Case #1
Managing Chronic Hepatitis B and Complications of Decompensated Cirrhosis

Kristen Godett, NP

Jessica Jennings, NP

Eugenia Tsai, MD

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Case

A 57-year-old male referred for new-onset abdominal swelling and abnormal liver tests.

- ROS: Fatigue, episodes of forgetfulness and confusion
- Medical history: None
- Medications: None
- OTC: Turmeric, was told he had elevated liver tests, so he started supplement for “liver health”.
- Social history: No alcohol use, no tobacco use, no history IVDU

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Physical Exam

- Vital Signs: Stable
- Eyes: Nonicteric
- Skin: No jaundice, +telangiectasia
- Abd: Distended, fluid wave, not tympanitic
- Lower extremities: No edema
- Neuro: AAOx4, no asterixis

https://www.thehealthsite.com/diseases-conditions/ascites/; https://healthjade.com/spider-angioma/

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Pertinent Initial Labs

Lab	Value
WBC	4.5
Hb	12.0
Plt	120
INR	1.2

Lab	Value
AST	78
ALT	97
ALP	110
Tb	1.5
Alb	3.0

What is causing elevated liver tests?

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Differential Diagnosis

- N[illegible]D/MA[illegible]D?
- Alc[illegible]
- Su[illegible]pplements/DILI?

- Viral?
- Autoimmune?
- Genetic?
- Rare??

What do you do next?

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Next Steps

- Chronic liver disease labs
  - Autoimmune workup (ANA, AMA, ASMA, immunoglobulins) negative
  - Hep C negative
  - Hep B: HBsAg positive, eAg positive, HBV DNA 780,000
  - Ceruloplasmin 25
  - Ferritin 100

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Abdominal US

- Free fluid surrounding liver
- Nodular contour of liver surface

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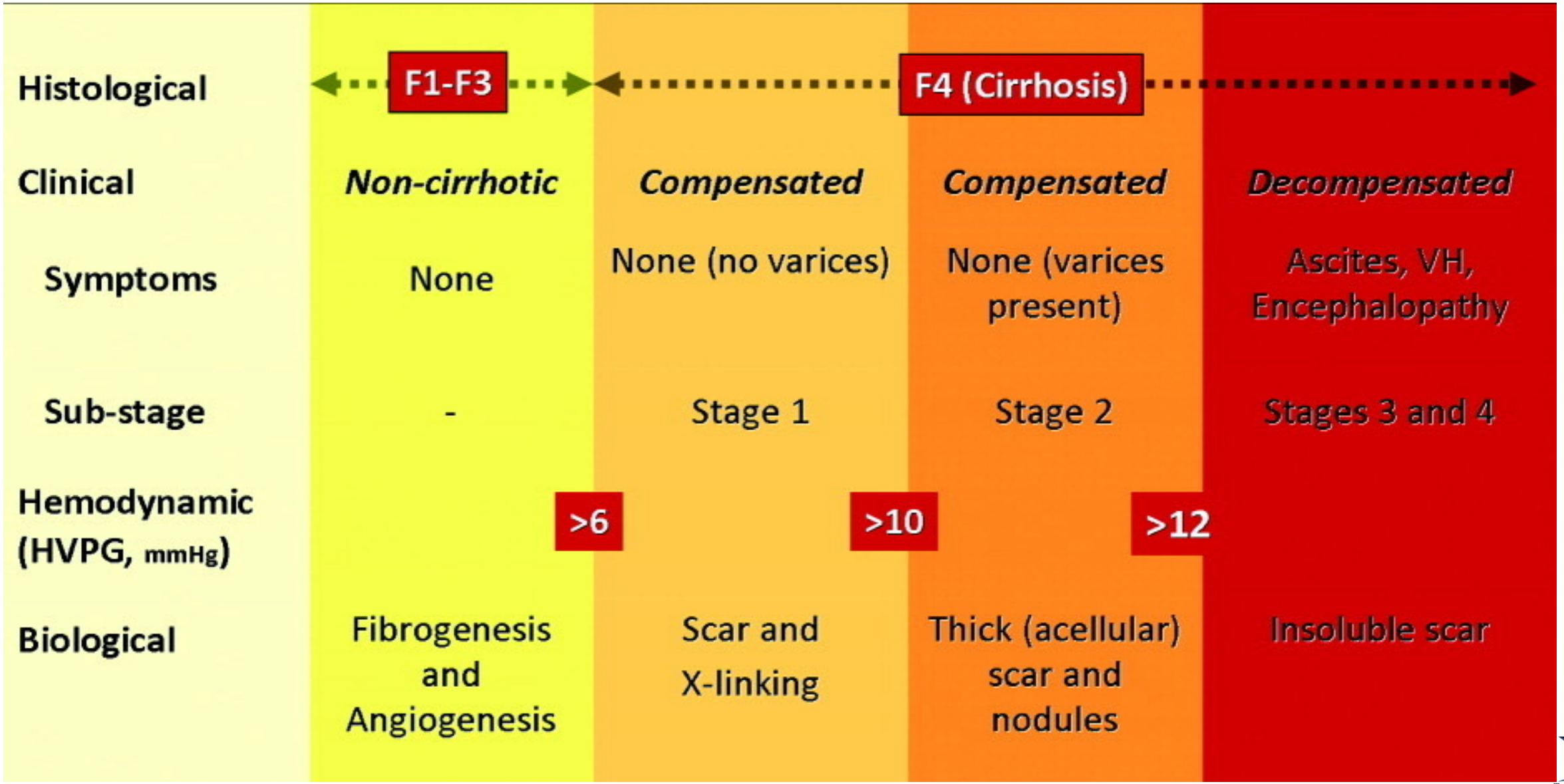
Cirrhosis Decompensations



AASLD 2010

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Assessment

Cirrhosis

Decompensated by ascites

Etiology: Chronic hepatitis B

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Managing Chronic Hepatitis B

Eugenia Tsai, MD

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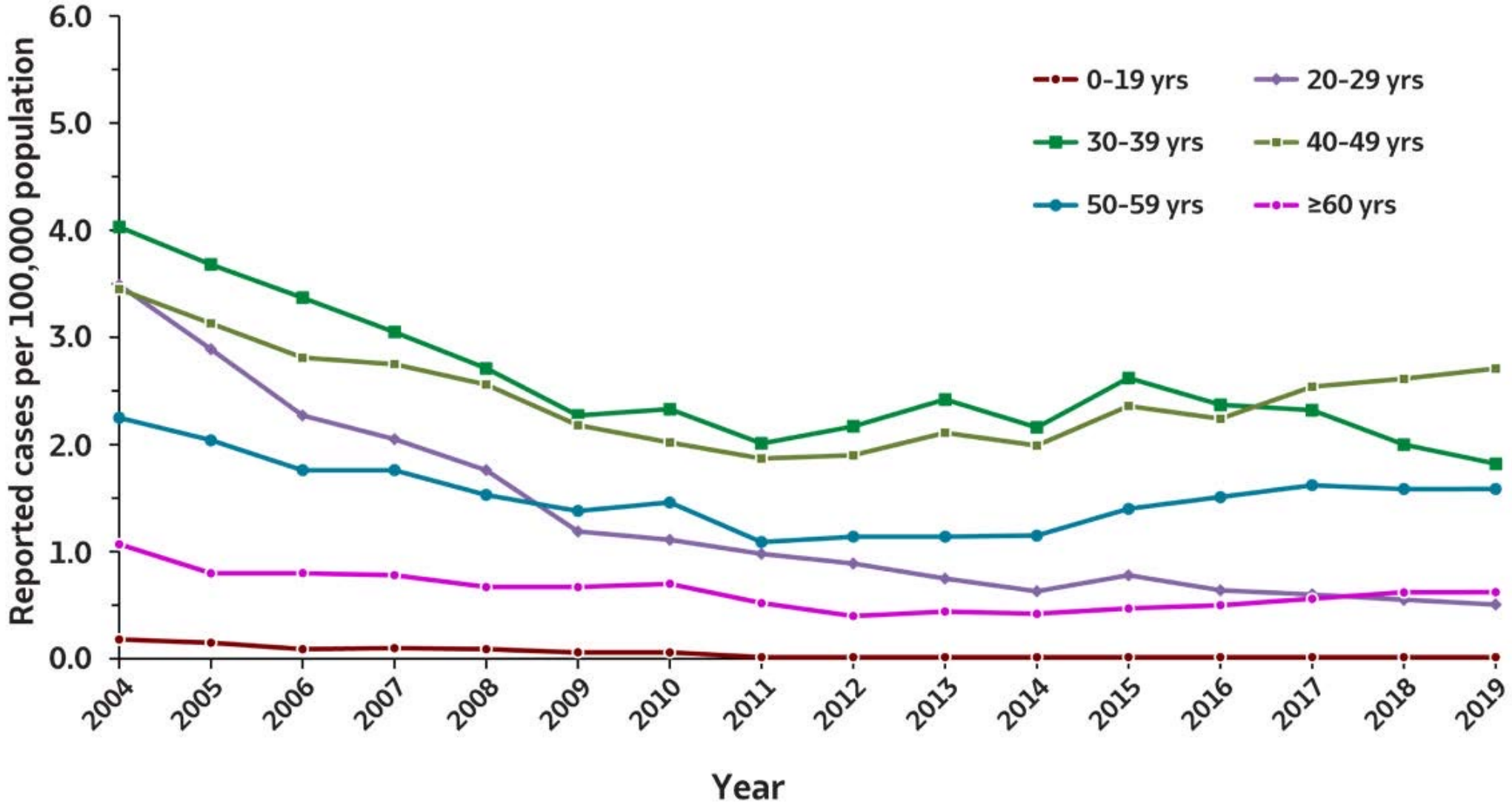
Acute Hepatitis B Virus Infection (2004-2019)



