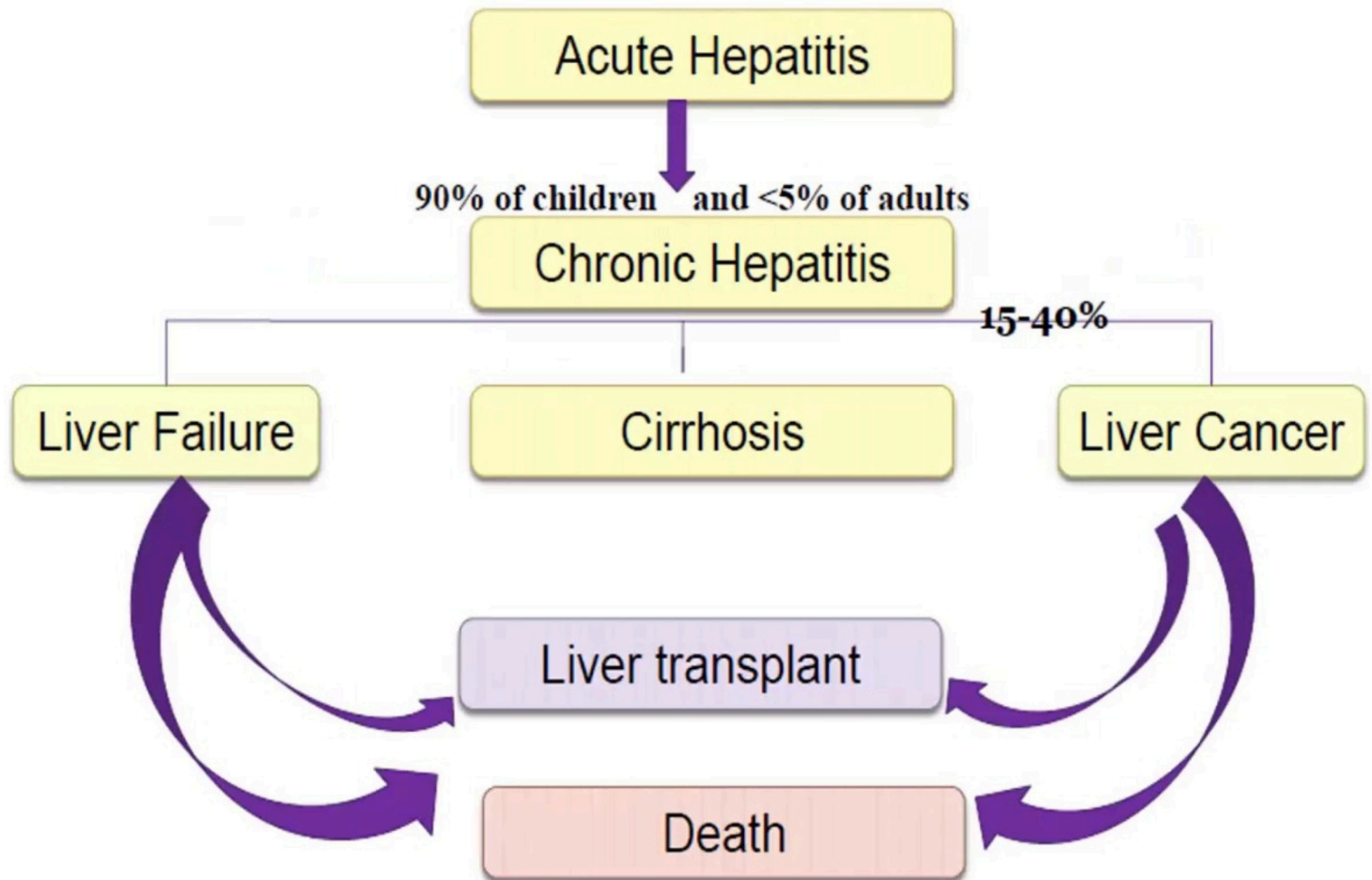


MANAGEMENT OF CHRONIC HEPATITIS B

•

Disease progression



Diagnostic Criteria

Chronic Hepatitis B (CHB)

1. HBsAg present for ≥ 6 months
2. Serum HBV DNA varies from undetectable to several billion IU/mL
3. Subdivided into HBeAg positive and negative. HBV-DNA levels are typically $>20,000$ IU/mL in HBeAg-positive CHB, and lower values (2,000-20,000 IU/mL) are often seen in HBeAg-negative CHB.
3. Normal or elevated ALT and/or AST levels
4. Liver biopsy results show chronic hepatitis with variable necroinflammation and/or fibrosis

