Cirrhosis and NAFLD

NDAFP 2024
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Objectives

1. Appreciate the **changing epidemiology** of advanced Liver Disease
2. Itemize the **various causes** of liver disease and **interventions** available including **NAFLD** (now metabolic dysfunction-associated steatotic liver disease (**MASLD**)
3. Appreciate the interventions necessary for ESLD and **Portal Hypertension**

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Etiology and Prevalence

- Chronic hepatitis B virus (HBV)
- Hepatitis C virus (HCV) infection
- Alcohol Use Disorder
- Nonalcoholic Steatohepatitis (NASH) now, metabolic dysfunction-associated steatotic liver disease (**MASLD**)

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Epidemiology Hepatitis B

- HBV 15th leading cause of mortality internationally
- 2010: 786,000 deaths, the vast majority being attributable to **liver cancer** (341,000 deaths) and **cirrhosis** (312,000 deaths)
- Most from **perinatal transmission** at birth
  - Horizontal transmission to/between young children
  - **Sexual contact**
  - **Injection drug use**
- In Asia, a greater proportion of women are highly infectious at childbearing age
  - Predominant HBV genotypes that influence the likelihood of HBeAg positivity
  - High levels of HBV DNA during peak childbearing age

MacLachlan JH, Cowie BC. Hepatitis B virus epidemiology. Cold Spring Harb Perspect Med. 2015 May 1;5(5):a021410. doi: 10.1101/cshperspect.a021410. PMID: 25934461; PMCID: PMC4448582.

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Hepatitis B Epidemiology continued

- ~30 million people living with Hep B
- 5-10% of **HIV** patients have **co-infection** with Hep B
- (Some places as high as 25%)
- "Hepatitis D" HDV is a satellite RNA virus, which only infects individuals also infected with HBV
- Globally, HDV infection occurs in ~5% of those living with HBV; however, the prevalence of coinfection varies widely and, in many areas, is not known
- In low-HBV-prevalence countries, HBV and HIV transmission largely occur in adulthood through sexual contact and injecting drug use

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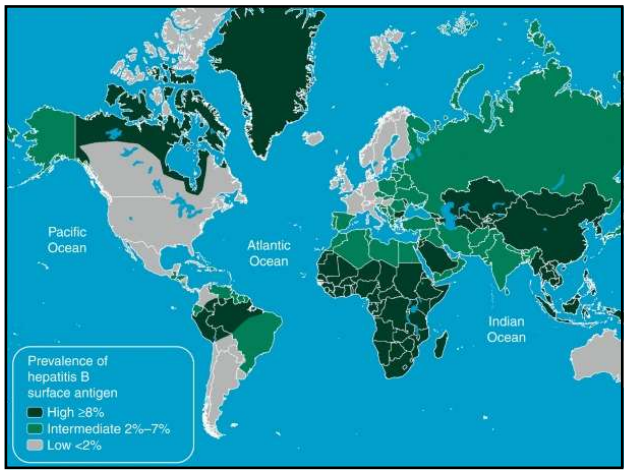

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Audience Response Question

A 30-year-old female who is hepatitis B surface antigen (HBsAg)-positive gives birth to a 2800-g (6 lb 3 oz) male. Which one of the following is essential in the care of this newborn during his first 12–24 hours of life?

A. A hepatitis profile
B. Adefovir dipivoxil (Hepsera)
C. Hepatitis A vaccine
D. Hepatitis B immune globulin and hepatitis B vaccine

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Hep B Transmission

- Mother-to-child transmission is responsible for more than **one-third** of chronic hepatitis B virus infections worldwide.
- Prevention of perinatal hepatitis B depends on the **timely administration of appropriate postexposure immunoprophylaxis** to infants born to mothers who are hepatitis B surface antigen (HBsAg)-positive or whose hepatitis B status is unknown.
- Perinatal transmission among infants born to HBsAg-positive mothers is **as high as 90%** without immunoprophylaxis, which has been shown to be **85%–95% efficacious for preventing mother-to-child transmission**.
- Approximately 1000 new cases of perinatal hepatitis B infection are identified in the United States each year.