CDC 2019

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Hepatitis B in United States

Hepatitis B in 2021

Acute Hepatitis B

2,045
There were 2,045 new cases of acute hepatitis B reported during 2021

13,300
There were 13,300 estimated acute hepatitis B virus infections during 2021

Chronic Hepatitis B

14,229
There were 14,229 cases of newly reported chronic hepatitis B during 2021

5.9
There were 5.9 newly reported cases of chronic hepatitis B per 100,000 people during 2021

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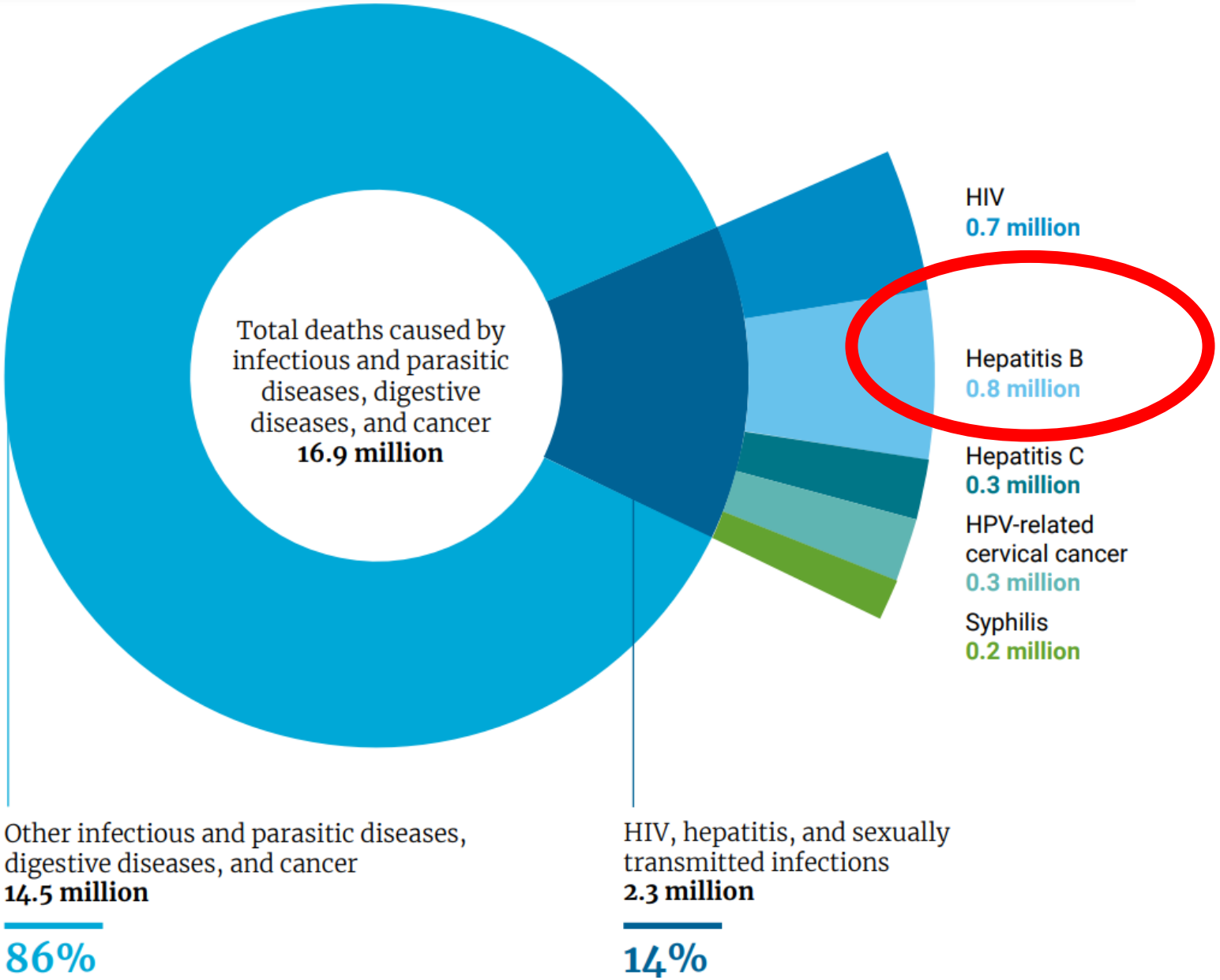
WHO 2021, CDC 2023

2019 Deaths from HBV



World Health Organization, Geneva 2021

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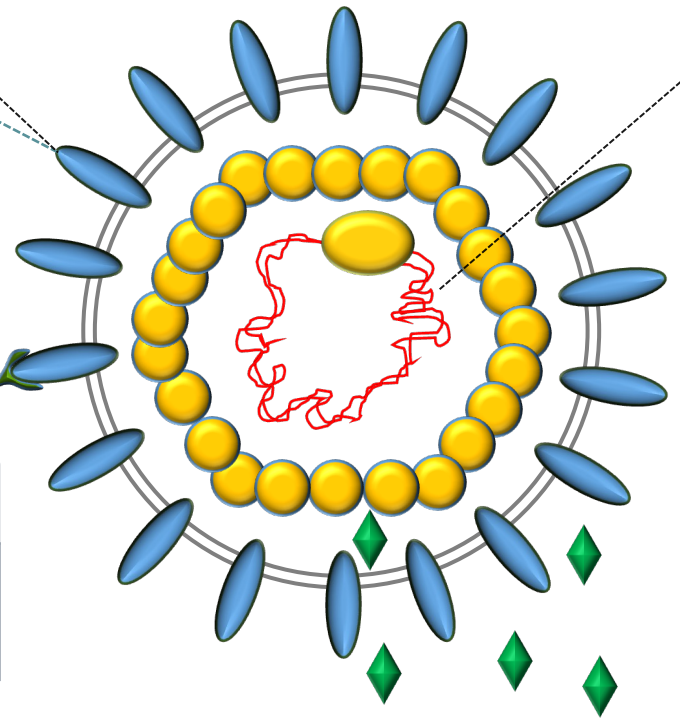
Serologic Markers in HBV Infection



HBsAg

- The HBV surface antigen is the standard marker of infection
- Presence in serum >6 months defines CHB

Anti-HBs

- Antibody to HBsAg
- Marker of immunity to HBV

HBV DNA

- Indicates ongoing viral replication
- Levels correlate with replication and infectivity

Anti-HBc

- Antibody to the HBV core antigen can be used as a marker of infection

HBeAg

- Hepatitis B e antigen is used clinically as index of viral replication and infectivity

Hepatitis B. WHO (2017)

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Interpreting HBV Screening Tests

Possible Test Results				
HBsAg	+	–	–	–
Anti-HBs	–	+/–	+	–
Anti-HBc	+	+	–	–
Interpretation	Acute or chronic infection*	Exposure to HBV At risk for reactivation	Immune due to vaccination	At risk for HBV infection
Action	Evaluation and further testing	Follow up as appropriate	No further action required	Vaccinate

*Patient is chronically infected if HBsAg+ for ≥6 months. Patients with acute infection will be positive for anti-HBc IgM.