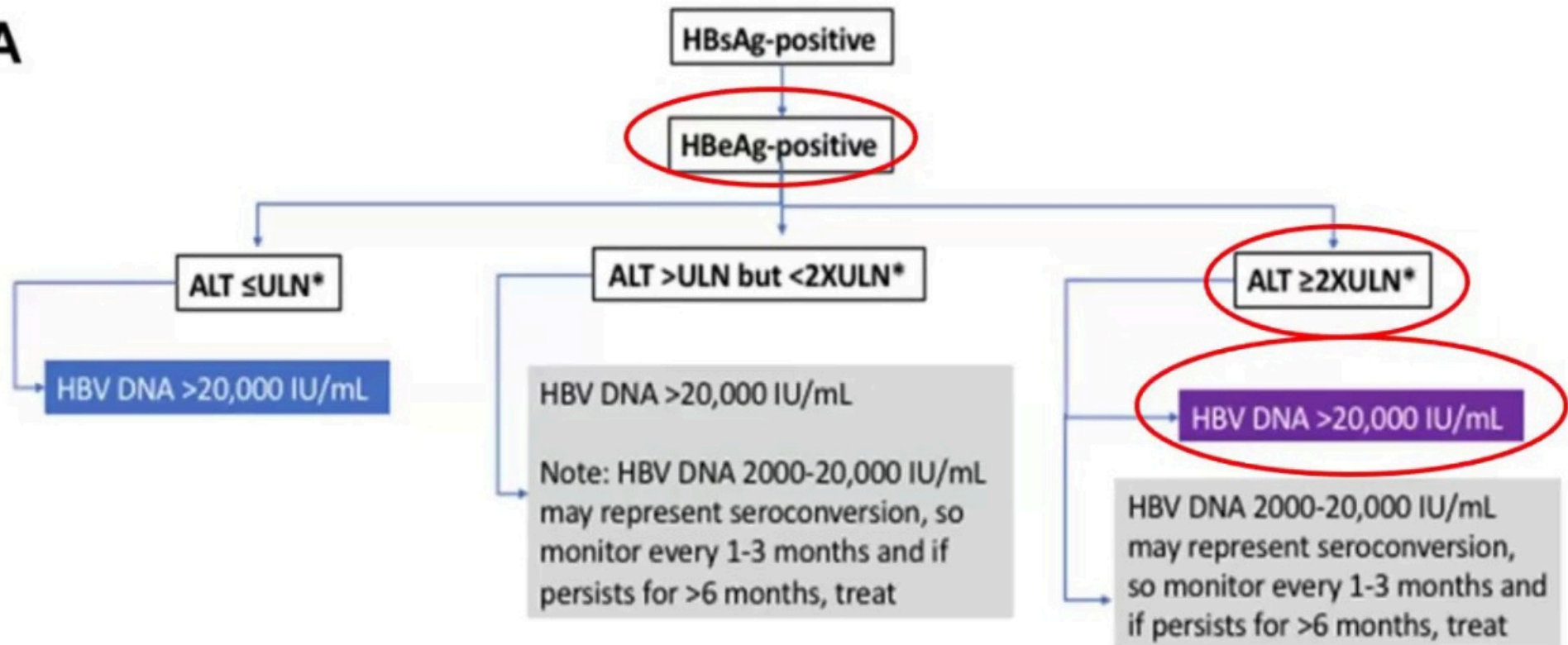
Goals of treatment

- Suppression of HBV replication to undetectable levels
- Decrease hepatic necroinflammation and fibrosis
- Prevent progression to cirrhosis, liver failure and HCC

WHO TO TREAT

Depends!

A



Recommendations:

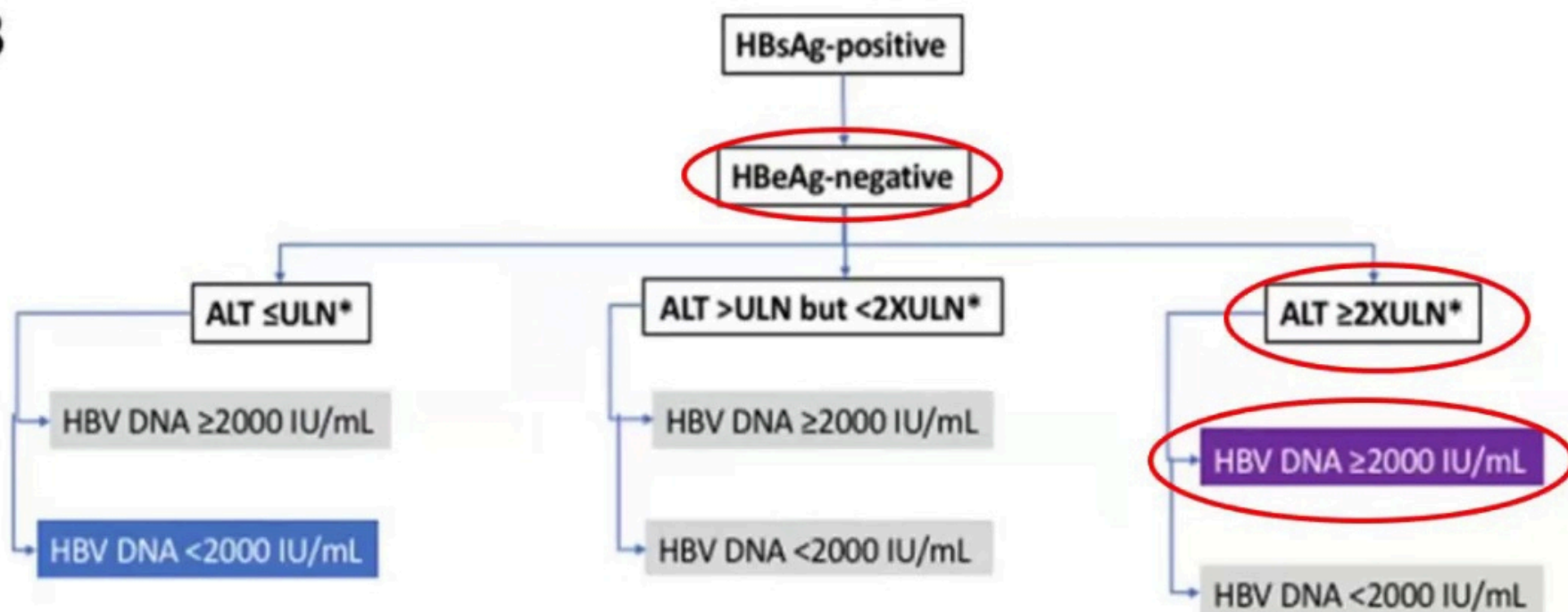
Treat

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.

If HBeAg Negative

B



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.

What to Use?

Injectables in HBV treatment

- Immunomodulators

Interferon alpha 2b

IFN

Peg- interferon
alpha 2a/2b

PEG IFN

Mode of Action

- Enhances phagocytic activity of macrophages
- Inhibits viral replication in virus-infected cells
- Increases cytotoxicity of lymphocytes for target cells

Pegylated IFN

- Addition of polyethylene glycol to standard IFN has several benefits:
 - ✓ Shields IFN from enzymatic degradation thus lowers systemic clearance
 - ✓ Allows less frequent dosing- once/week SC
 - ✓ Achieves higher & more sustained IFN serum concns

Oral drugs: Nucleoside/nucleotide Analogues

Lamivudine

3TC/LAM

Entecavir

ETV

Adefovir

ADV

Telbivudine

LdT

Tenofovir

TDF

Mode of Action

- Mainly act by inhibition of HBV DNA polymerase enzyme activity resulting in decrease of viral replication

