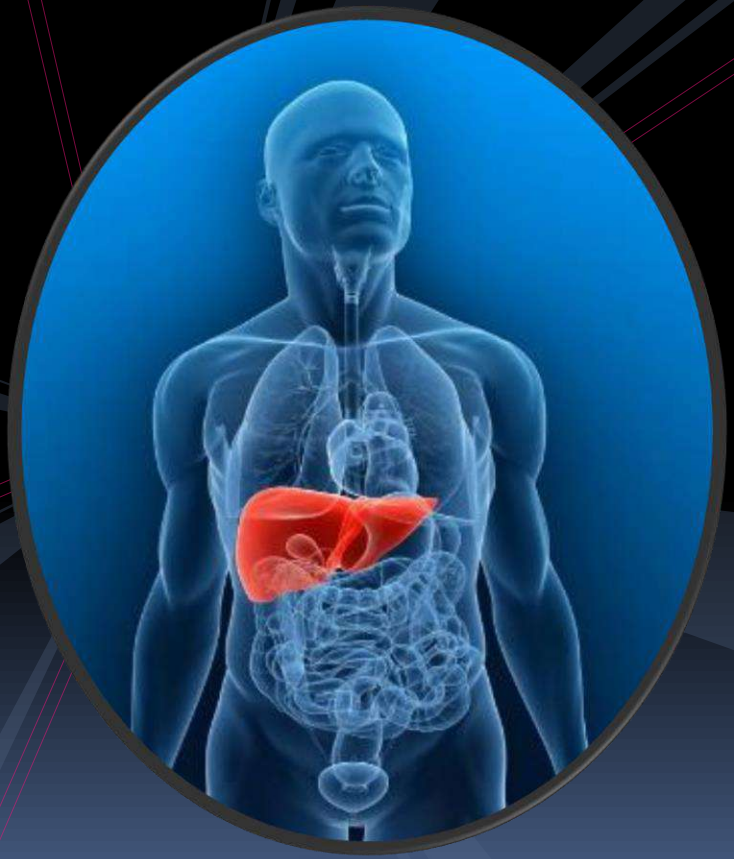
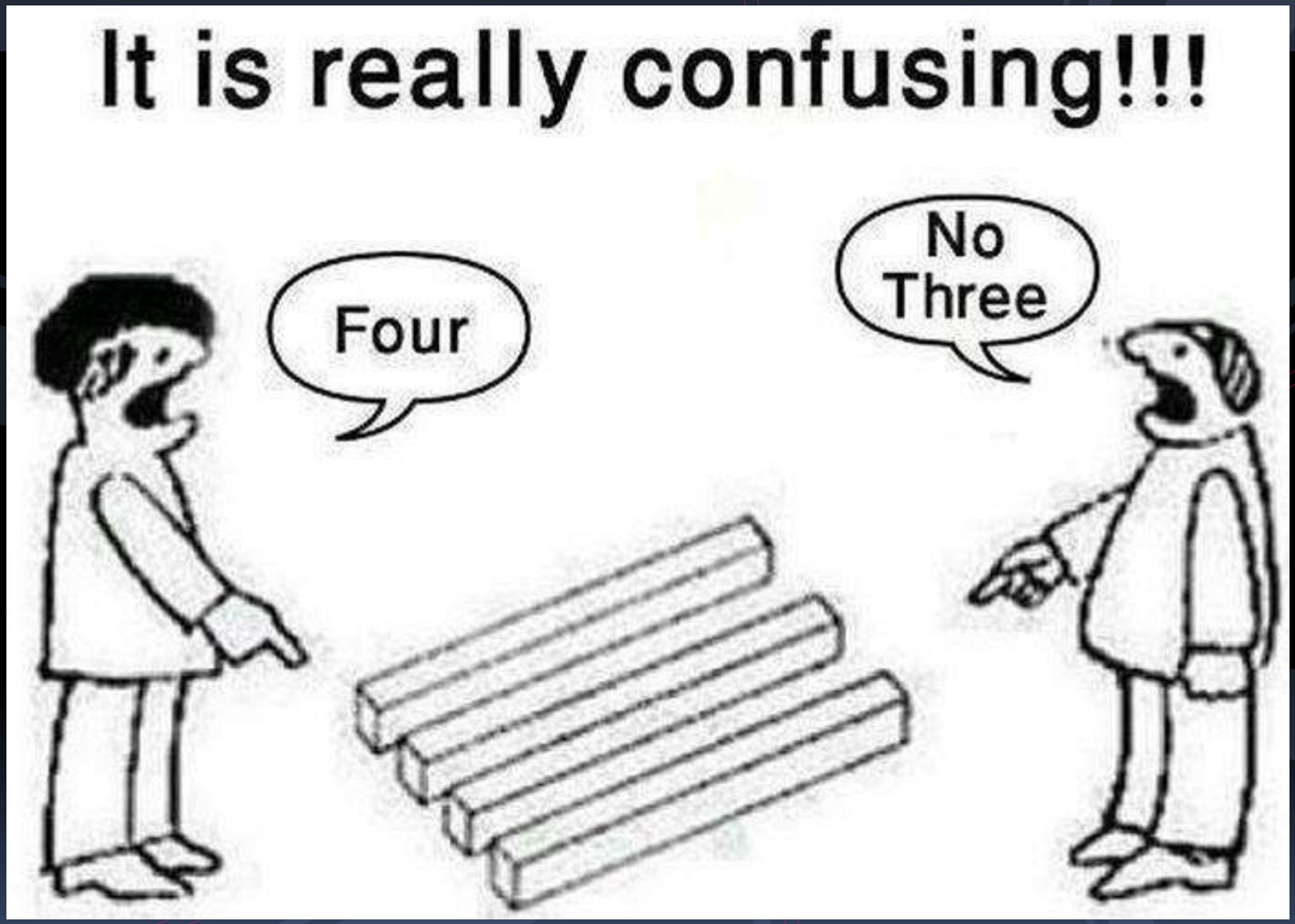
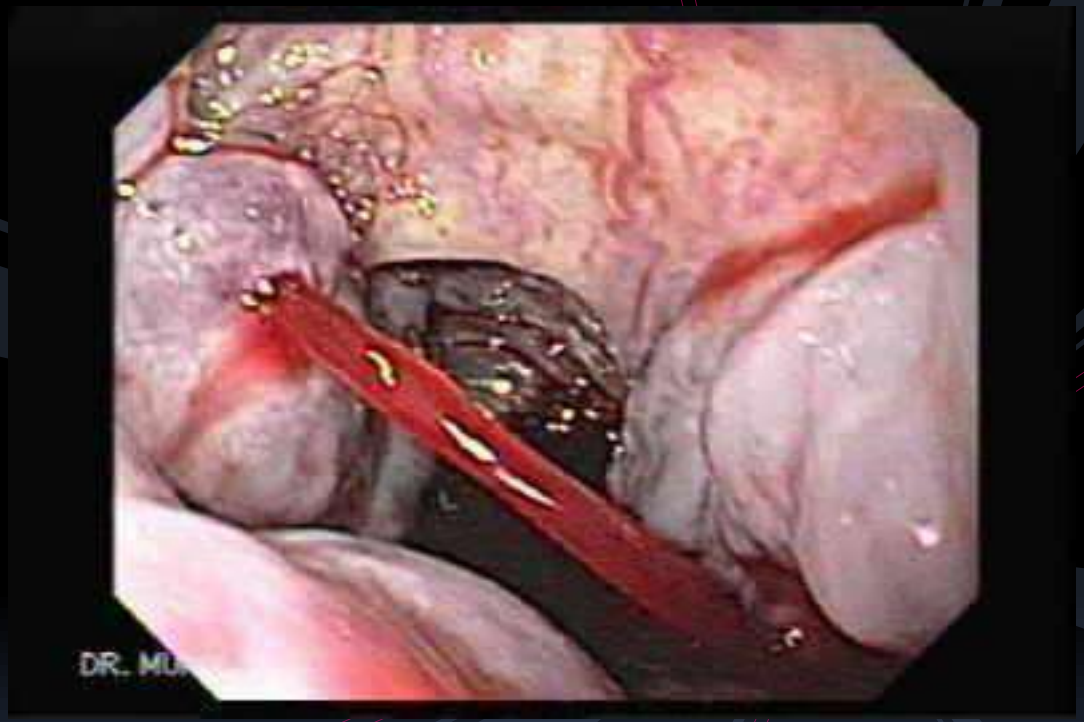
HOW TO PRESCRIBE MEDICATIONS IN PATIENTS WITH CHRONIC LIVER DISEASE