Terrault NA et al. *Hepatology*. 2018; Abara WE et al. *Ann Intern Med*.

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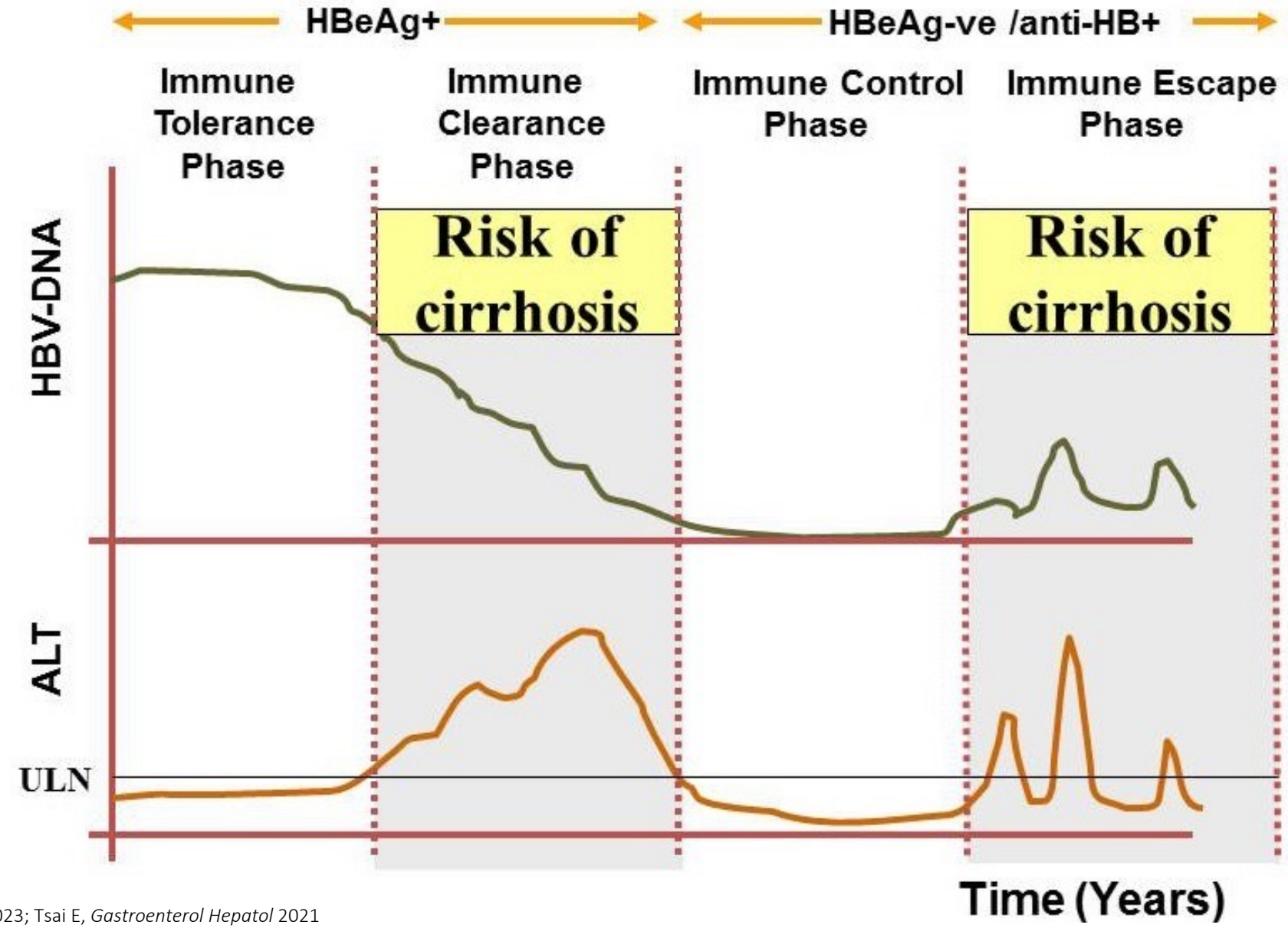
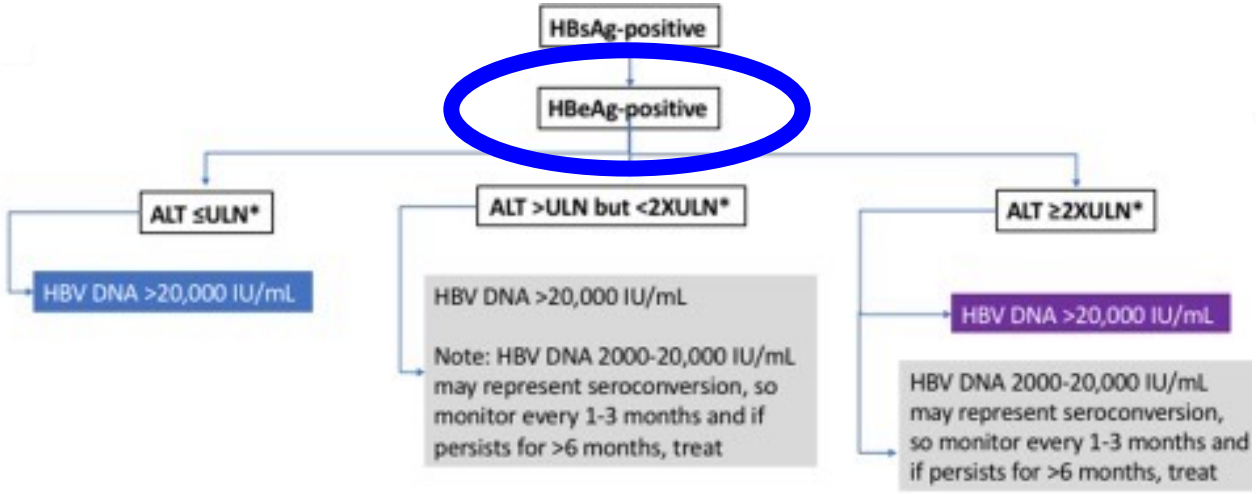
Phases of HBV infection



GPnotebook *accessed Aug* 2023; Tsai E, *Gastroenterol Hepatol* 2021

When to Treat

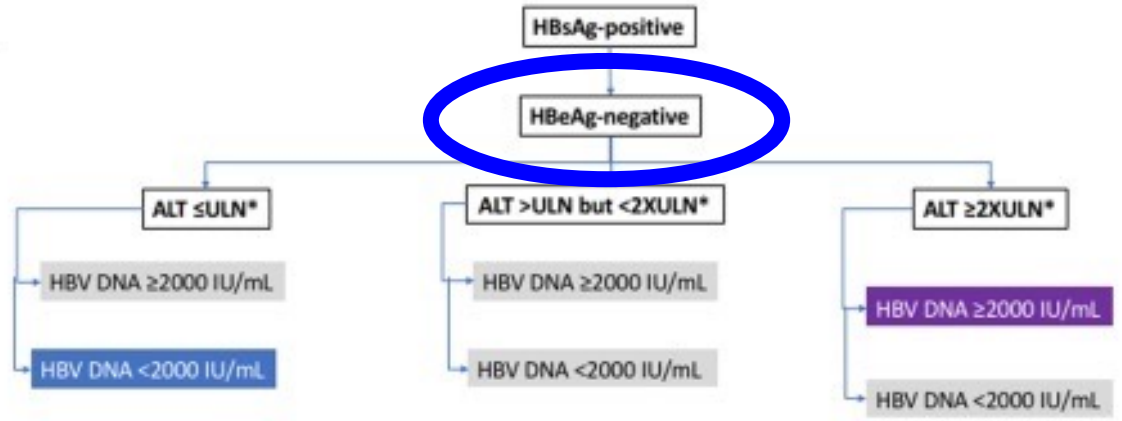


Recommendations:

Treat

Do not treat. Monitor with ALT and HBV DNA levels every 3-6 months and HBeAg every 6-12 months.