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Hep B Transmission continued

- A hepatitis profile to check for HBsAg and antibody to HBsAg is **indicated between 9 and 12 months of age**.
- This profile is recommended after completion of the hepatitis B vaccine series, not in the newborn period.
- The ACIP recommends the initiation of routine **hepatitis A immunization between 1 and 2 years** of age.
- This is a two-dose series that can be integrated into the routine childhood vaccination schedule.

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Epidemiology Hepatitis C

- HCV is one of the most common chronic infectious diseases worldwide, affecting an estimated 150 to 170 million people globally
- Between 7 and 20 million people with Hep C are thought to be coinfected with HBV 2-8% of total
- The USPSTF subsequently recommended universal HCV screening for adults aged 18 to 79 years in March 2020
- Incidence of acute hepatitis C in the United States increased 124% from 2013 through 2020

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Guideline Summary 2023 Infectious Disease Society of America (ISDA)

- Universal HCV antibody screening with reflex HCV RNA
- The simplified HCV treatment algorithm now includes persons living with HIV
- A new algorithm for incomplete treatment <7 days of DAA therapy
- Emerging data highlight the safety and efficacy of HCV DAA treatment in persons who have undergone solid organ transplantation
- Treatment is recommended for infected persons residing in jail or prison

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Addressing Hepatitis C infection in Incarcerated Individuals

- 3.0% to 34.6% exceeding 1.7% in general population
- >90% reenter the general population contributing to HCV spread
- Should have opt-out HCV testing that consists of HCV antibody testing & reflex HCV RNA testing
- Should receive a recommended course of antiviral treatment while incarcerated
- To prevent HCV reinfection and reduce the risk of progression
  - **harm reduction and evidence-based treatmen**t for underlying substance use disorders (**SUD**)
- Addressing **hazardous alcohol use** among persons slows progression, transmission and recividism

Busschots D, Kremer C, Bielen R, et al. Hepatitis C prevalence in incarcerated settings between 2013–2021: a systematic review and meta-analysis. BMC Public Health 2022; 22:2159.

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Special Populations

- HIV/HCV-coinfected persons
- People who inject drugs (PWID)
  - Annual testing
  - Active or recent drug use or concern for reinfection is not a contraindication to HCV treatment (95% response)
- Men who have sex with men (MSM)
- Maternal-Child transmission increasing
  - Recent increase in HCV infection among women of childbearing age
  - Vertical is the primary route of HCV transmission in children

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MSM

- HCV testing at HIV PrEP initiation and at least annually thereafter (while on PrEP) is recommended for MSM not living with HIV
- All MSM should be counseled about the risk of sexual HCV transmission with high-risk sexual and drug use practices and educated about measures to prevent HCV infection or transmission

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Eligibility for Simplified HCV regimen

- Adults with chronic HCV infection, including persons living with HIV
- Infected with any genotype
- Have not previously received HCV treatment
- Without cirrhosis or with compensated cirrhosis (Child-Pugh A) determined by
  - Liver stiffness (>12.5 kPa by FibroScan
  - FIB-4 >3.25
  - Noninvasive serologic test
  - Liver biopsy
  - Liver nodularity or splenomegaly
  - Platelet Count < 150,000/mm^3

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4 Components to achieve 95% Sustained Viral Response

1. Minimal monitoring included no pretreatment genotyping
2. Dispensing the entire treatment course at entry, no scheduled on-treatment visits or laboratory monitoring
3. Remote contact at week 4 to assess DAA adherence
4. At week 22 to schedule SVR assessment at week 24.

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Direct-Acting Antiviral (DAA)

- Shortening the duration of glecaprevir/pibrentasvir therapy to 8 weeks for persons with compensated cirrhosis. SVR12 = 98%
- Except those with a short life expectancy that cannot be remediated by HCV therapy, liver transplantation, or another directed therapy
- Expanding the pool of clinicians who provide HCV treatment

EXPEDITION-8 trial. J Hepatol 2020; 72:441–9.