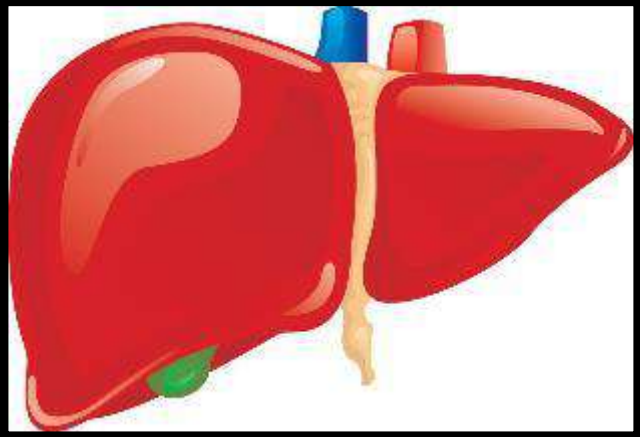
Miguel de Varona Negron, M.D.
Auxilliary Professor of Medicine
Division Of Gastroenterology
and Hepatology
UPR School of Medicine




It is really confusing!!!
Four
No
Three


DR. MU

Introduction



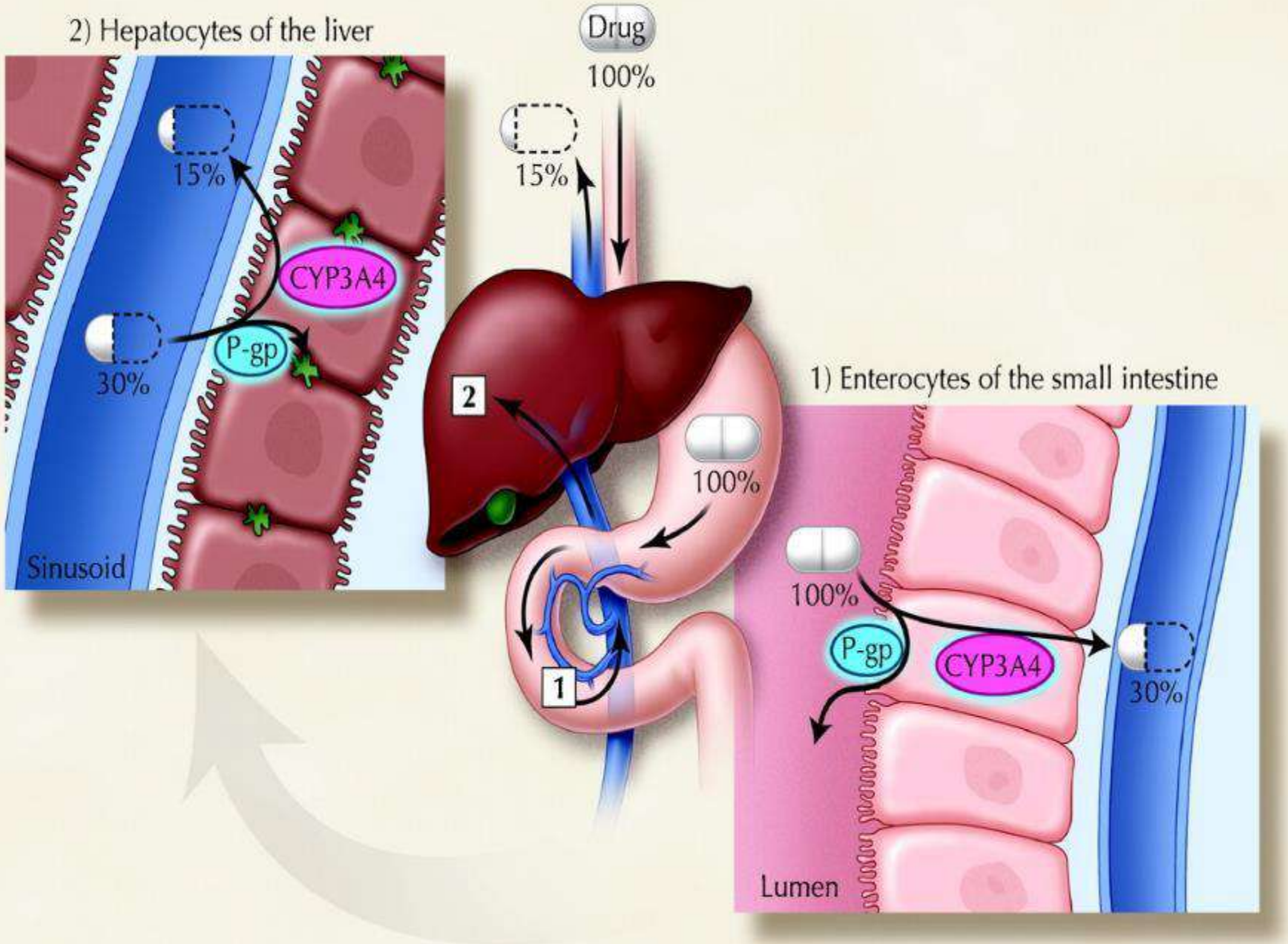
- Liver is a primary site of drug metabolism
- The liver plays a central role:
  - absorption
  - distribution
  - elimination
- Dose adjustment in patients with liver dysfunction is therefore essential for many drugs

Introduction

- Almost 50% of the drugs are associated with some sort of liver injury
- Nearly 100 drugs are known to cause fulminant hepatic failure
- 10% of all adverse drug reactions are hepatotoxicity
- 30% of cirrhotic patients suffer adverse drug reactions
  - 80% could be prevented

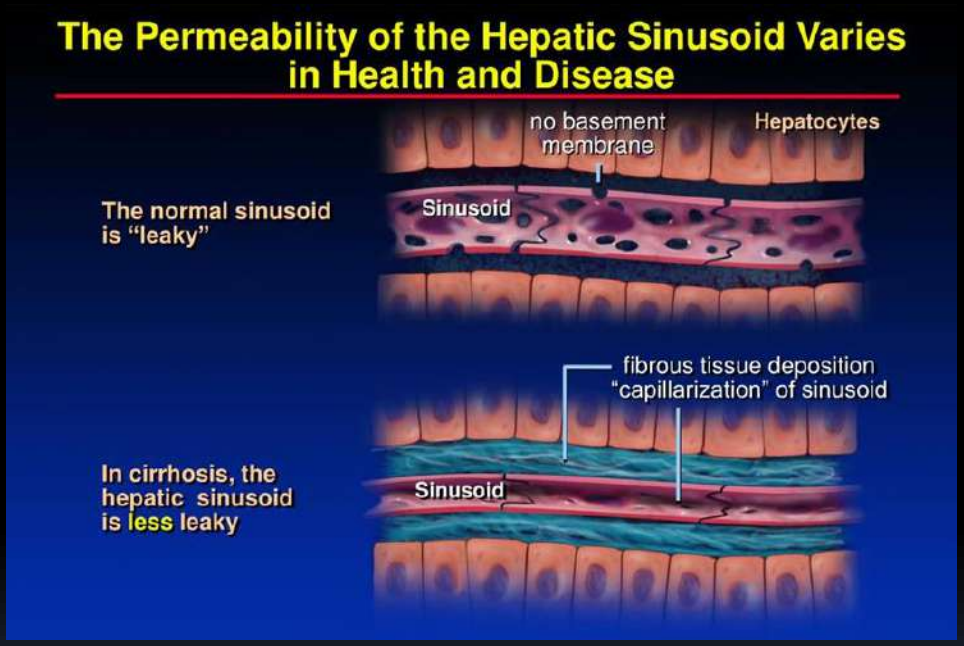
Hepatic Pathophysiology

- Any compound entering the body must eventually be eliminated by:
  - metabolism
  - excretion via the urine or bile/feces
- **"First pass effect"**
  - Responsible for the pre-systemic elimination
    - Small bowel epithelium
    - Liver