Exclude other causes of ALT elevation and assess disease severity with non-invasive tests and/or liver biopsy. If staging indicates ≥F2 or ≥A3, treat. If other causes of ALT >ULN excluded and elevation persists, treat, especially if age >40.



Recommendations:

Treat

Do not treat. Monitor with ALT and HBV DNA levels every 3-6 months and HBsAg annually.

If ALT ≤ULN, monitor ALT and HBV DNA every 3 months for 1 year, then every 6 months.
If ALT elevated, exclude other causes of ALT elevation and assess disease severity with non-invasive tests and/or liver biopsy. If staging indicates ≥F2 or ≥A3, treat. If persistent ALT >ULN with HBV DNA ≥2000 IU/mL, treat, especially if age >40.

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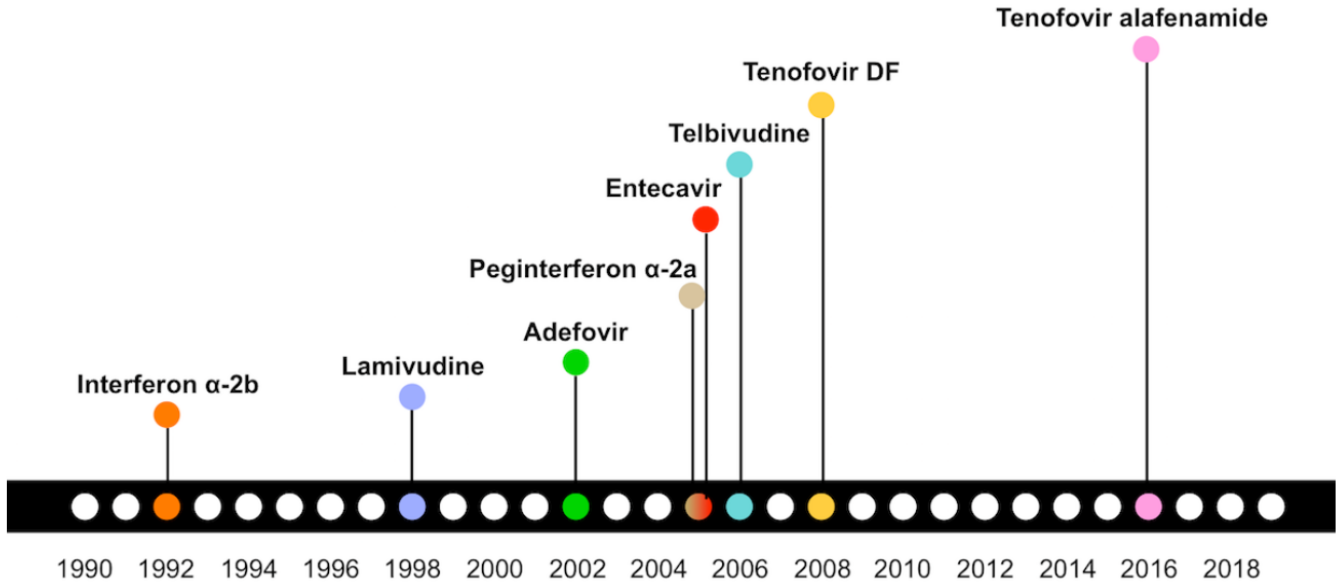
FDA-Approved Agents for Treatment of HBV

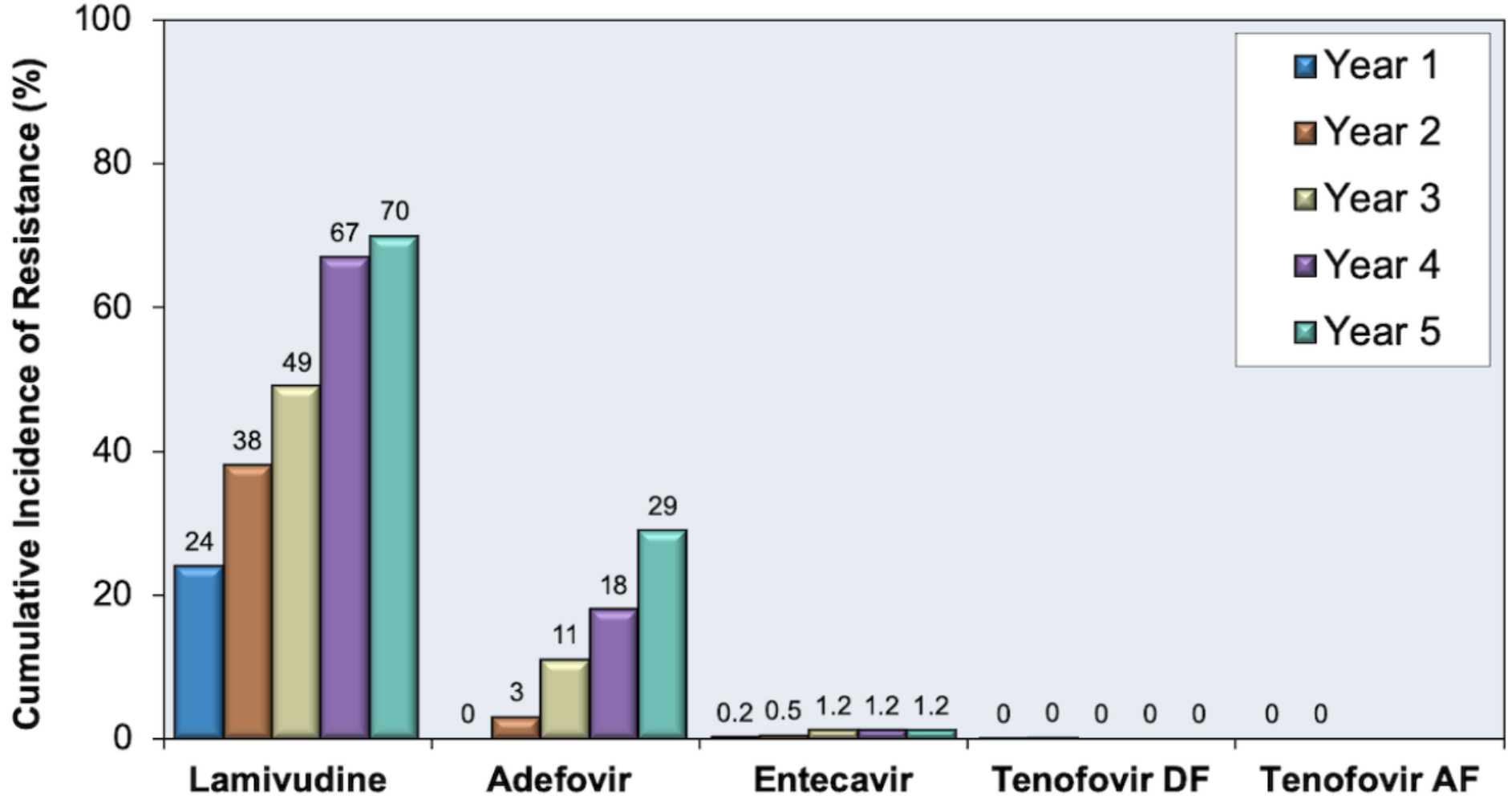


Key Characteristics of Oral Antiviral Agents Used to Treat HBV*

Medications	Trade Name	Category	Oral Dosing (Adults)	Potency	Barrier to Resistance
Adefovir	*Hepsera*	Nucleotide analogue	10 mg once daily	Low	Moderate
Entecavir	*Baraclude*	Nucleoside analogue	0.5 mg once daily^	High	High
Lamivudine	*Epivir-HB*	Nucleoside analogue	100 mg once daily	Moderate	Low
Tenofovir alafenamide	*Vemlidy*	Nucleotide analogue	25 mg once daily	High	High
Tenofovir DF	*Viread*	Nucleotide analogue	300 mg once daily	High	High