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Pretreatment Assessment

- Fib-4 score
- Assess for cirrhosis
- Obtain CBC
- Hepatic function panel
- eGFR
- Medication Reconciliation
- Drug-drug interactions
- Quantitative HCV RNA
- HIV antibody test
- Hep B sAG
- Pregnancy Test
- Education about DAA administration
  - Adherence
  - Prevention
  - Reinfection
  - Avoiding excess alcohol

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On Treatment Monitoring

- Monitor patients taking hypoglycemic meds
- INR if on warfarin
- No labs required for other patients
- In-Person, telehealth or phone visit for support or symptom assessment

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Posttreatment Assessment of Cure (SVR)

- Quantitative HCV RNA and hepatic function test
  - Undetectable = (virologic cure)
  - Transaminase normalization
- Assess for other causes of liver disease if ALT and / or AST remain elevated

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Follow up post-treatment

Regardless of Cure:
advise against excess alcohol

If Cure is Achieved
- No Follow up recommended
- If at risk for reinfection, counsel for risk reduction
- HCVRNA annually or with elevated ALT and/or AST

If Cure is Not Achieved
- Refer to HCV specialist
- Until retreatment, assess for progression q 6-12 m with
- LFT, CBC, INR

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able 1. Recommendations for Initial Treatment of Hepatitis C Virus–Infected Adults

egimen	Genotype	Classification	Duration	Rating	Caveats and Other Considerations
eatment-naive without cirrhosis or with compensated cirrhosis Glecaprevir/pibrentasvir	1–6	Recommended	8 wk	I, A[a]	
ofosbuvir/velpatasvir	1–6	Recommended	12 wk	I, A[b]	For genotype 3 infection with compensated cirrhosis, NS5A RAS testing is recommended. If baseline NS5A RAS Y93H is present, add weight-based ribavirin or choose another recommended regimen.
edipasvir/sofosbuvir	1, 4, 5, 6	Recommended	12 wk	I, A[c]	Not recommended for genotype 6e infection if subtype is known.
	1 without cirrhosis	Recommended	8 wk	I, B	Applicable to patients without cirrhosis who are not living with human immunodeficiency virus and whose HCV RNA is <6 million IU/mL.
lbasvir/grazoprevir	1b, 4	Recommended	12 wk	I, A[d]	
	1a	Alternative	12 wk	I, A	For genotype 1a infection, NS5A RAS testing is recommended. If baseline RASs are present (ie, substitutions at amino acid positions 28, 30, 31, or 93), another recommended regimen should be used.
ofosbuvir/velpatasvir + weight-based ribavirin	3	Alternative	12 wk	IIa, A	Applicable to genotype 3 infection with compensated cirrhosis and baseline NS5a Y93 RAS.
ofosbuvir/velpatasvir/ voxilaprevir		Alternative	12 wk	IIa, B	Applicable to genotype 3 infection with compensated cirrhosis and baseline NS5a Y93 RAS.
eatment-naive with decompensated cirrhosis					
ofosbuvir/velpatasvir + weight-based ribavirin	1–6	Recommended	12 wk	I, A[e]	Low initial dose of ribavirin (600 mg) is recommended for patients with CTP class C cirrhosis; increase as tolerated.
ofosbuvir/velpatasvir	1–6	Recommended	24 wk	I, A[e]	Applicable to patients who are ribavirin ineligible.
edipasvir/sofosbuvir + weight-based ribavirin	1, 4, 5, 6	Recommended	12 wk	I, A[f]	Low initial dose of ribavirin (600 mg) is recommended for patients with CTP class C cirrhosis; increase as tolerated.
edipasvir/sofosbuvir	1, 4, 5, 6	Recommended	24 wk	I, A[f]	Applicable to patients who are ribavirin ineligible.

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Metabolic Dysfunction Associated Steatotic Liver Disease (MASLD)

- Hepatic steatosis
- Plus one of the following:
  - Overweight/obese
  - T2DM or
  - Evidence of two or more features of metabolic dysfunction. (1in 3 US adults)
    - Large waistline
    - HTN
    - High Blood Sugar
    - High Triglycerides
    - Low HDL

Eslam M, Newsome PN, Sarin SK, et al. A new definition for metabolic dysfunction-associated fatty liver disease: an international expert consensus statement. J Hepatol 2020;73:202–9.