2) Hepatocytes of the liver
Drug
100%
15%
15%
CYP3A4
P-gp
30%
Sinusoid
2
1) Enterocytes of the small intestine
100%
100%
P-gp
CYP3A4
30%
1
Lumen

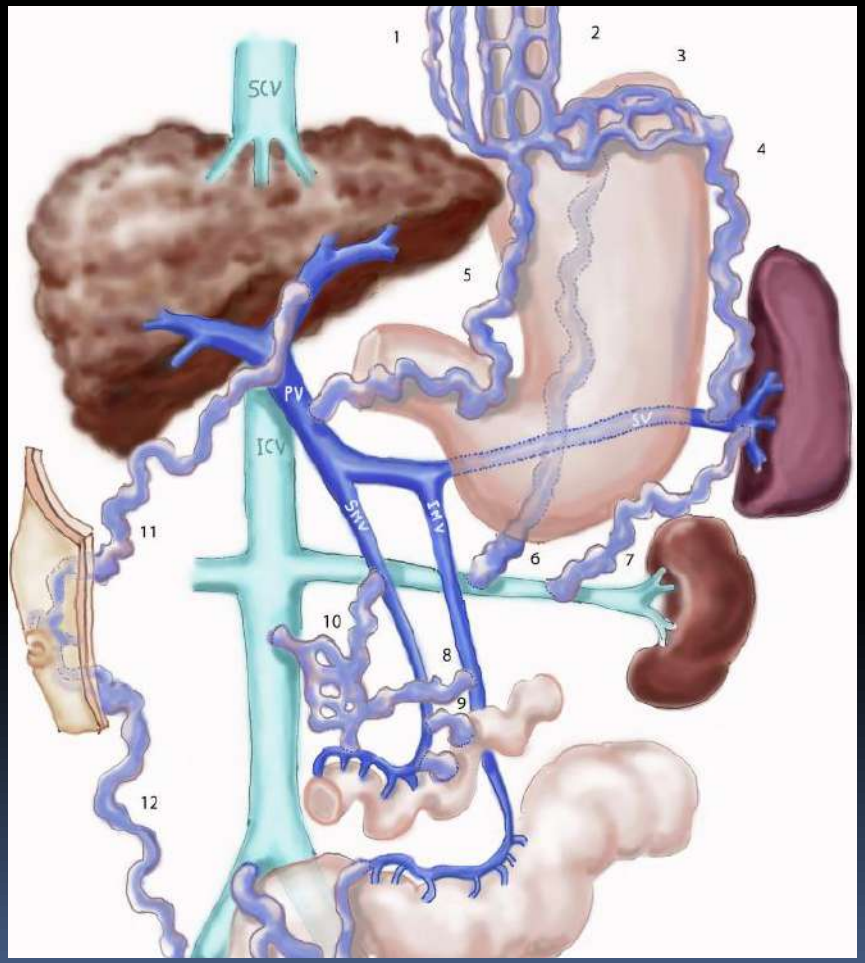
IMPACT OF CIRRHOSIS ON PHARMACOKINETICS

- Alterations in hepatic blood flow
  - decreased portal blood flow
  - increased hepatic arterial resistance
  - capillarization of the hepatic sinusoids



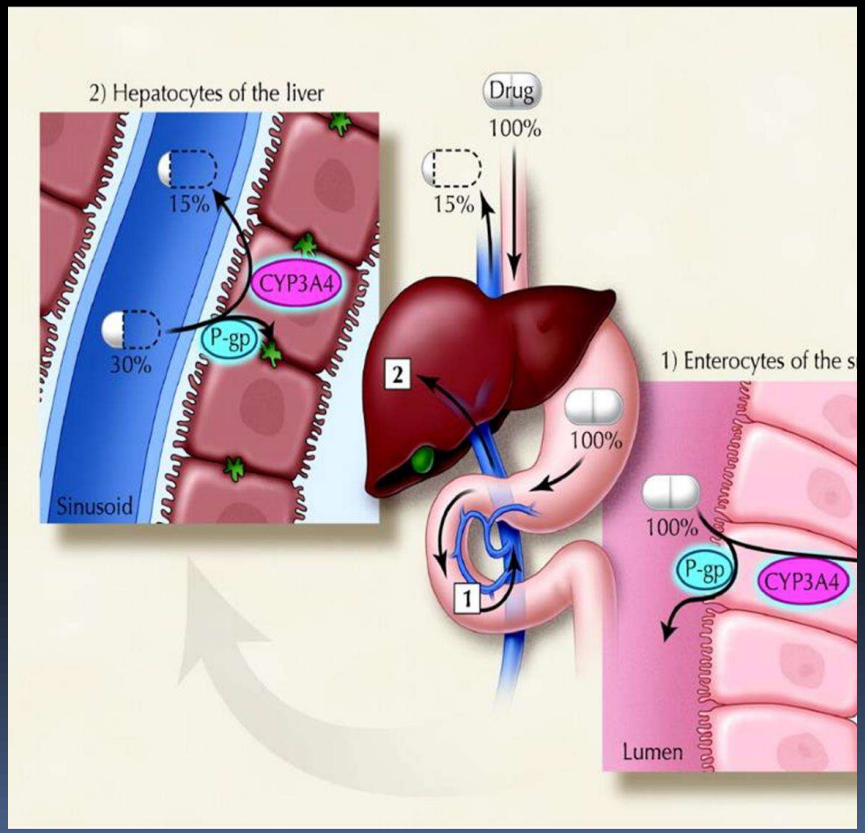
IMPACT OF CIRRHOSIS ON PHARMACOKINETICS

- Portosystemic shunting
  - may permit cardioactive substances to bypass the liver
    - prolongation of the QTc interval



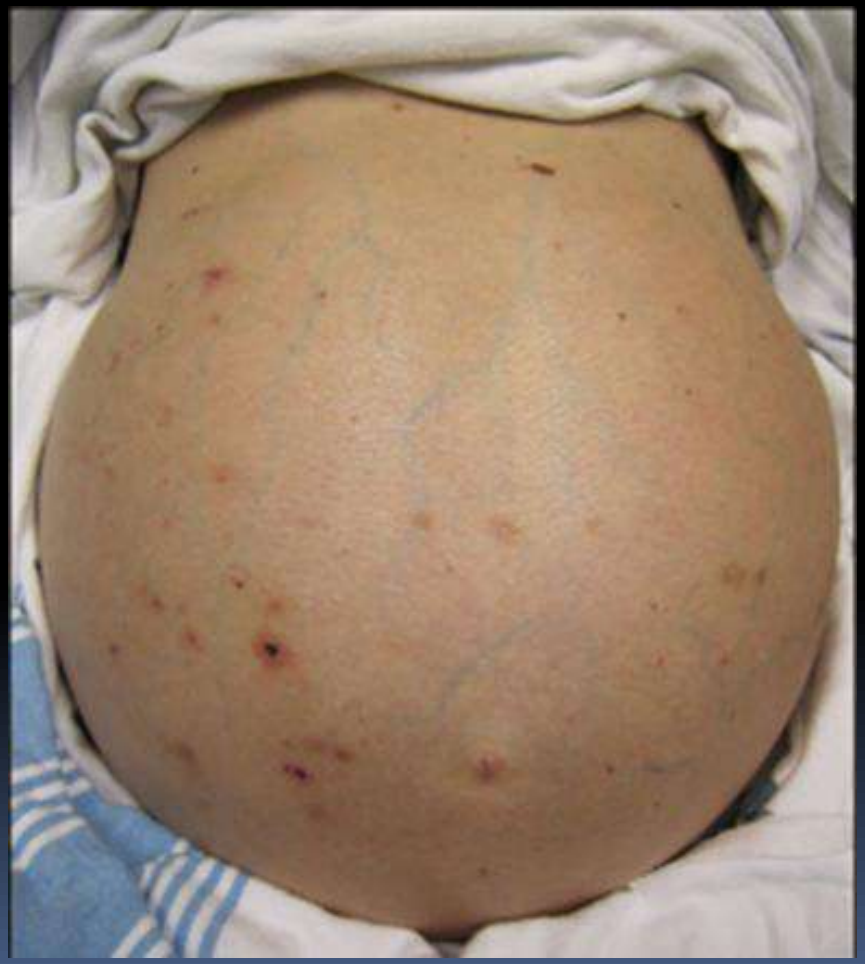
IMPACT OF CIRRHOSIS ON PHARMACOKINETICS

- Changes in cytochrome P450 activity
- Hypoalbuminemia
  - impaired production
  - dilution from fluid retention
  - high-binding profile to albumin = more unbound drug in the serum
- Cholestasis