Antiviral agent	Potency against HBV	Resistance barrier	Activity against HIV	Cost
Interferons	Moderate	Not applicable	Moderate	High
Tenofovir	High	High	High	Low (high in Hong Kong and other Asian countries)
Entecavir	High	High	Weak	High
Emtricitabine	Moderate	Low	High	Low
Telbivudine	High	Low	Unclear	High
Lamivudine	Moderate-high	Low	High	Low
Adefovir	Low	Moderate	None (at 10 mg dose)	High

Preferred Agents

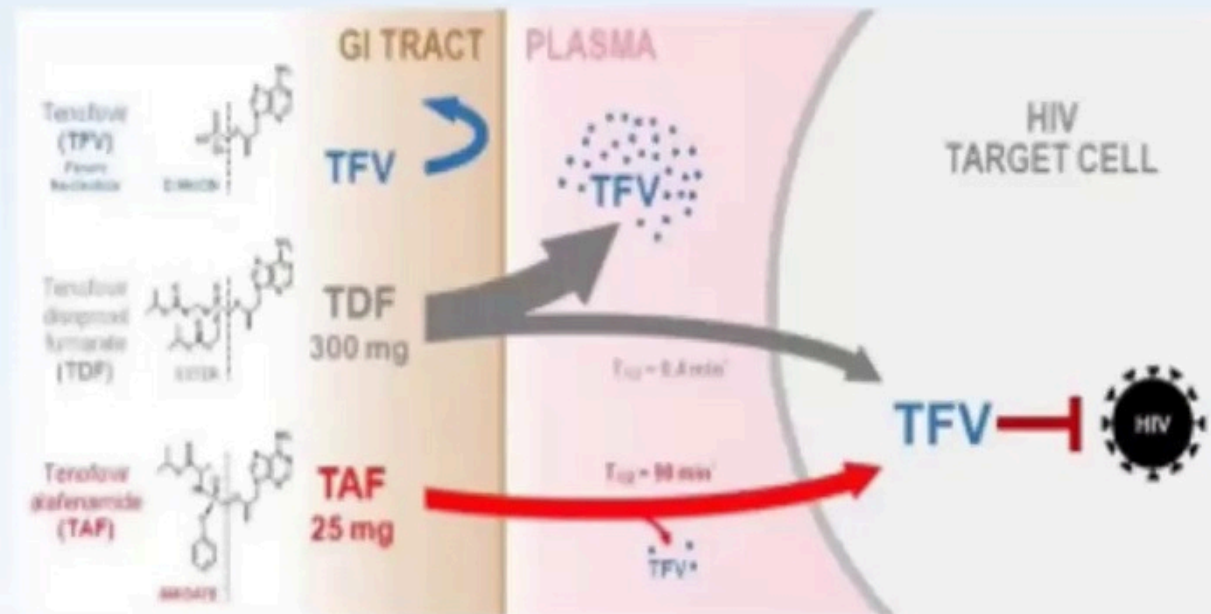
AASLD 2018 Guidelines

(American Association for the Study of Liver Diseases)

DRUG	ADVERSE EFFECTS
Peg IFN α2a (adults) IFN α2b (children)	Flu-like symptoms, fatigue, cytopenia, Autoimmune disorders (adults) Anorexia, weight loss (children)
Tenofovir disoproxil fumarate	Nephropathy, Fanconi syndrome, osteomalacia, lactic acidosis
Tenofovir alafenamide	Lactic acidosis
Entecavir	Lactic acidosis

TDF vs TAF

Tenofovir Alafenamide (TAF)



- 91% lower plasma TFV levels minimize renal and bone effects while maintaining high potency for suppressing HIV
 - less effect on renal tubular and overall proteinuria and eGFR than TDF
 - little to no effect on bone density

Lee W, AAC, 2005; Birkus G, AAC, 2007; Babusis D, Mol Phar, 2013; Ruane P, JAIDS, 2013; Sax P, JAIDS, 2014; Sax P, Lancet, 2015

ACTHIV
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FOR THE TREATMENT OF HIV

Others

AASLD 2018 Guidelines

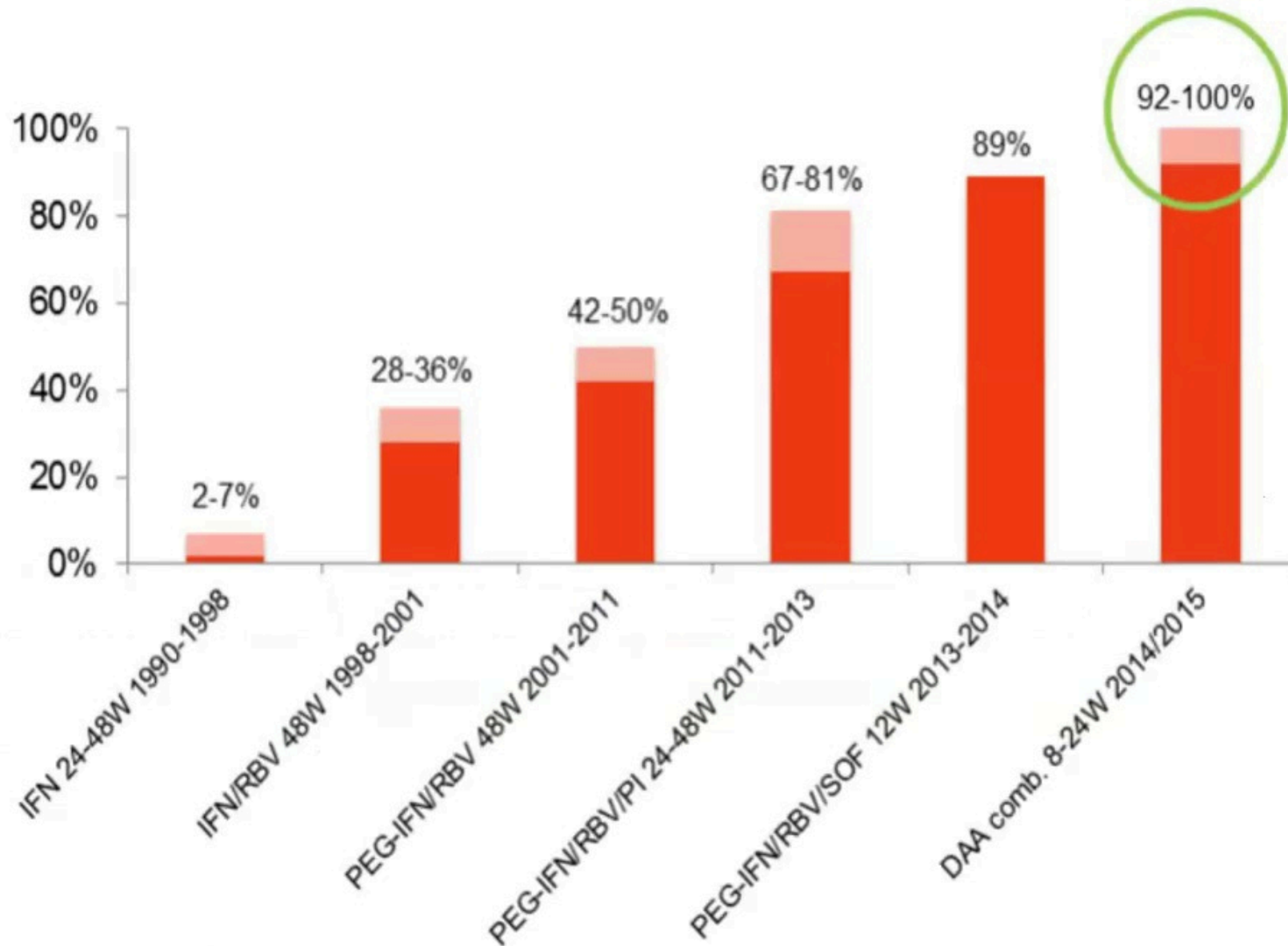
DRUG	ADVERSE EFFECTS
Lamivudine	Pancreatitis, Lactic acidosis
Adefovir	Acute renal failure, Fanconi syndrome, Lactic acidosis
Telbivudine	Creatine kinase elevation, myopathy, peripheral neuropathy, lactic acidosis