Kim HN *Hepatitis B Online*; updated 2020, accessed Aug 2023

Cumulative Incidence of HBV Resistance



EASL 2017

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Recompensation

- Treatment can lead to profound viral suppression
  - Amelioration of necroinflammation
  - Regression of fibrosis in most patients with chronic hepatitis B
- Recompensation
  - No further occurrence of decompensating events as a result of the removal or effective control of the underlying etiology.
- BAVENO VII criteria (fulfillment of all 3):
  1. Removal/suppression/cure of the primary etiology of cirrhosis
  2. Resolution of ascites (off diuretics), encephalopathy (off lactulose/rifaximin), and absence of recurrent variceal hemorrhage (for at least 12 months)
  3. Stable improvement of liver function tests (albumin, INR, bilirubin)

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Update: All adults should be tested at least once for hepatitis B. Have you been tested?

- Hepatitis B infection can cause liver cancer and early death
- Most people with the virus don't know they have it
- Treatment is available — schedule your screening today

CDC

bit.ly/mr7201a1

MARCH 10, 2023

MMWR

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The CDC recommends:

1. Hepatitis B vaccination for all adults aged 19 to 59 years

2. Hepatitis B testing for all adults at least once in their lifetime (**new**)

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So Back to Our Case

- HBsAg positive, HBeAg positive, HBV DNA 780,000 and ALT >2xULN
- Would you start Hep B treatment?

- Started Vemlidy for chronic HBV in our decompensated cirrhosis patient.
- Started diuretics for ascites.

At 4 week follow up

- Abdominal distention resolved.
- Worsening forgetfulness and confusion.

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Any ideas on what could be the cause of patient's confusion?

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Understanding Hepatic Encephalopathy

Kristen Godett, NP

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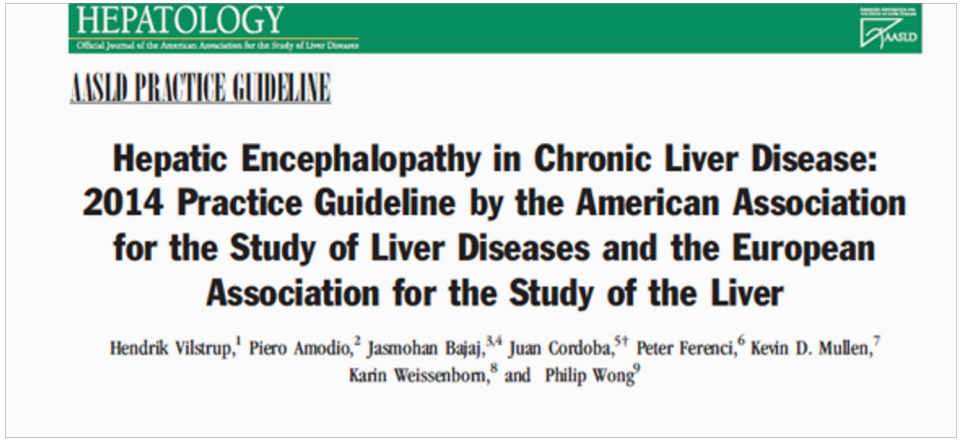
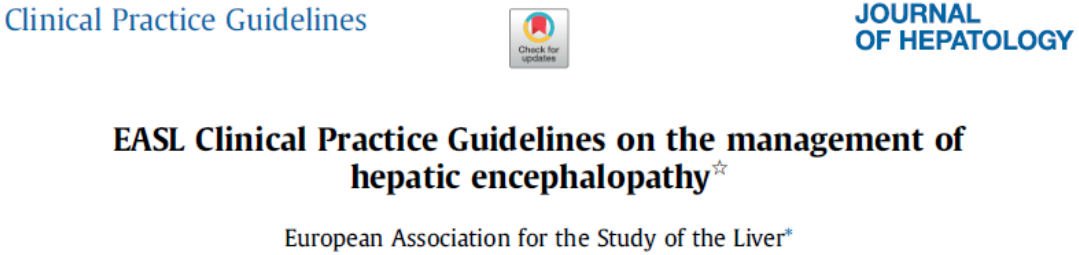
Hepatic Encephalopathy (HE)


HEPATOLOGY
Official Journal of the American Association for the Study of Liver Diseases

AASLD PRACTICE GUIDELINE

Hepatic Encephalopathy in Chronic Liver Disease: 2014 Practice Guideline by the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver

Hendrik Vilstrup,[1] Piero Amodio,[2] Jasmohan Bajaj,[3,4] Juan Cordoba,[5†] Peter Ferenci,[6] Kevin D. Mullen,[7] Karin Weissenborn,[8] and Philip Wong[9]


Clinical Practice Guidelines

JOURNAL OF HEPATOLOGY

EASL Clinical Practice Guidelines on the management of hepatic encephalopathy☆

European Association for the Study of the Liver*

- Hepatic encephalopathy is a brain dysfunction caused by liver insufficiency and/or portal systemic shunting.
- It manifests as a wide spectrum of neurological or psychiatric abnormalities ranging from subclinical alterations to coma.

Vilstrup H et al. *Hepatology*. 2014; EASL CPG. *Journal of Hepatology.* 2022.

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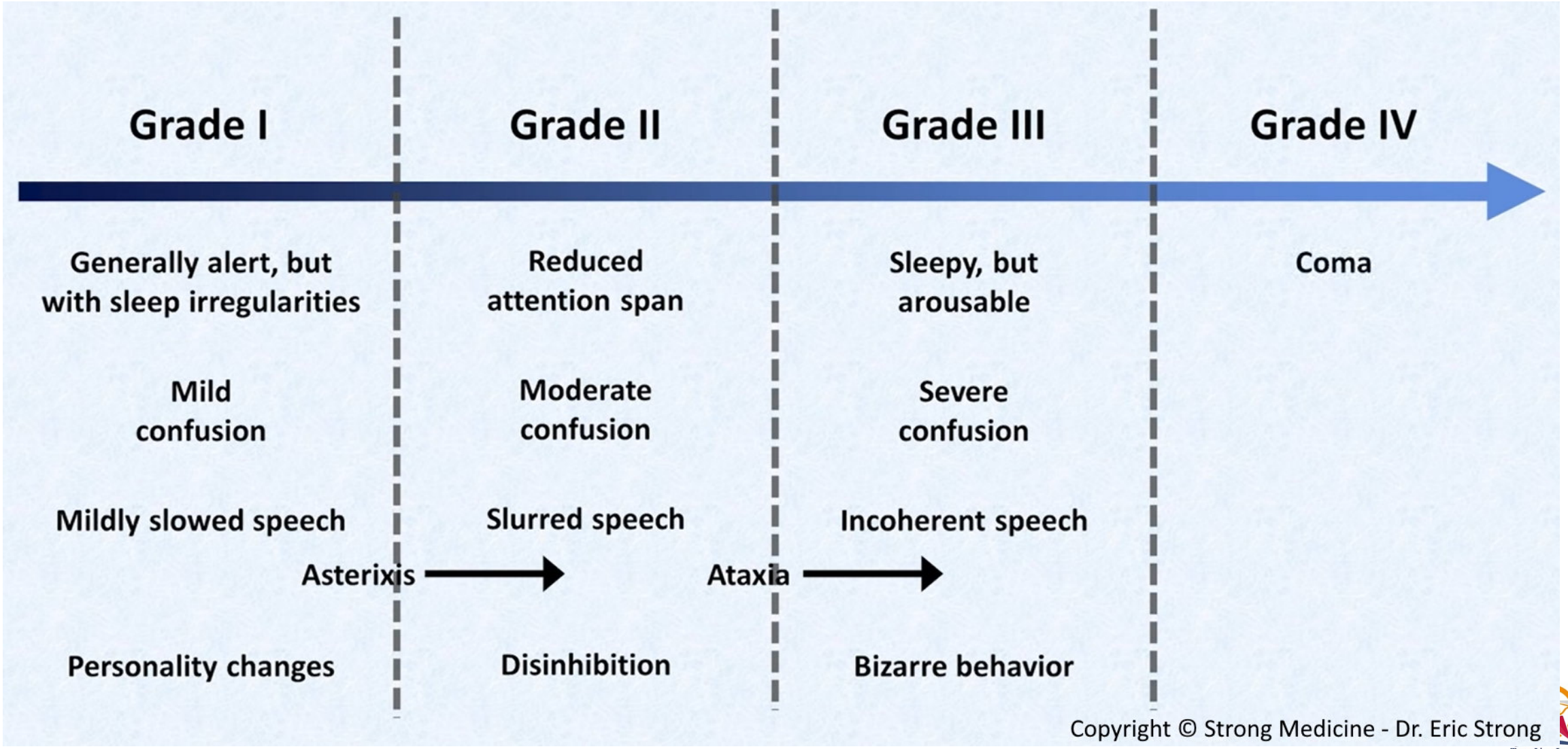
Hepatic Encephalopathy



