

MMF: Mechanism of Action

- MMF is labeled for use in preventing rejection after solid organ transplantation
- MMF is a prodrug of mycophenolic acid
  - Inhibits the activity of the type II isoform of inosine-5'-monophosphate dehydrogenase
  - Type II isoform is present in immune cells
  - Selectively suppresses both T- and B-cell lymphocyte proliferation
- MMF also inhibits monocytes



https://step1.medbullets.com/immunology/105068/immunosuppressive-drugs

Research Article
DILI, Autoimmune, Cholestatic and Genetic Diseases

JOURNAL OF HEPATOLOGY

An open-label randomised-controlled trial of azathioprine *vs.* mycophenolate mofetil for the induction of remission in treatment-naive autoimmune hepatitis

Romée J.A.L.M. Snijders[1,2,4,†], Anna E.C. Stoelinga[2,†], Tom J.G. Gevers[3,4,2,4], Simon Pape[1,2,4], Maaike Biewenga[2], Maarten E. Tushuizen[7], Robert C. Verdonk[8], Hendrik J.M. de Jonge[9], Jan Maarten Vrolijk[7], Sjoerd F. Bakker[8], Thomas Vanwolleghem[5,2,4], Ynto S. de Boer[10,2,4], Martine A.M.C. Baven Pronk[11], Ulrich Beuers[12,2,4], Adriaan J. van der Meer[13], Nicole M.F. van Gerven[14], Marijn G.M. Sijtsma[15], Brechje C. van Eijck[16], Manon C. van IJzendoorn[17], Margot van Herwaarden[18], Floris F. van den Brand[19], Kerem Sebib Korkmaz[20], Aad P. van den Berg[21,22], Maureen M.J. Guichelaar[23], Amar D. Levens[24], Bart van Hoek[2,4], Joost P.H. Drenth[1,2,4,*], on behalf of the Dutch Autoimmune Hepatitis Working Group

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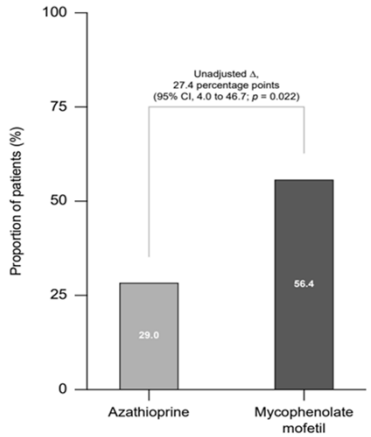
Check for updates

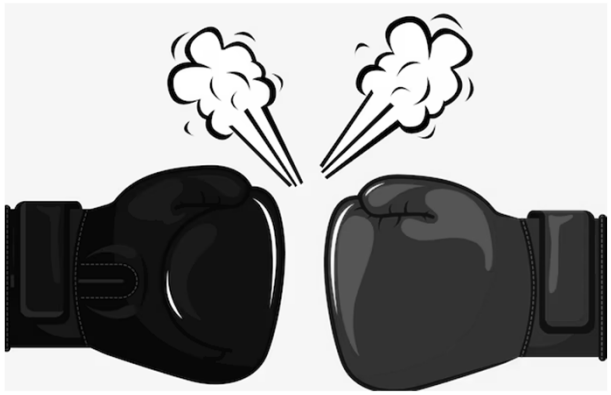


- Overall, 37 (94.9%) patients in the MMF group and 23 patients (74.2%) in the azathioprine group completed treatment
- At week 24, the proportion of patients with biochemical remission was 56.4% in the MMF group (22 of 39 patients) vs. 29.0% in the azathioprine group (9 of 31 patients) (95% CI, 4.0 to 46.7; p = 0.022)
- This difference was also observed in the analysis utilizing only the data available at the 24-week timepoint (p = 0.031).
- Two patients (5.1%) in the MMF group and eight patients (25.8%) in the azathioprine group discontinued treatment owing to AEs/SAEs

MMF vs Azathioprine

MMF

- Side effect profile: MMF better tolerated than AZA
- Rapidity of action: MMF >> AZA
- Cirrhosis: MMF fewer side effects than AZA
- Works better (?)



AZA

- Dosing: Aza once daily > MMF BID
- Cost: Aza cheaper than MMF
- Reproduction: AZA safe in pregnancy, MMF teratogenic

Take Home Points

- Early diagnosis of steatotic liver disease is critical to altering the natural course of the disease process
- New pharmacologic therapy for MASLD/MASH!
- Combination therapy for HCC is a wave of the future
- Expanding liver transplant offers more patients curative treatment
- Consider mycophenolate mofetil for treatment of autoimmune hepatitis

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