PEG IFN vs Nucleos(t)ide Analogues

	(PEG-)IFN	NAs
Advantages	• Finite duration • Absence of resistance • Higher rates of anti-HBe and anti-HBs seroconversion with 12 mo of therapy	• Potent antiviral effect • Good tolerance • Oral administration
Disadvantages	• Moderate antiviral effect • Inferior tolerability • Risk of adverse events • Subcutaneous injections	• Indefinite duration • Risk of resistance • Unknown long-term safety

CURRENT MANAGEMENT OF HEPATITIS C

Development of HCV therapy: 1986 - 2016



Goal of treatment

- The goal of treatment of HCV-infected persons is to reduce all-cause mortality and liver-related health adverse consequences, including end-stage liver disease and hepatocellular carcinoma, by the achievement of virologic cure as evidenced by an SVR.

HCV replication and drug targets

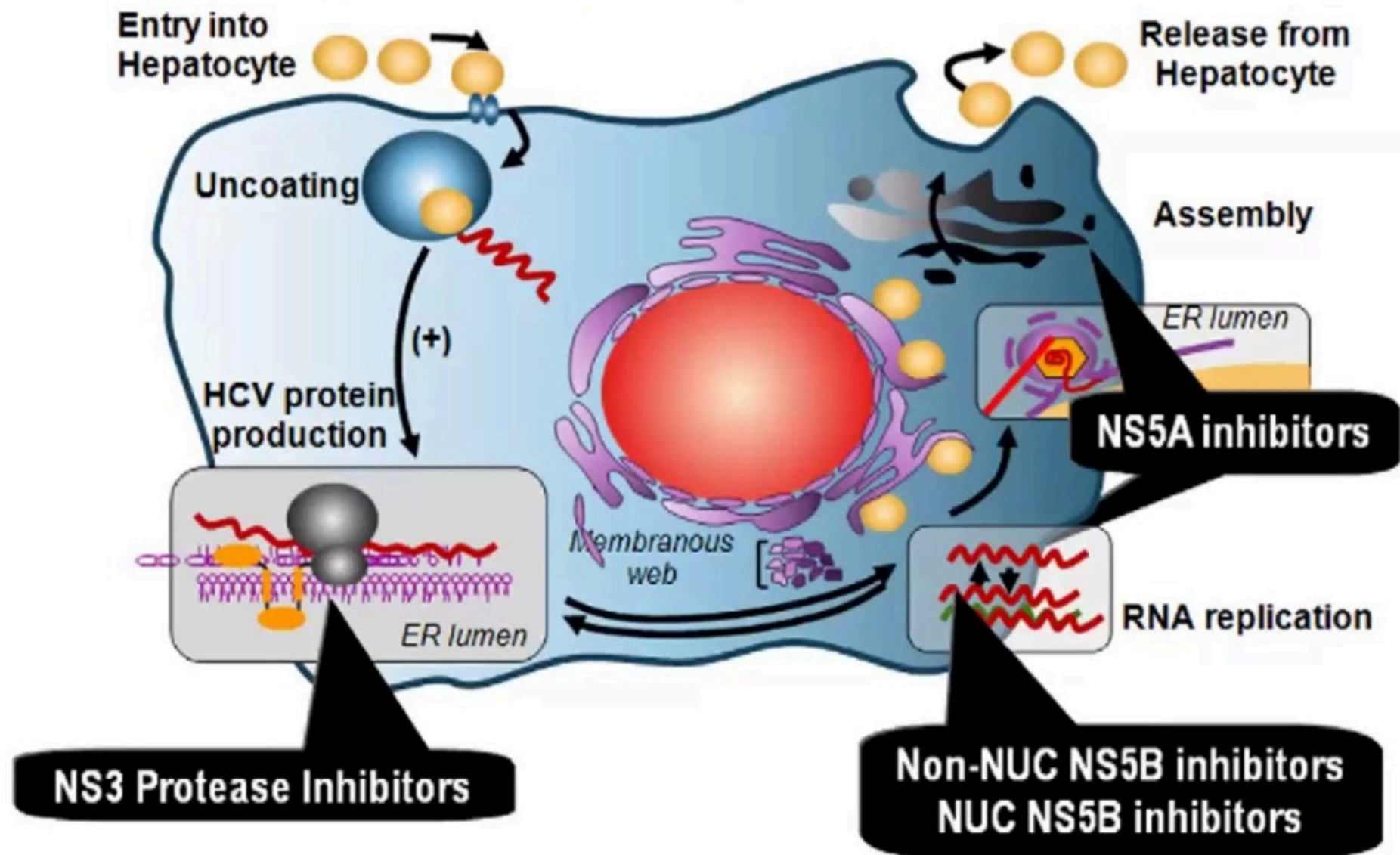
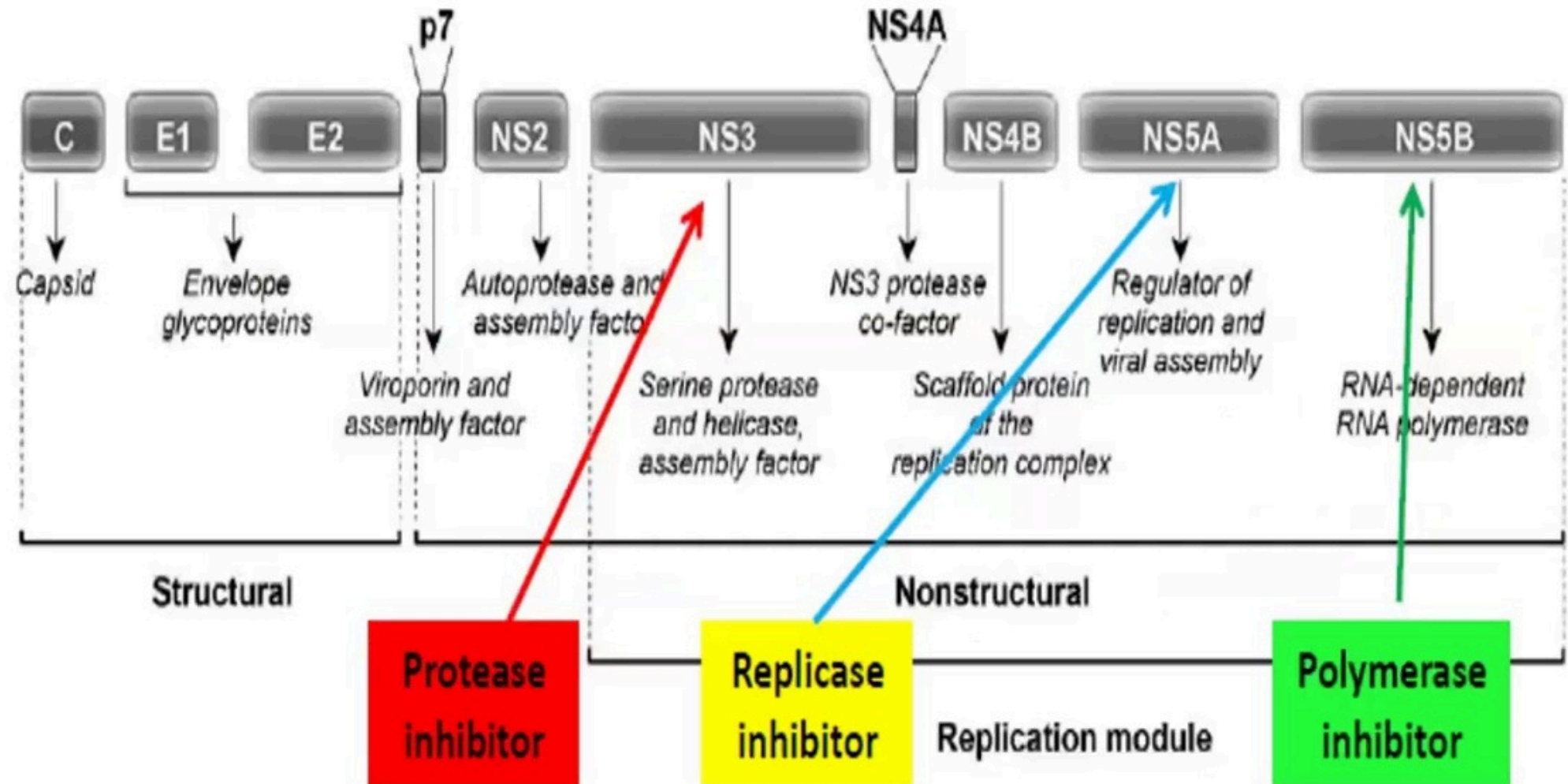
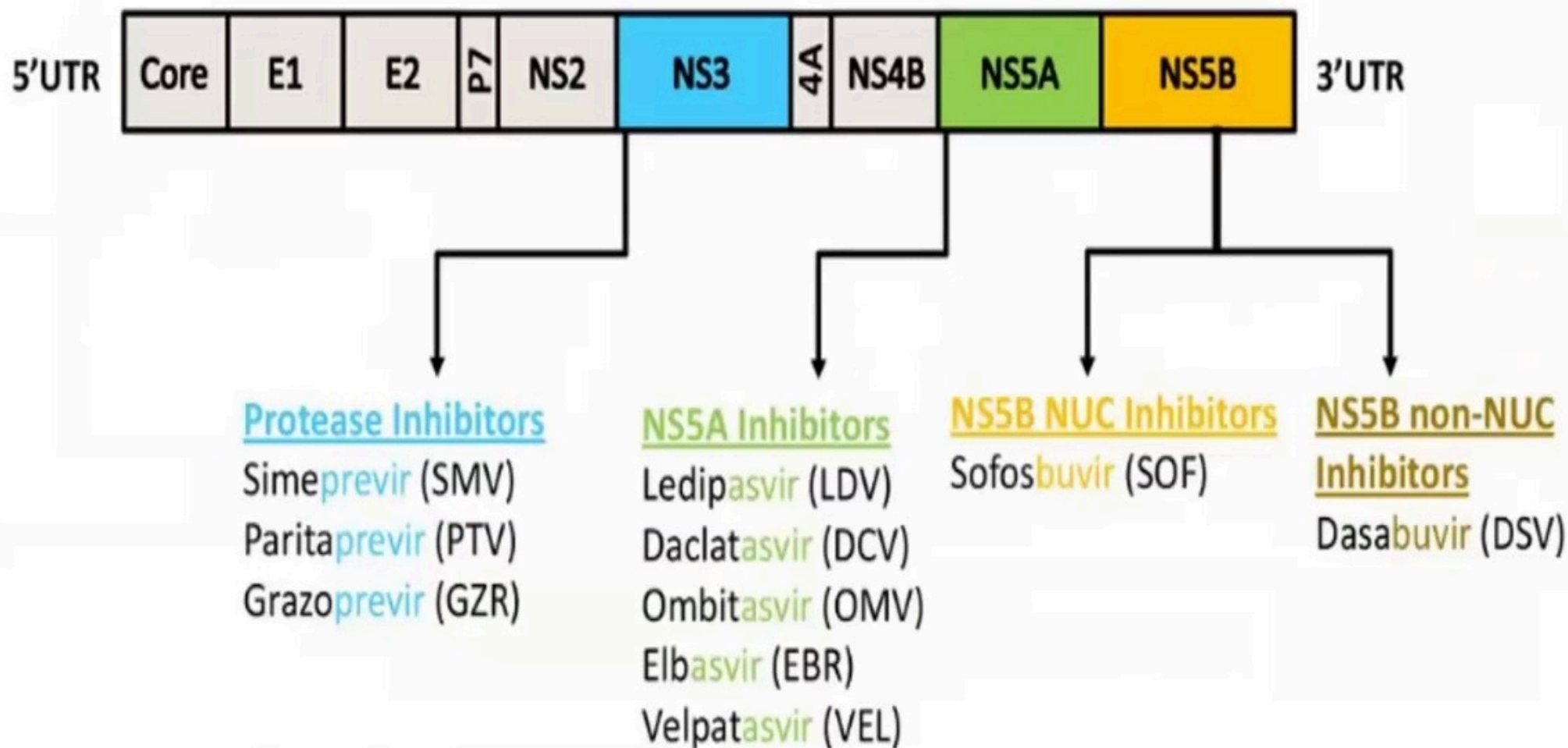