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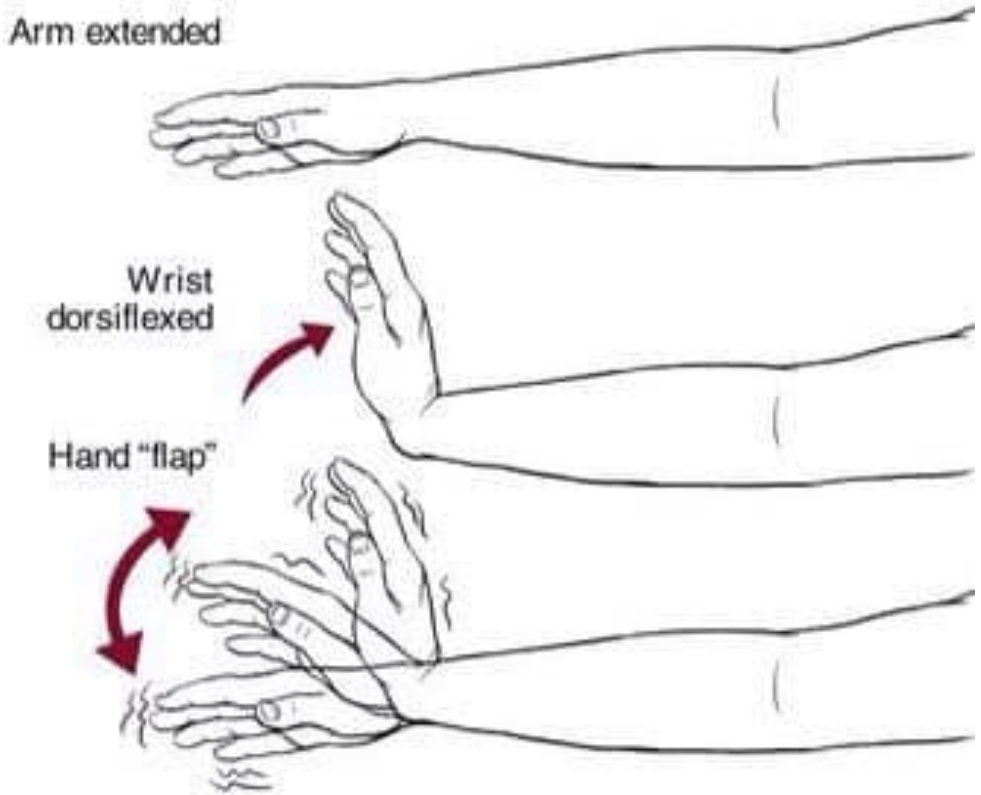
Physical Exam Findings for HE



Multiple factors effect accuracy of measured serum ammonia:

1. Fist clenching & use of tourniquet can falsely increase
2. Dependent on time to processing

Poor diagnostic accuracy for hepatic encephalopathy:

*given ammonia >55

- Sensitivity : 47%
- Specificity: 78%
- PPV: 77%
- NPV: 49%

Ammonia levels not associated with resolution of hepatic encephalopathy

TAKE HOME POINT:
Use your clinical evaluation to determine severity and tailor treatment to clinical findings

Ninan J & Feldman L. Aug 2017

Journal of HOSPITAL MEDICINE

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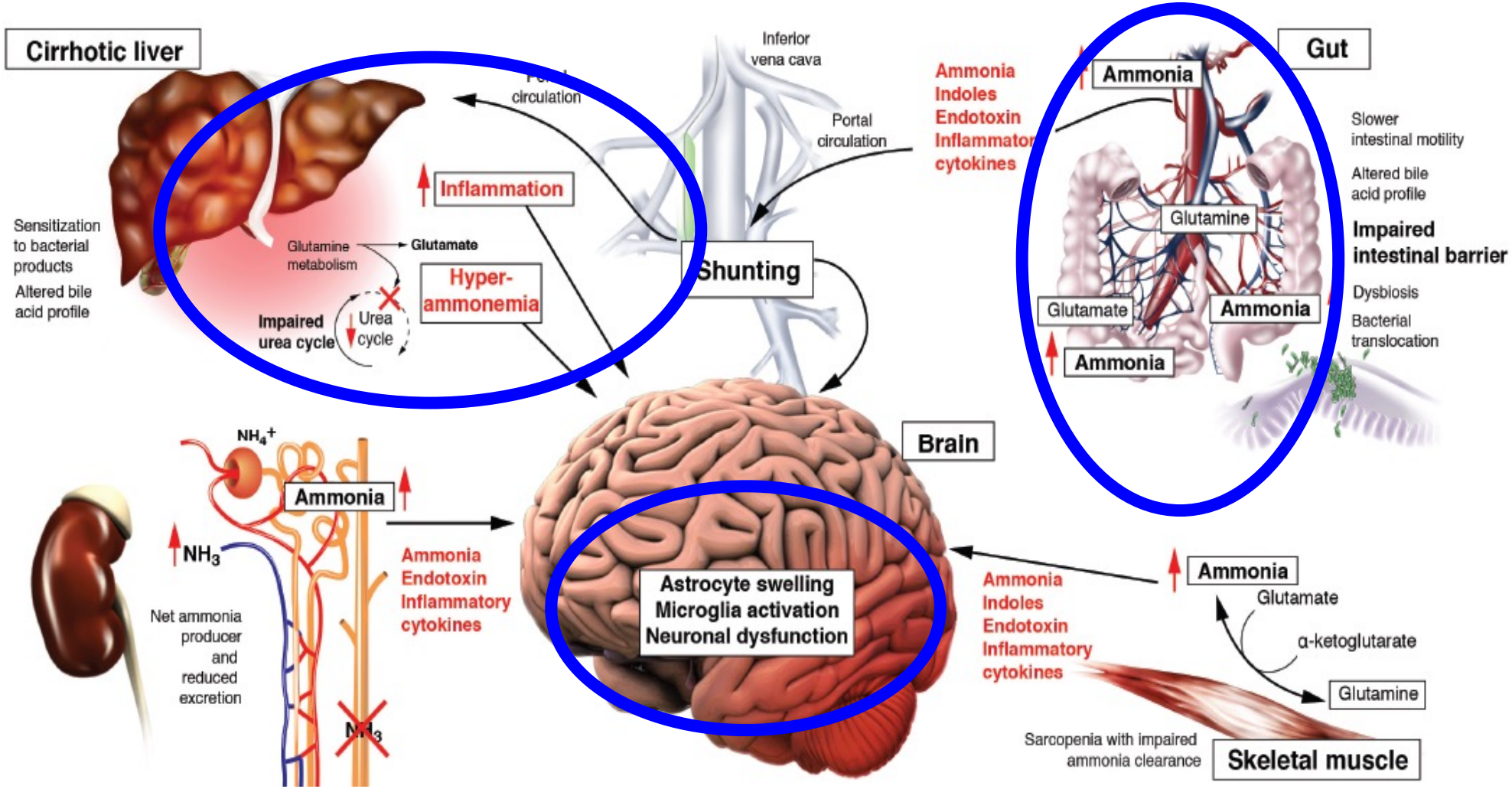
Pathophysiology of HE



Bajaj JS. *Hepatology*. 2015; Dasarathy et al. *J Hepatol*. 2016.