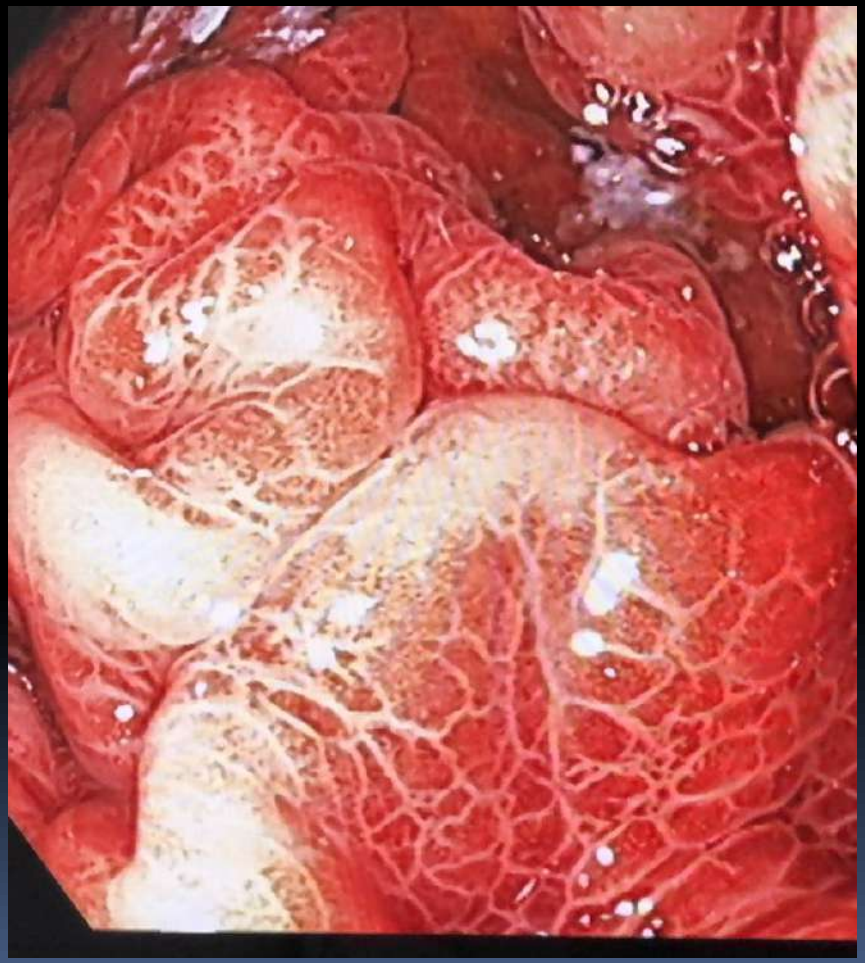
IMPACT OF CIRRHOSIS ON PHARMACOKINETICS

- Cholestasis
  - Impaired bilirubin secretion and bile formation = increase serum drug levels
- Portal hypertension
  - Ascites
    - impact the volume of distribution
    - intestinal edema and impaired permeability



IMPACT OF CIRRHOSIS ON PHARMACOKINETICS

- Portal gastropathy
  - impact absorption of oral medications
  - impact the drug's bioavailability
- Renal blood flow
  - impact renal blood flow
  - decreased renal clearance of medications



Liver Function Assessment

- Patients with well compensated cirrhosis and near normal synthetic function will have a lesser extent of impaired drug metabolism as compared to patients with decompensated cirrhosis , synthetic dysfunction and portal hypertension

Liver Function Assessment

- No evidence-based guidelines exist for the use of medications in patients with liver cirrhosis

- **Child-Pugh** score and **MELD** score are used for prediction of impaired liver function

Child-Turcotte-Pugh Score

Clinical and Lab Criteria	Points*		
	1	2	3
Encephalopathy	None	Mild to moderate (grade 1 or 2)	Severe (grade 3 or 4)
Ascites	None	Mild to moderate (diuretic responsive)	Severe (diuretic refractory)
Bilirubin (mg/dL)	< 2	2-3	>3
Albumin (g/dL)	> 3.5	2.8-3.5	<2.8
Prothrombin time			
Seconds prolonged	<4	4-6	>6
International normalized ratio	<1.7	1.7-2.3	>2.3

Child-Turcotte-Pugh Class obtained by adding score for each parameter (total points)
Class A = 5 to 6 points (least severe liver disease)
Class B = 7 to 9 points (moderately severe liver disease)
Class C = 10 to 15 points (most severe liver disease)

MELD Score

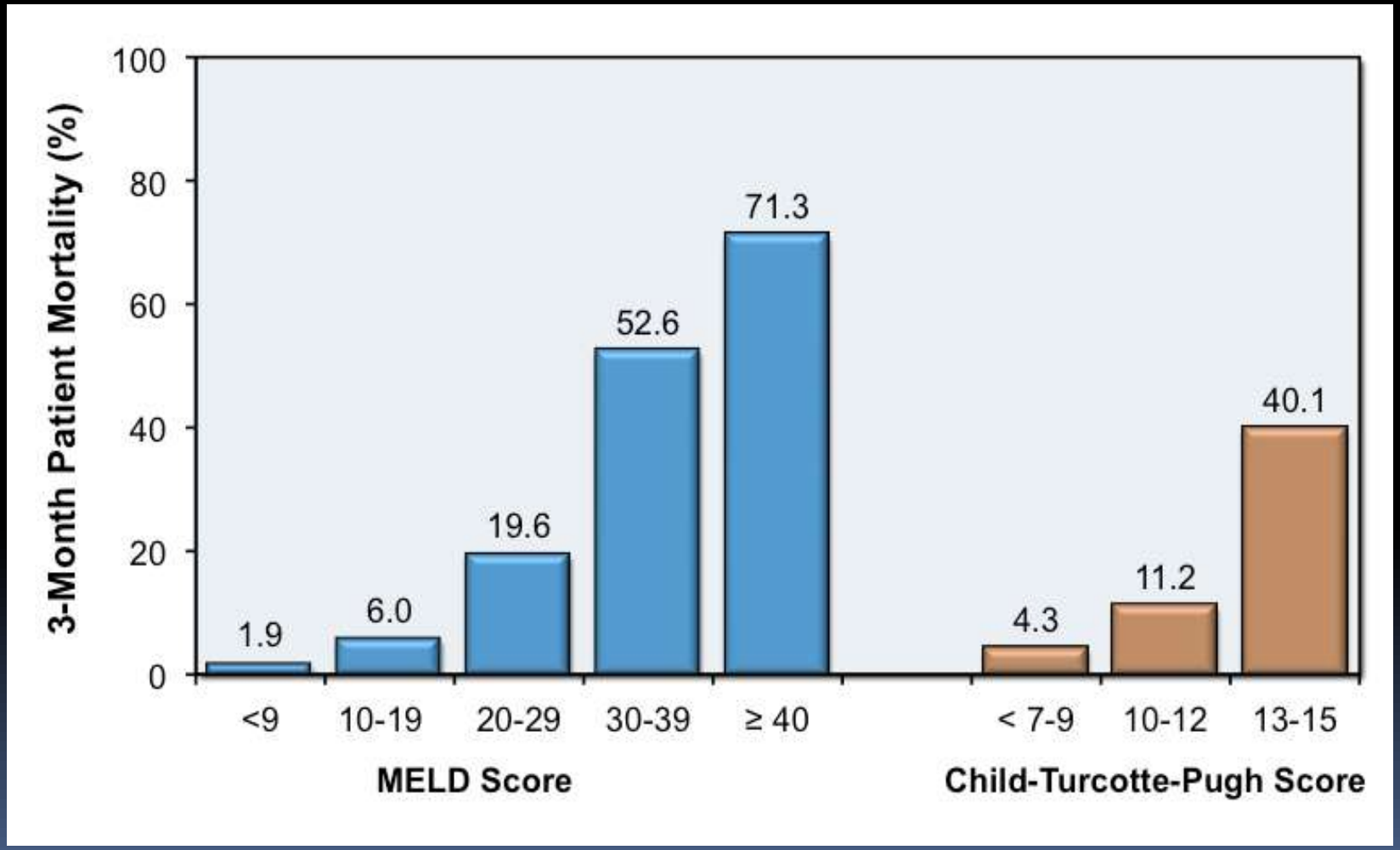
Model for End Stage Liver Disease (MELD)