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Epidemiology of MASLD

- Most common liver disease worldwide and the leading cause of liver-related morbidity and mortality
- 44.5% in men and 31.8% in women
- Highest estimate for North America is (47.8%)

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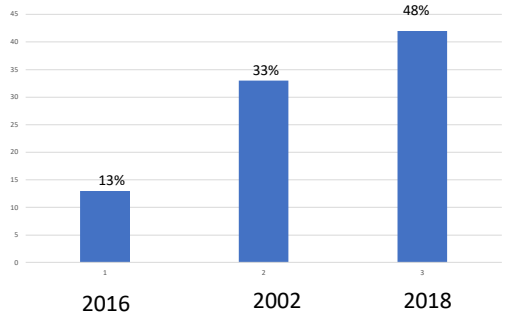
Epidemiology of Obesity
% of Adult US population



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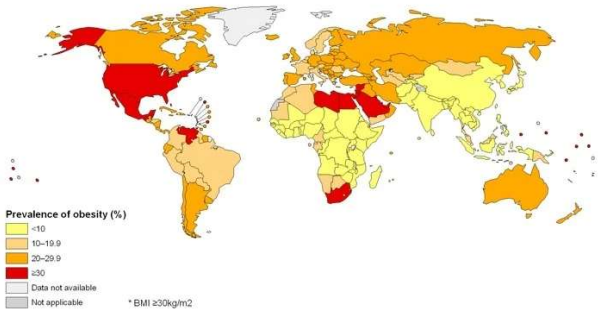
Global Obesity Trends (W.H.O.)



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Testing For MDAFLD

- Risk stratification for significant or advanced fibrosis in NAFLD
- Fibrosis-4 index
- NAFLD fibrosis score
- Biomarkers of fibrosis (such as the Enhanced Liver Fibrosis test)
- Transient Elastography

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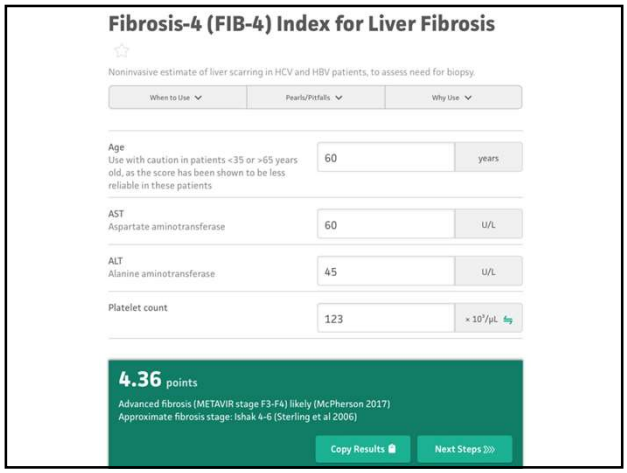

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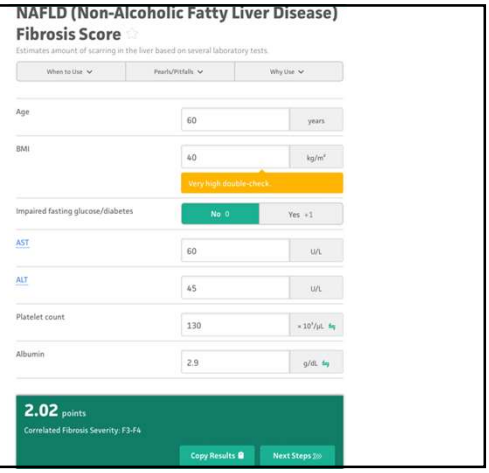