Figure 1: Specific targets of the direct acting antiviral agents.

HCV structural and non structural proteins



Approved HCV Direct-acting Antiviral (DAA) Agents



- Cure rates can be optimized by:
 - ✓ Combining drugs with synergistic antiviral effects
 - ✓ Modifying treatment duration

Sofosbuvir has

low toxicity,
high barrier to resistance,
and minimal drug interactions with other DAAs

making it the ideal candidate to become **backbone** for
several IFN-free regimens.



Introduction

Practice Guidance |  [Free Access](#)

Hepatitis C Guidance 2019 Update: American Association for the Study of Liver Diseases–Infectious Diseases Society of America

RECOMMENDED REGIMENS*

Glecaprevir (300 mg) / pibrentasvir (120 mg)
taken with food for a duration of 8 weeks

Sofosbuvir (400 mg) / velpatasvir (100 mg)
for a duration of 12 weeks



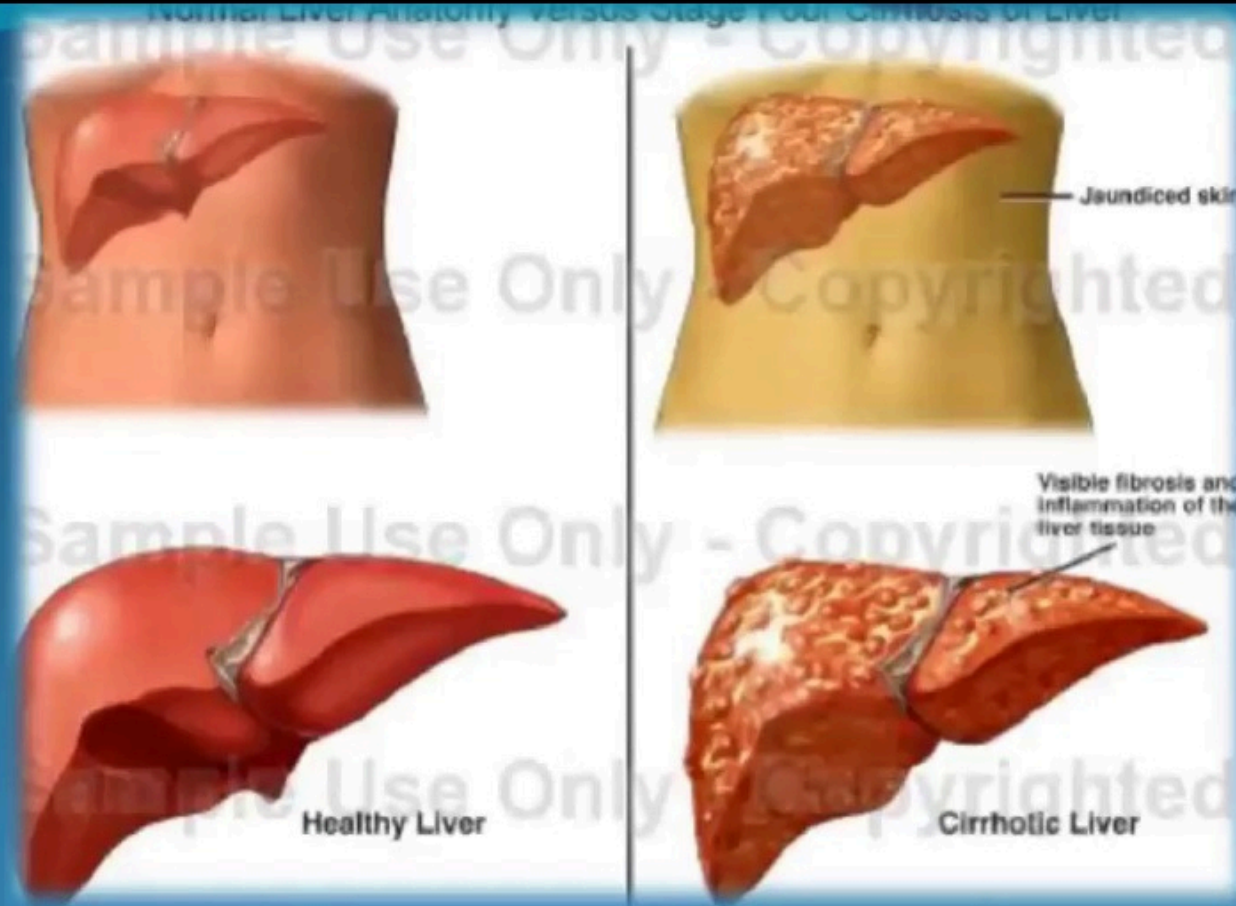
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Pages 686-721