MELD score= 10x[0.957x log e (creatinine) + log e (bilirubin) + 1.12 x log e (INR)] + 6.43

3 month mortality according to MELD score

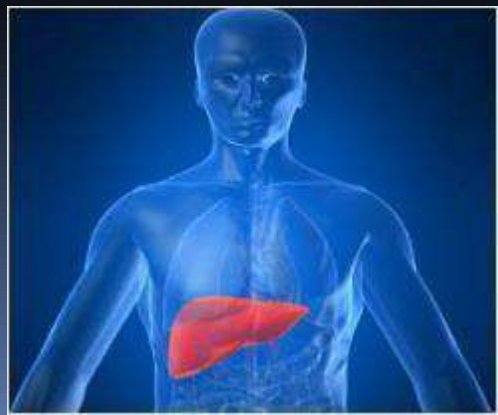
MELD score	<=9	10-19	20-29	30-39	>=40
Hospitalized pt.	4%	27%	76%	83%	100%
Outpatient cirrhotic	2%	6%	50%		

3-Month Patient Mortality

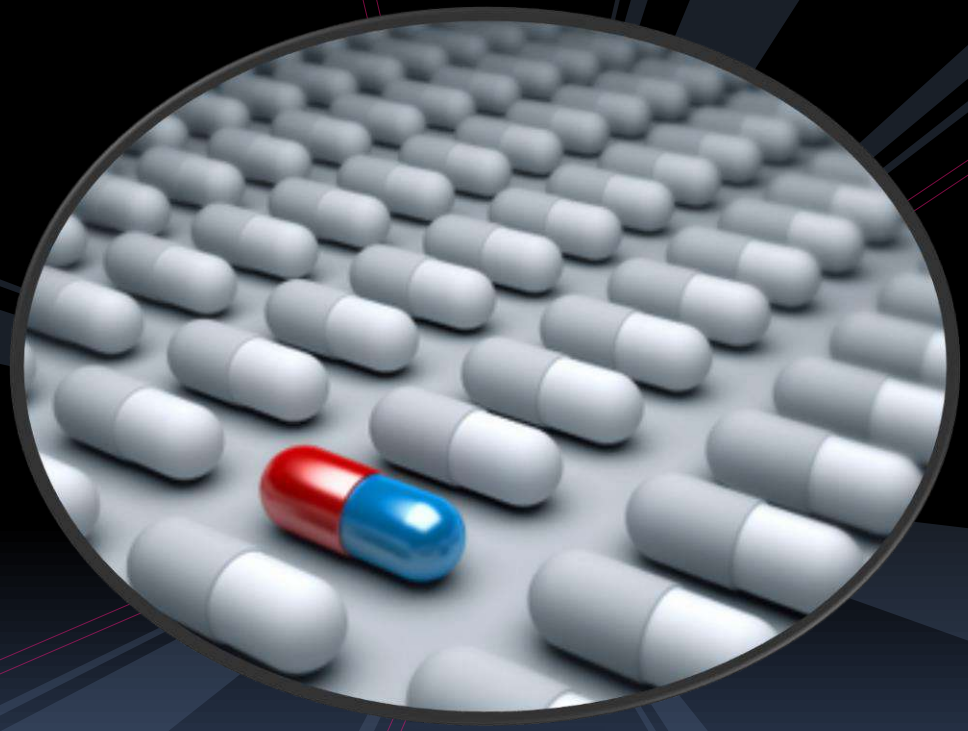


Child-Pugh and MELD Scores

- These classification schemes lack the sensitivity to quantify the specific ability of the liver to metabolize individual drugs



Drug Prescribing



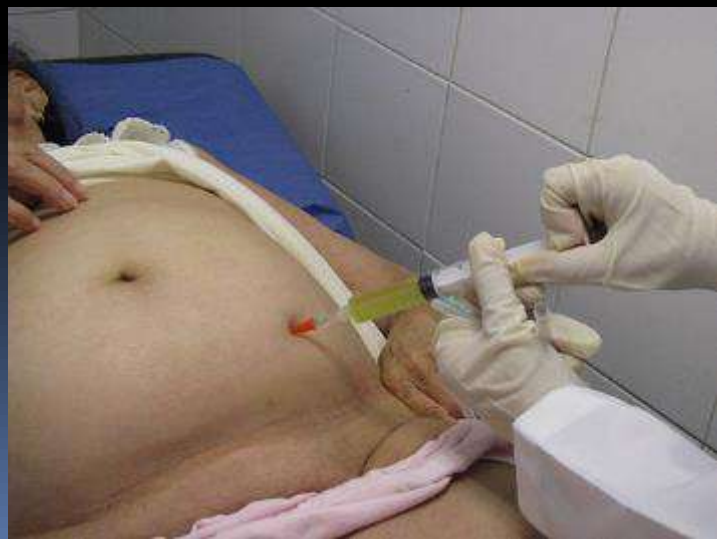
Prescribing Medications

- Drug dosing should be individualized
- Toxicity is accentuated by factors like nutritional status, renal function and drug-drug interactions
- If possible, measure drug level in the blood
- Educate patient to recognize signs of liver injury (nausea, jaundice, abdominal pain)
- Monitoring of the liver function at frequent intervals is highly recommended

ANTIBIOTICS

Antibiotic Dosing in Cirrhosis

- Liver is an important site of removal of blood borne bacteria
- 5 to 7 fold increase in bacteremia due to suppressed immunity
- Frequent use of antibiotics for therapeutic or prophylactic purpose



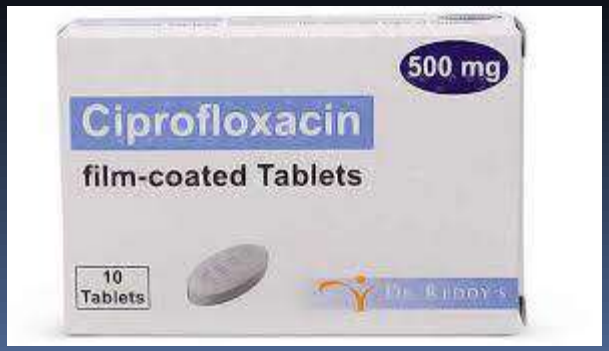
Antibiotics Dosing in Cirrhosis

- **Macrolide** antibiotics are excreted and detoxified by the liver and should be used with caution in cirrhotic patients
  1. Erythromycin
  2. Azithromycin
  3. Chloramphenicol
  4. Clindamycin