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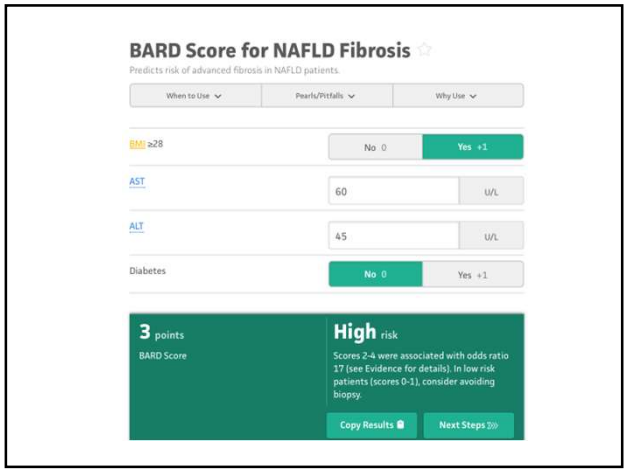

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Magnetic Resonance Imaging

- Biomarker-based prevalence reports underestimate NAFLD prevalence by approximately half, compared with imaging modalities
- Biopsy is gold standard but has morbidity, sampling errors and cost
- Non-invasive magnetic resonance proton density fat fraction
  - "Gold Standard"

Caussy C et al Noninvasive, quantitative assessment of liver fat by MRI-PDFF as an endpoint in NASH trials. Hepatology. 2018; 68: 763-772

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American College of Radiology Guidelines

- MR Elastography is the most accurate for dx and staging of fibrosis but not universal availability
- U/S Shear wave elastography (SWE) has some limitations in obese people
- US and CT are the preferred modality for screening for HCC in those with cirrhosis

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American College of Radiology Guidelines elevated LFT

Variant 1: **Abnormal liver function tests. Hepatocellular predominance with mild aminotransferase increase. Initial imaging.**

Procedure	Appropriateness Category	Relative Radiation Level
US abdomen	Usually Appropriate	O
US duplex Doppler abdomen	Usually Appropriate	O
US shear wave elastography abdomen	May Be Appropriate	O
MR elastography abdomen	May Be Appropriate	O
MRI abdomen without and with IV contrast with MRCP	May Be Appropriate	O
MRI abdomen without IV contrast with MRCP	May Be Appropriate	O
CT abdomen and pelvis without IV contrast	May Be Appropriate	☢☢☢
US abdomen with IV contrast	Usually Not Appropriate	O
CT abdomen and pelvis with IV contrast	Usually Not Appropriate	☢☢☢
CT abdomen and pelvis without and with IV contrast	Usually Not Appropriate	☢☢☢☢

https://acsearch.acr.org/docs/3158167/Narrative accessed 12_17_2023

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American College of Radiology Guidelines Liver fibrosis

Variant 1: **Chronic liver disease. Diagnosis and staging of liver fibrosis. Initial imaging.**

Procedure	Appropriateness Category	Relative Radiation Level
US shear wave elastography abdomen	Usually Appropriate	O
MR elastography abdomen	Usually Appropriate	O
MRI abdomen without and with IV contrast	May Be Appropriate	O
CT abdomen with IV contrast multiphase	May Be Appropriate	☢☢☢☢
MRI abdomen without and with hepatobiliary contrast	May Be Appropriate	O
MRI abdomen without IV contrast	May Be Appropriate	O
US abdomen	May Be Appropriate	O
US duplex Doppler abdomen	May Be Appropriate	O
US abdomen with IV contrast	May Be Appropriate	O
CT abdomen without and with IV contrast	Usually Not Appropriate	☢☢☢☢
CT abdomen without IV contrast	Usually Not Appropriate	☢☢☢
FDG-PET/CT skull base to mid-thigh	Usually Not Appropriate	☢☢☢☢

https://acsearch.acr.org/docs/3098416/Narrative/ accessed 12_17_2023

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Treatment for MDAFLD

- Lifestyle and behavior change
- There are **no drugs** licensed for MDAFLD
- Several drugs are currently in advanced phase trials
- Vitamin E research is inconclusive
- Pioglitazone also inconclusive
- Statins are safe but don't address MDAFLD

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Other Causes of Cirrhosis

- Hemochromatosis
- Primary Biliary Cirrhosis
- Wilson Disease…. Remember Copper
- Toxic Liver Disease
  - Poisons and Medications
  - Including Acetaminophen
- Alcohol

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Alcohol with other Liver Disease

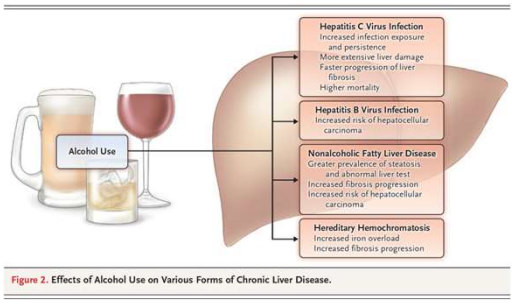

Figure 2. Effects of Alcohol Use on Various Forms of Chronic Liver Disease.