This article also appears in:
[AASLD Practice Guidelines](#)

MANAGEMENT OF LIVER CIRRHOSIS



- FIBROSIS and a conversion of the normal hepatic architecture into structurally ABNORMAL NODULES
- Destruction of hepatocytes and their replacement by fibrous tissue

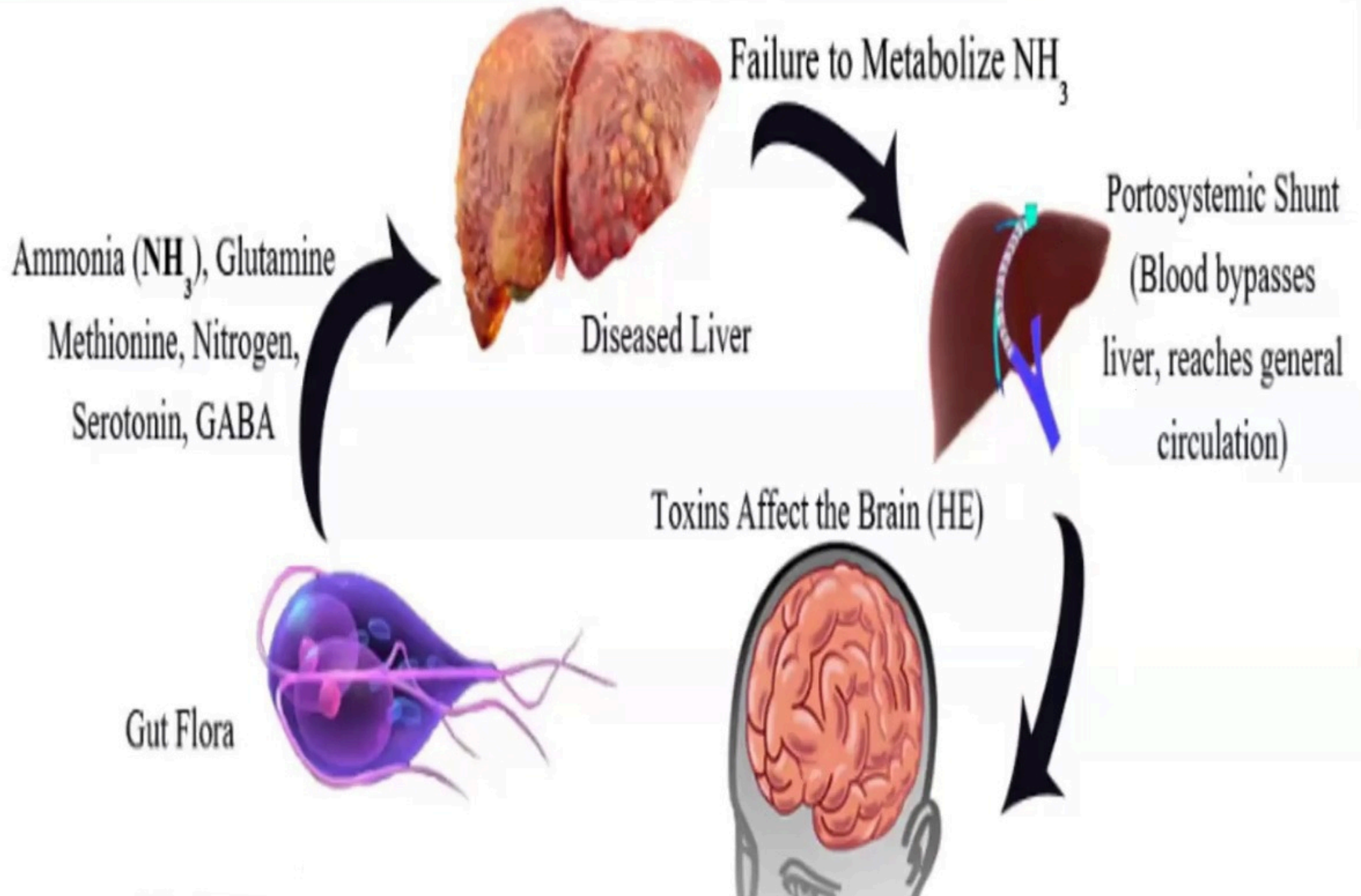
Pathophysiologic outcomes of Cirrhosis

- Portal hypertension
- Ascites, edema
- Pleural effusion
- Esophageal varices,
- Hepatic encephalopathy,
- Coagulation disorders

a. Hepatic Encephalopathy

- Reversible impairment of neuropsychiatric abilities associated with impaired hepatic function
- Due to accumulation of gut-derived nitrogenous substances in the systemic circulation

Hepatic Encephalopathy (HE)



Management Approach

- Reduce production of blood ammonia
 - Limit dietary protein intake
 - Enhance removal of nitrogenous cpds- use of Lactulose 30-45ml TID
- ✓ Osmotic laxative
- ✓ A/e: flatulence, diarrhea, abd cramps

Role of antibiotics

- For reduction of intraluminal urease-producing bacteria that may lead to excess ammonia production