* Watch for QTc prolongation

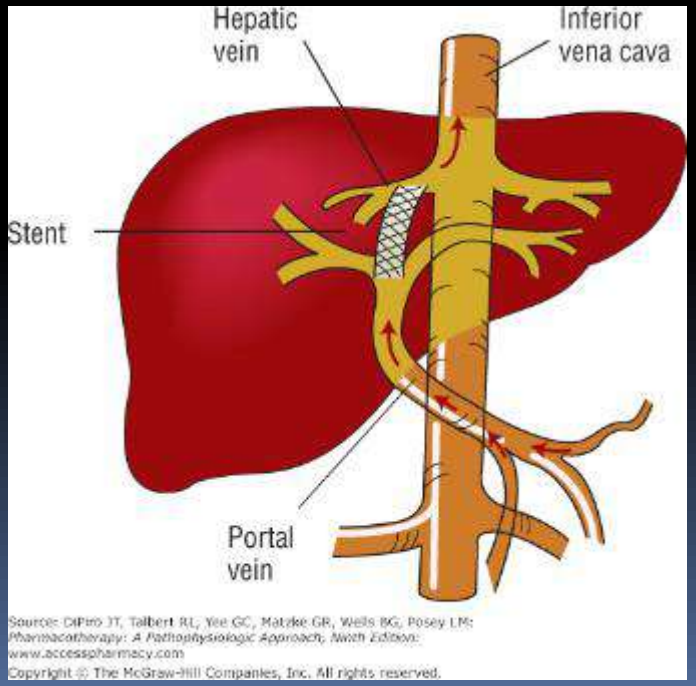
Fluoroquinolones

- Among the most used in cirrhotic patients
  - Treat and prevent SBP
- Norfloxacion, ciprofloxacin, levofloxacin
  - No extensive hepatic metabolism
  - Adjustment needed with renal impairment
- Watch for QTc prolongation
  - TIPS patients

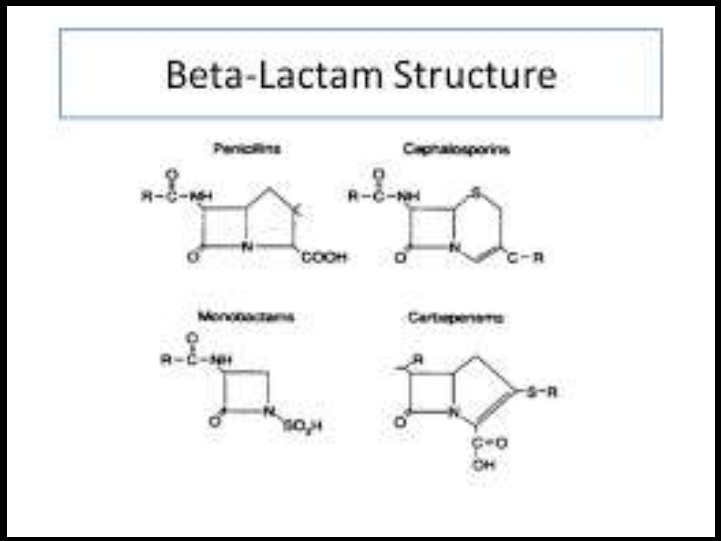


TIPS and PS Shunts

- Loss in first pass metabolism of midazolam
  - Nifedipine as well
- Baseline QTc interval prolongation
  - SBP prophylaxis
    - Fluoroquinolones



Beta-Lactamic Antibiotics



- This family includes:
  - Penicillin derivatives
  - Cephalosporins
  - Monobactams
  - Carbapenems
- Monitor for beta-lactam associated leukopenia
- Cefepime induced encephalopathy

Metronidazole

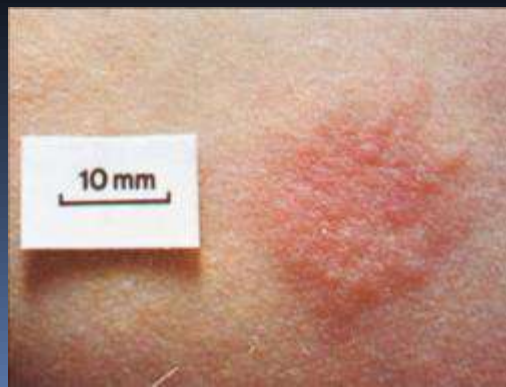
- Reduce dose by 50% in patients with severe cirrhosis (Child Class C) or renal insufficiency
- Use bid schedule instead of tid

Antifungals

- Ketoconazole, voriconazole, fluconazole and miconazole though hepatotoxic can be used with caution in patients with cirrhosis
- Monitor drug concentration in serum
- Newer antifungal agents
  - Echinocandins

Antibiotics

- Tetracycline, Isoniazid and Rifampin have prolonged half life in patients with cirrhosis
- Antituberculosis therapy (ATT) is associated with hepatotoxicity in 10%
- ATT in Child Class A cirrhosis is the same as non-cirrhotic population.
- Pyrazinamide should be avoided in Child B-C disease.



Antituberculosis Therapy

- Isoniazid may accumulate in advanced cirrhosis.
- Rifampin is eliminated in bile
  - Bilirubin elevation due to competitive inhibition
  - Hepatotoxicity is increased with Isoniazid

Anti-viral agents

- HIV therapy
- Anti Hepatitis C agents
  - Limitations according to Child score
- Anti Hepatitis B agents
  - Tolerated in decompensated cirrhotic patients

ANESTHETIC AGENTS

Anesthetic Agents

- General anesthesia reduces the hepatic blood flow resulting in decompensation
- Halothane should be avoided
- Isoflurane, desflurane are safe since they are not significantly metabolized by the liver
- Fentanyl and Propofol are good agents for combination anesthesia
- Consider spinal anesthesia

ANALGESICS

Analgesics

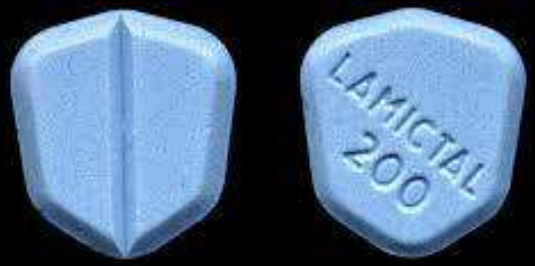
- Pain management in cirrhosis is a challenging task
- Analgesic choice depends on etiology of cirrhosis, renal function, liver transplant candidacy, drug interactions, adherence
- Analgesics are associated with severe complications
  1. NSAID's: GI bleeding and renal failure; refractory ascites
  1. Opioids: encephalopathy

Analgesics

- Acetaminophen at a dose <2g/day is a safe option
- Tramadol 25 mg every 8 hours can be used
- Fentanyl topical patch can be used or oral hydromorphone (avoid combinations)
- Neuropathic pain: Gabapentin, pregabalin, nortryptyline and desipramine can be used

ANTICONVULSANTS

Anticonvulsants



- Phenytoin
  - Generally avoided in cirrhosis
    - Lower plasma concentration needed
  - Avoid in alcoholic patients
- Carbamazepine
  - Avoid in cirrhosis; may induce decompensation.
- Valproate can be hepatotoxic
  - May precipitate encephalopathy
    - Hyperammonemia