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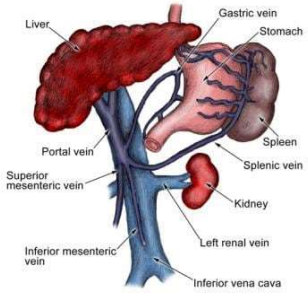
NOW… Transition to Cirrhosis



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Prognosis ~ 10 x worse!

- **Compensated** cirrhosis risk of death **4.7** x the general population
- **Decompensated** cirrhosis is associated with a risk that is **9.7** x
- Decompensated, if still drinking…. < 6m

9.7x

4.7x

Baseline

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Life Expectancy

- Life expectancy of a patient with **compensated** cirrhosis is 10 to 13 years
- Life expectancy may be as low as **2 years** if there is **decompensation**
- Cirrhosis from alcohol, 65% of the patients who abstain from drinking alcohol are alive at 3 years
- **0% (NOONE)** alive at 3 years if **continue drinking** alcohol

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Mean Arterial Pressure (Nitric Oxide) and prognosis

- Probability of survival among patients with a mean arterial pressure of **82 mm Hg** or less was 20% at 24 months and 0% at 48 months
- If MAP > 82: 70% at 24 months and 50% at 48 months

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Vasodilation Hypothesis Adaptive Compensatory Response

- Peripheral vasodilation
- Reduced systemic vascular resistance
- Fluid sequestration in peritoneum
- Arterial underfilling
- Neurohormonal salt retention
- Renin-Angiotensin-Aldosterone system activation
  - To counteract low arterial pressures
- Plasma and blood volume increase but effective arterial volume is reduced
- Sodium Retention and Ascites

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Cirrhosis Sequelae

- Progressive liver injury and **fibrosis** resulting in portal hypertension and **decompensation**
- Ascites
- Spontaneous bacterial peritonitis (SBP)
- Hepatic encephalopathy
- Variceal hemorrhage
- Hepatorenal syndrome
- Hepatocellular carcinoma
- Splenomegaly and Thrombocytopenia

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Ascites Management

- Diagnosis of Ascites: Physical Exam
  - Circumference, Percussion, Puddle Sign?
  - Imaging: U/S, CT
  - Serum-ascites albumin gradient (SAAG) helps determine whether peritoneal fluid is a transudate or an exudate.
- Quantification with u/s or Paracentesis
- Low Volume Paracentesis with u/s guidance
- High Volume Paracentesis (>5L) needs albumin replacement
- Ascitic Fluid Assessment:
  - Infected or not? WBC and culture
  - Malignant or not?
- For Pleural Effusion avoid Thoracentesis!

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Ascites

- Ascitic Fluid Assessment:
  - Infected or not? WBC and culture
  - Malignant or not?
- Sodium restriction (i.e., no more than 2,000 mg per day)
- Diuretics (e.g., oral spironolactone [Aldactone] 100 mg and furosemide [Lasix]) 20 mg
- Complete abstention from alcohol
- For Pleural Effusion avoid Thoracentesis!