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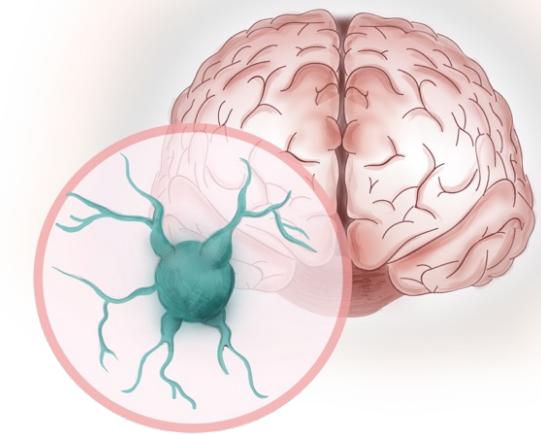
Precipitating Factors for HE



Increased ammonia production

- GI hemorrhage
- Excessive dietary protein (rare)
- Electrolyte imbalance (e.g., hypokalemia, hyponatremia)
- Constipation

Portosystemic shunts

- Spontaneous
- Iatrogenic (e.g., TIPS)

Other

- Drugs (e.g., opioids, benzodiazepines, sleep aids)
- Infections (e.g., SBP)
- Portal vein thrombosis
- Dehydration
- Malnutrition, sarcopenia

TIPS, transjugular intrahepatic portosystemic shunt; SBP, spontaneous bacterial peritonitis.
Vilstrup H et al. *Hepatology*. 2014;60(2):714-735.

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Approaches to HE Treatment

Four-pronged approach to management

- Initiation of care for AMS
- Search and treat alternative causes of AMS
- Identify and treat precipitating factors
- Commence empirical HE treatment

Vilstrup H et al. *Hepatology*. 2014.

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Treatment Options for HE

Drug Name	Drug Class	Indication
Lactulose	Poorly absorbed disaccharide	Decrease blood ammonia concentration Prevention and treatment of portal-systemic encephalopathy
Rifaximin	Non-aminoglycoside semi-synthetic, non-systemic antibiotic	Reduction in risk of overt hepatic encephalopathy (HE) recurrence
Neomycin	Aminoglycoside antibiotic	Not to be used, renal and ototoxic risk
Metronidazole	Synthetic antiprotozoal and antibacterial agent	Not approved for HE
Vancomycin	Aminoglycoside antibiotic	Not approved for HE

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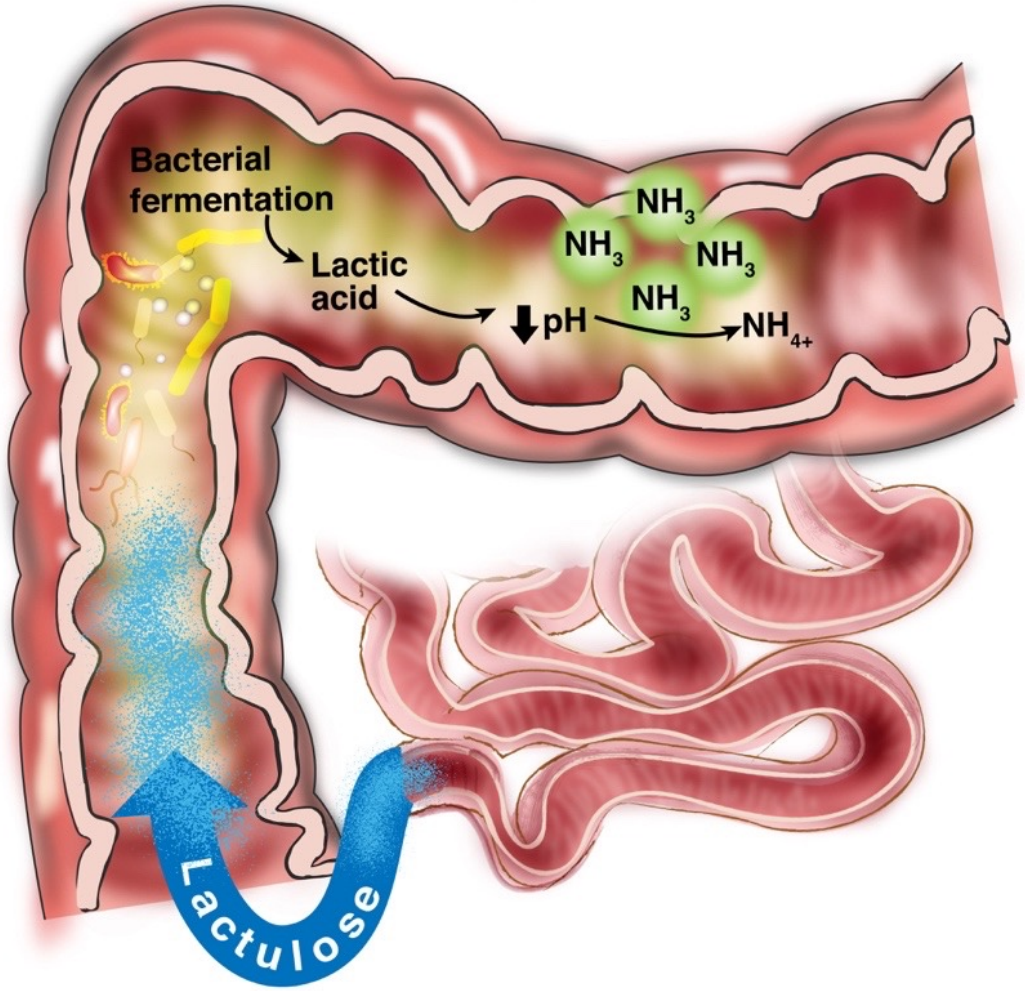
Lactulose for HE

- Current mainstay of HE therapy[1,2]
- Mechanism of action[2-5]
  - Non-absorbable disaccharide fermented by bacterial flora in the colon and metabolized to lactic acid, lowering colonic pH
  - Protonated NH_{4+} no longer easily absorbed across epithelial GI barrier
  - Cathartic effect can increase fecal nitrogen excretion with up to a 4-fold increase in stool volume



1. Vilstrup H et al. *Hepatology*. 2014;60(2):714-735; 2. Mullen KD et al. *Semin Liver Dis.* 2007;27(Suppl 2):32-47; 3. Conn HO et al. *Gastroenterology*. 1977;72:573-583; 4. Sharma P, Sharma BC, et al. *J Clin Exp Hepatol.* 2015;5:S82-S87; 5. Morgan MY et al. *Metab Brain Dis.* 2016;31:1361-1364.