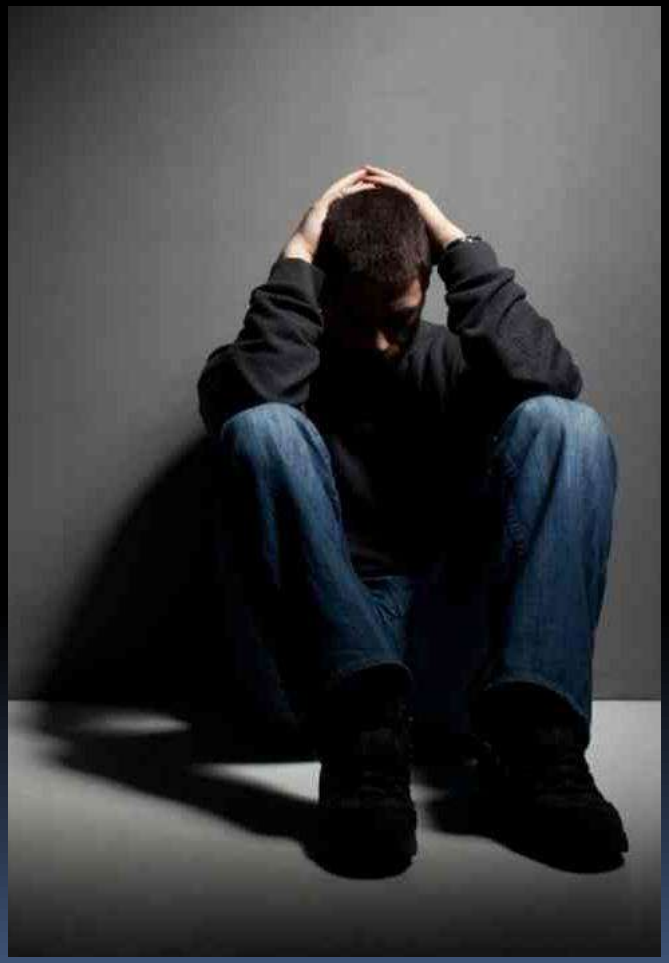
Anticonvulsants

- Levetiracetam (Keppra): safe
  - Adjust if renally impaired
- Topiramate
  - Avoid combination with enzyme inducers
  - Avoid in renal impairment (CrCl<60ml/min)
- Lamotrigine (Lamictal)
  - Reduce 25% dosing if moderate to severe hepatic impairment without ascites.
  - Reduce 50% dosing if moderate to severe hepatic impairment with ascites.

Frequently Prescribed Drugs

Antidepressants and Antacids

Antidepressants



- Selective Serotonin Reuptake Inhibitors
  1. Fluvoxamine (Luvox™)
  2. Paroxetine (Paxil™)
  3. Fluoxetine (Prozac™)

    - Need dose modification in patients with cirrhosis (usually decreased by 50%)

Anti-psychotics

- Haloperidol (Haldol)
  - Avoid with active alcohol consumption
  - Avoid in TIPS or surgical shunts
    - May induce QTc prolongation
- Olanzapine (Zyprexa)and Quetiapine (Seroquel)
  - Need lower doses because they undergo extensive CYP metabolism

Dyspepsia/Reflux/Peptic Ulcer

- Proton Pump Inhibitors
  - Esomeprazole is preferred due to unchanged pharmacokinetics
- H-2 blockers
  - Avoid cimetidine
    - Encephalopathy
  - Famotidine is preferred
- Avoid metoclopramide (Reglan)

Miscellaneous

- Methadone
  - Generally safe in cirrhotic patients
  - Good info in HCV/IVDA/cirrhosis studies
- Buprenorphine
  - Watch for QTc prolongation

- Cannabis
  - Delta-9-THC
    - CB1/CB2 receptors
  - Hep C studies (cross-sectional) show fibrosis progression
  - HepC/HIV studies show no significant increase in fibrosis progression
  - Encephalopathy

CARDIOVASCULAR

Cardiovascular

- Patients with nonalcoholic steatosis-related cirrhosis have increased incidence of dyslipidemia, hypertension and coronary artery disease
- Captopril, Amiodarone and Ticlopidine can cause hepatotoxicity and should be used with caution
- Statins appear to be remarkably safe in patients with liver cirrhosis

Angiotensin-Converting Enzyme (ACE) Inhibitors

- Enalapril
  - ✓ Changes in biotransformation were not clinically significant
  - ✓ Antihypertensive effect or ACE inhibition not affected
- Ramipril
  - ✓ Start at 5 mg or lower and titrate in patients with cirrhosis
- Lisinopril
  - ✓ Excreted unchanged in the urine (no dose adjustment needed)

Angiotensin II Receptor Antagonist

- Losartan (Cozaar™)
  - ✓ Bioavailabilty is doubled in patients with hepatic impairment
  - ✓ Lower initial doses are therefore recommended
- Irbesartan (Avapro™)
  - ✓ No significant changes in plasma concentration, renal clearance and accumulation index compared to normal volunteers
  - ✓ No adjustments necessary in hepatic insufficency

- Valsartan (Diovan™)
  - ✓ In mild to moderate hepatic impairment, a twofold increase in plasma concentration-time curve value was observed when compared to healthy volunteers
  - ✓ Use with caution, dose adjustment generally not needed in mild to moderate liver disease

Calcium Channel Blockers

Verapamil, Diltiazem, Nifedipine

- Metabolized by the liver and undergo extensive first pass metabolism
- 50% decrease in clearance leading to a marked increase in half-life
- Lower initial and maintenance doses are recommended

Amlodipine

- Prolonged half-life in cirrhotic patients
- Decrease initial and maintenance dose in half
- Titrate up at 14 days interval
- Lower extremity edema

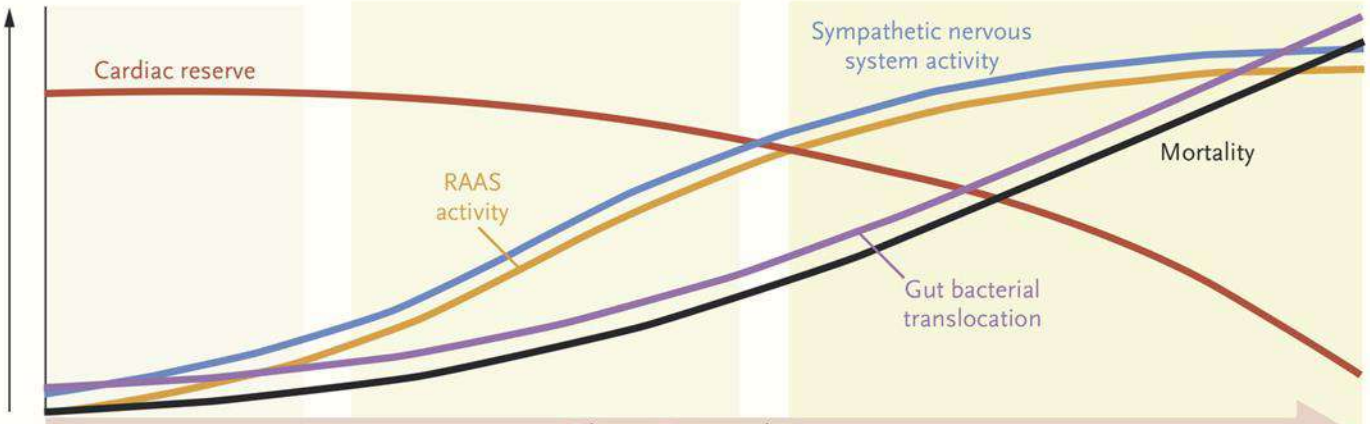
Beta adrenergic Blockers

Carvedilol (Coreg)

- Extensively metabolized in the liver
- 36% decrease in plasma clearance
- Significant increase in bioavailability observed in cirrhosis
- Reduction in initial dosage in patients with compensated cirrhosis
- Manufacturer recommends not to administer in clinically manifested hepatic impairment

Non-selective Beta Blockers

- Nadolol
  - Preferred because of a once daily dose
- Propanolol
  - Twice daily dosing
- Labetalol
  - Beta and Alpha blockade
  - Avoided in liver disease
- Nevibolol
  - Can increase portal pressures



Early Cirrhosis

Beta-blockers not indicated in early cirrhosis and do not prevent development of variceal bleeding and may increase adverse events
Cardiac reserve at baseline
Sympathetic nervous system and RAAS activity at baseline
Low risk of gut bacterial translocation and death

Beta-blocker window opens — start beta-blocker

Decompensated Cirrhosis (medium-to-large varices)

Beta-blockers indicated for primary prophylaxis of variceal bleeding
Beta-blockers indicated for secondary prophylaxis of variceal bleeding
Cardiac reserve intact but steadily declining
Sympathetic nervous system and RAAS activity increasing to compensate for decreasing arterial blood pressure
Increased risk of gut bacterial translocation and death