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Spontaneous Bacterial Peritonitis (SBP)

- A neutrophil count >250/mL = high risk for SBP
- Start immediate empiric antibiotic therapy.
- SBP is associated with a high mortality rate in patients with cirrhosis and ascites (SOR A)
- Bacterial infections account for 25%–46% of hospitalizations due to acute decompensation events in patients with cirrhosis
- Cultures may be helpful but are negative in a significant percentage of patients with SBP
- Cultures may take 48–72 hours and waiting on results would delay treatment in high-risk patients
- Long-term prophylaxis with norfloxacin or trimethoprim/sulfamethoxazole is indicated after first episode

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Varices

- Upper endoscopy to evaluate for varices. Endoscopic banding is the standard treatment, but sclerotherapy with vasoconstrictors (e.g., octreotide) also may be used
- Transjugular intrahepatic portosystemic shunt (TIPS) has been effective in reducing portal hypertension and improving symptoms of hepatorenal syndrome
- Can reduce gastrointestinal bleeding in patients with refractory variceal hemorrhage but worsen encephalopathy

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Other Critical Liver Functions

- Decreased protein manufacture causing edema
- Decreased coagulation proteins- check INR
- Detoxification by glucuronyl transferase and other processes
- Metabolism of medications - adjust dosages
  - Avoid benzodiazepines
- Decreased metabolism of nutrients
- Decreased effective storage of energy

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Hepatic Encephalopathy Sx

- Sleep-wake cycle disturbance
- intellectual function deterioration
- memory loss
- Inability to communicate effectively at any level
- Personality changes
- Possibly, displays of inappropriate or bizarre behavior

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Hepatic encephalopathy

- Difficult management problem
- Frequent readmissions
- Absorption of toxins from micro bacterial fermentation
- Neomycin was previously recommended
- Now Fixadomycin (DIFICID)
  - Need to consider Needy MEDS ($4,800/ mo Good Rx)
- Also Lactulose
- Psychological inventories
- Identifying a care-giver to administer lactulose

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Variceal hemorrhage

- Non Selective Beta Blockers for Prevention
- Endoscopic Diagnosis
- Endoscopic Treatment
- Octreotide for acute bleed
- Endoscopic Surveillance
- Prognosis declines with every bleed
- The Window Hypothesis for Beta Blockers

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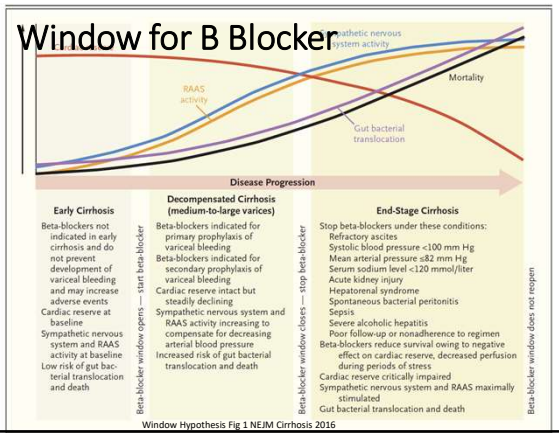
Window for B Blocker



Window Hypothesis Fig 1 NEJM Cirrhosis 2016

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Splenomegaly & Thrombocytopenia

- A low platelet count should be a clue to consider portal hypertension & splenomegaly
- Usually improves if liver disease improves
- Criteria for Platelet Transfusion ~ 25
- Caution with anticoagulants and antiplatelets
- Not only Monitor INR
- Monitor clotting time?
- When considering risk/ benefit of a surgery, consider bleeding risk

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Hepatocellular carcinoma HCC

- Obesity
- Diabetes
- Steatohepatitis
- Metabolic associated fatty liver

- Each independently associated with an increased **risk of hepatocellular carcinoma.**

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Liver Transplant?

- **Early referral** to a transplant subspecialist is recommended
- Liver Transplant is effective at both survival and cost-effectiveness even for those with Alcohol Use Disorder
- Potential transplant recipients need time for patients, families, referring physicians, and transplant centers to meet and identify any potential problems
- Increasing pool of liver donors

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Summary

- Epidemiology: Hep C & MASLD
  - Hep C Universal Screening
  - Perinatal Hep B intervention
  - Universal Hep B vaccination
- Interventions:
  - Diet/Exercise/Weight Management for MASLD
    - Evaluate for fibrosis
    - Try to prevent progression of fibrosis
  - Alcohol Abstinence for all causes of Liver Disease
  - Transplant Evaluation
  - Itemize all the related Portal Hypertension Complications.
- Early Liver Transplant Evaluation

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