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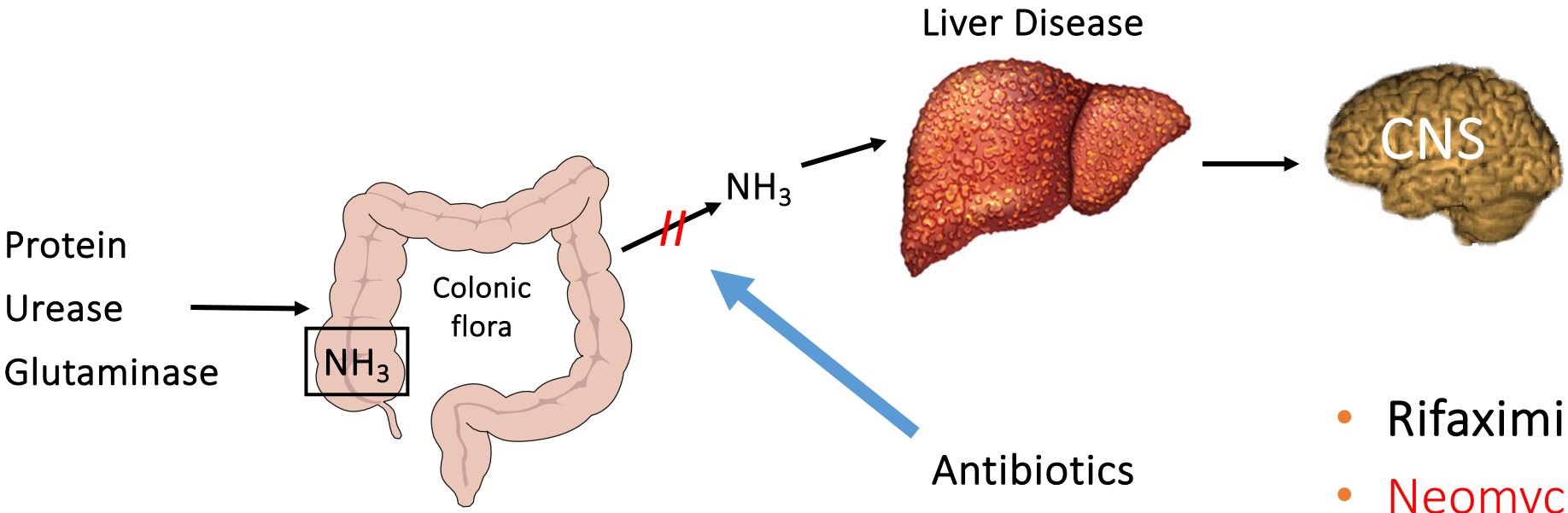
Antibiotics



- Rifaximin
- Neomycin
- Metronidazole
- Vancomycin
- Nitazoxanide

Antibiotics treat HE by

- Decreasing the bacteria that produce NH_3
- Modulating gut microbiota function
- Influencing bile acid, inflammatory mediators, neurotoxins
- Inhibiting enterocyte glutaminase

Gerber T, Schomerus H, et al. *Drugs*. 2000; Dasarathy S et al. *Indian J Gastroenterol*. 2003; Bajaj J et al. *Aliment Pharmacol Ther*. 2016.

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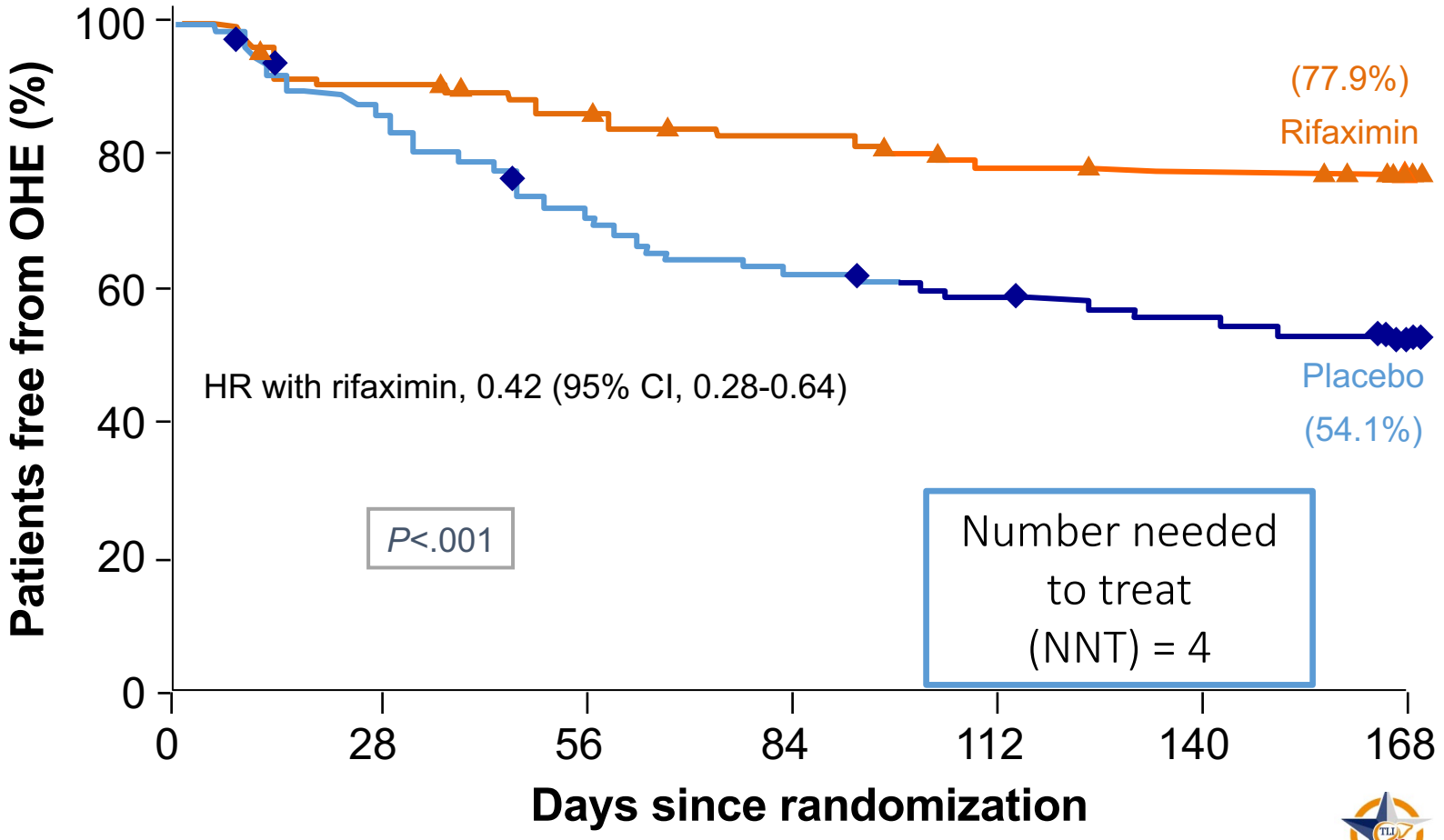
Secondary Prophylaxis of Overt HE: Rifaximin vs. Placebo

- RCT (n = 299)
- 2 or more prior overt HE events
- Rifaximin vs placebo
- **91% on lactulose in both arms**
- 6-month treatment
- Endpoint: Overt HE



Bass NM et al. *N Engl J Med*. 2010.

Management Goals for HE

- Provision for supportive care
- Identification and removal of precipitating factors (e.g., infection, GI bleed, dehydration)
- Correct electrolyte abnormalities
- Diet: Daily energy intake between 35-40 kcal/kg ideal body weight, daily protein intake of 1.2-1.5 g/kg/day (do not restrict protein), small meals/liquid nutritional supplements throughout the day with late-night snack
- Assessment of the need for long-term therapy
  - Control of potential precipitating factors
  - Higher likelihood of recurrent encephalopathy
  - Assessment of the need for liver transplantation
- Difficult on the caregiver so ensure necessary support

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HE Management for our Patient

- Lactulose initiated
- Along with rifaximin twice daily
- Resolution of confusion, better sleep cycles

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Overall Management Plan

Jessica Jennings, NP

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Overall Management Plan for Our Patient

- HBV management: Vemlidy, lifelong
- Ascites management: Started on furosemide 40 mg/d and spironolactone 100 mg/d
- HE management: Lactulose (titrate to bowel movements) + rifaximin
- HCC screening: Q6 month abdominal US + AFP
- Esophageal varices screening: Refer for EGD - clinically significant portal hypertension (Plt and kPa)
- Frequency of follow up: 3 months initially → 6 months when stable

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Q&A/Panel Discussion

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