DRUG	NOTES	ADVERSE EFFECTS
Neomycin	✓ Aminoglycoside antibiotic ✓ Poorly absorbed from the gut	Rare- Nephro- & ototoxicity
Rifaximin	✓ Derivative of rifampin ✓ Inhibits bacterial protein synthesis ✓ Absorption <0.5% ✓ Reduced risk of CYP450 mediated drug interactions	Flatulence, constipation
Metronidazole	✓ Undergoes reduction within anaerobic bacteria, with accumulation of toxic products	Peripheral neuropathy Nausea, metallic taste Disulfiram effect

b. Management of Ascites

- Fluid restriction
- Sodium restriction <2g day
- Avoid NSAIDs
- Oral diuretics:
 - ✓ Starting dose: Spironolactone 100mg/Furosemide 40mg
 - ✓ Increase every 3 to 5 days, max dose 400mg/160mg

DRUG	NOTES	ADVERSE EFFECTS
Furosemide	✓ Inhibits the Na/K/2Cl transporter in the loop of henle	Ototoxicity Hypovolemia Hyperuricemia Hypomagnesemia K+ wasting
Spironolactone	✓ Aldosterone antagonism in the collecting tubules	Hyperkalemia Gynecomastia

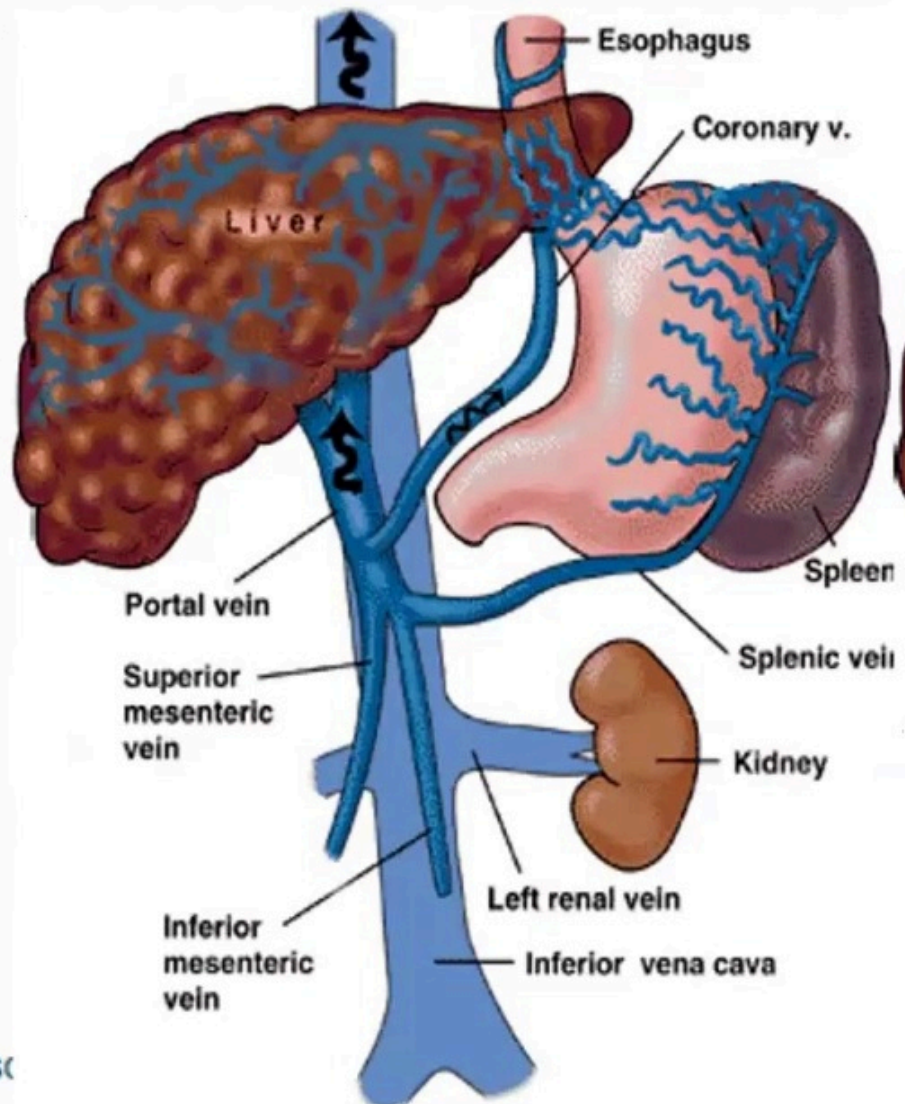
c. Spontaneous bacterial peritonitis

- Bacterial infection of preexisting ascitic fluid without evidence of an intra-abdominal source
- Usually caused by gram negative organisms:
 - ✓ *Escherichia coli*
 - ✓ *Klebsiella pneumoniae*

Treatment

- ✓ 3rd generation Cephalosporins
 - Ceftriaxone 2g/d
 - Cefotaxime 2g TID
- ✓ Fluoroquinolones- Ciprofloxacin, Levofloxacin
- ✓ Duration of Rx: 5-10 days

d. Esophageal varices & portal hypertension



Approach

- Primary prophylaxis to prevent bleeding
- Mx of variceal hemorrhage
- Secondary prophylaxis to prevent bleeding in those who have had a previous bleed

Bleeding prophylaxis

- Use of beta blockers to decrease blood flow to mesenteric vessels
 - ✓ Propranolol 20mg TID/ Carvedilol 6.25mg/Nadolol 20mg
 - ✓ Titrated to achieve heart rate of 55-60bpm, or 25% lower than baseline heart rate
 - ✓ A/e: Bronchospasm, glucose intolerance

Acute variceal bleed

- IV fluids/colloids/blood transfusion
- Vasoactive therapy to decrease portal blood flow:
 - **Octreotide**
 - ✓ Somatostatin analogue
 - ✓ 50-100mcg stat, 25-50mcg/hr
 - **Terlipressin**
 - ✓ Vasopressin analogue
 - ✓ A/e: spasm of coronary vessels with resultant angina

Definitive Mx

- Endoscopic band ligation
 - Endoscopic injection sclerotherapy- injection of sclerosants eg.
 - ✓ Ethanolamine
 - ✓ Sodium tetradecyl sulfate
 - ✓ Polidocanol
 - ✓ Sodium morrhuate
-

e. Coagulation defects

- Due to reduced synthesis of coagulation factors
- Mx:
 - ✓ Fresh frozen plasma
 - ✓ Vitamin K

THE END