Beta-blocker window closes — stop beta-blocker

End-Stage Cirrhosis

Stop beta-blockers under these conditions:
- Refractory ascites
- Systolic blood pressure <100 mm Hg
- Mean arterial pressure ≤82 mm Hg
- Serum sodium level <120 mmol/liter
- Acute kidney injury
- Hepatorenal syndrome
- Spontaneous bacterial peritonitis
- Sepsis
- Severe alcoholic hepatitis
- Poor follow-up or nonadherence to regimen

Beta-blockers reduce survival owing to negative effect on cardiac reserve, decreased perfusion during periods of stress
Cardiac reserve critically impaired
Sympathetic nervous system and RAAS maximally stimulated
Gut bacterial translocation and death

Beta-blocker window does not reopen

Alpha-Adrenergic Blockers

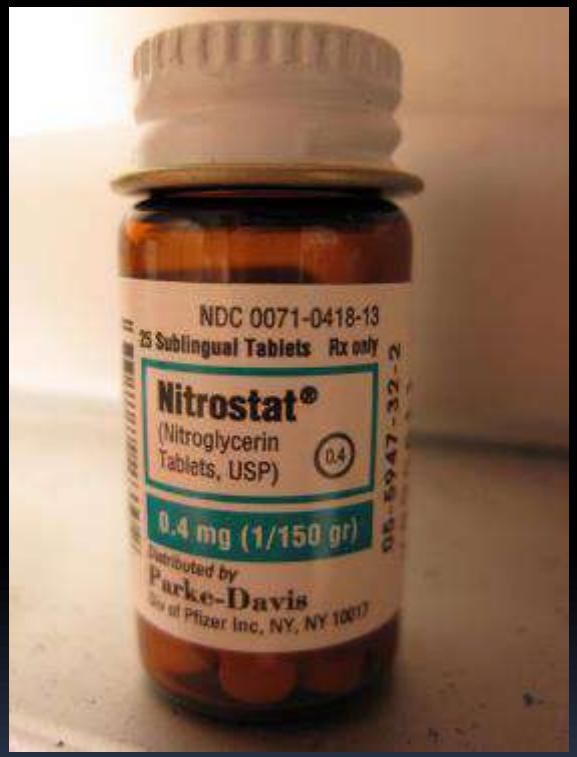
Terazosin

- Extensively metabolized by the liver
- 90% bioavailability
- Hepatic impairment prolongs its effect
- Dose should be reduced, use with caution

Vasodilators

Nitroglycerin

- Very rapid and nearly complete hepatic metabolism
- Lower dose recommended in hepatic impairment because bioavailability may increase



Antiplatelets

Clopidogrel

- Dosage adjustment is not required in patients with mild to moderate hepatic impairment
- Caution recommended in patients with severe hepatic disease

Anticoagulants

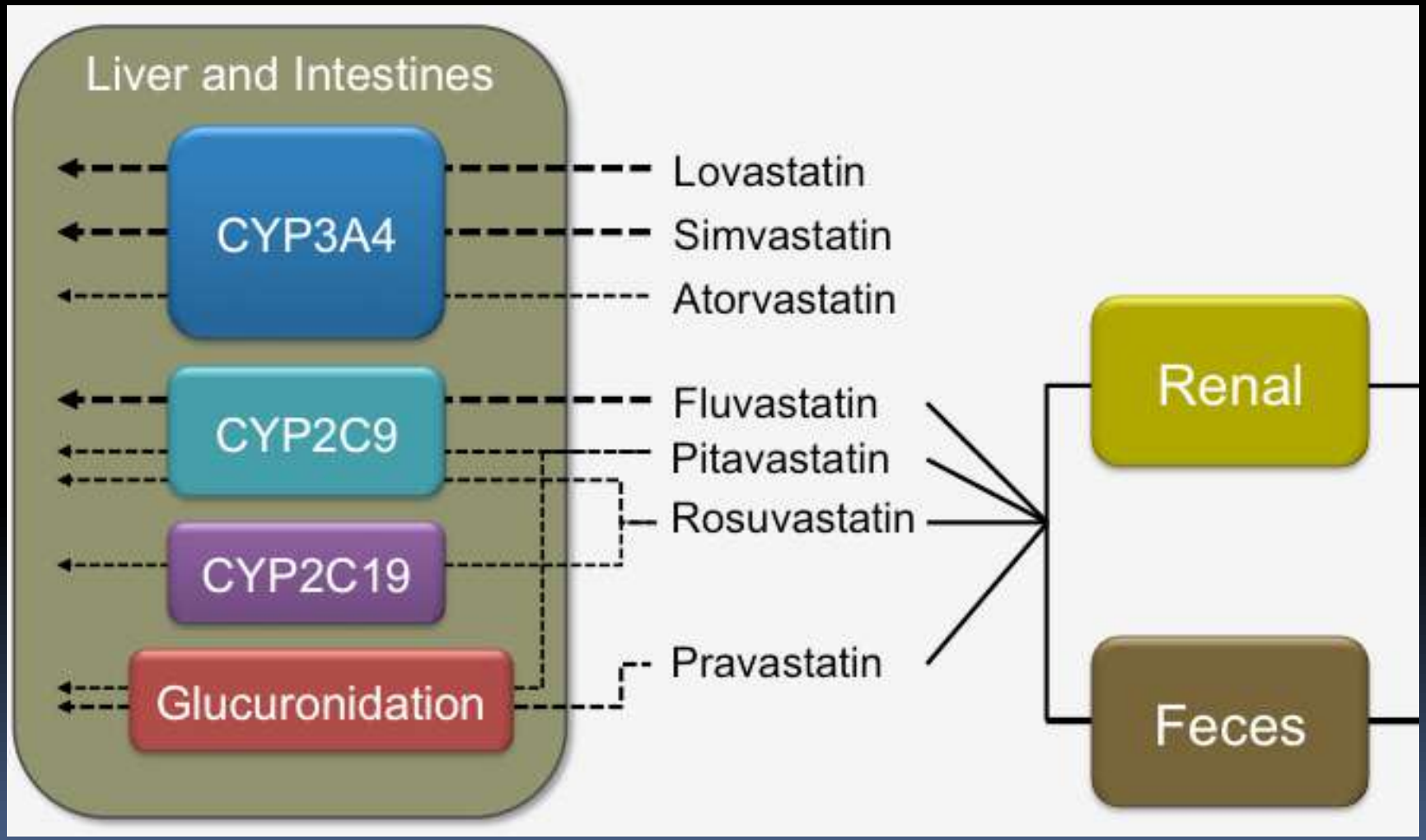
- Xarelto
  - Avoid in Child B-C
- Eliquis
  - Avoid in Child C
- Pradaxa
  - Prodrug
  - Not affected by the CYP 450
- Coumadin
  - Effects on MELD/Child

How to use STATINS in patients with Liver Disease

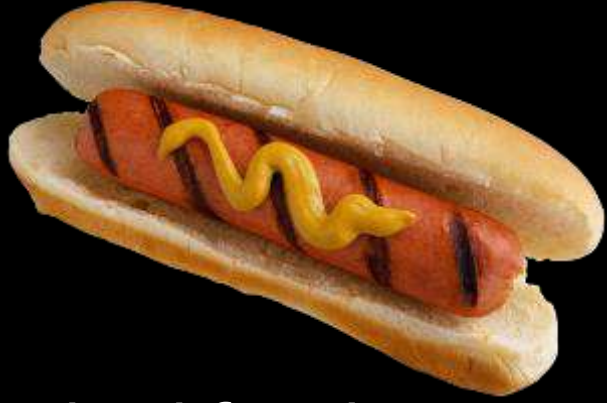
Metabolism of Statins

- Fist-pass hepatic metabolism
- Cytochrome P450 system
  - ✓ May utilize different isoenzymes
  - ✓ Monitor other drug levels metabolized by the same isoenzyme (eg, Phenytoin)
- 10-20 fold increase in levels of statins in ***advanced*** cirrhosis
  - ✓ Patients with cirrhosis typically have low cholesterol levels and do not require these agents

Metabolism of Statins



Statins

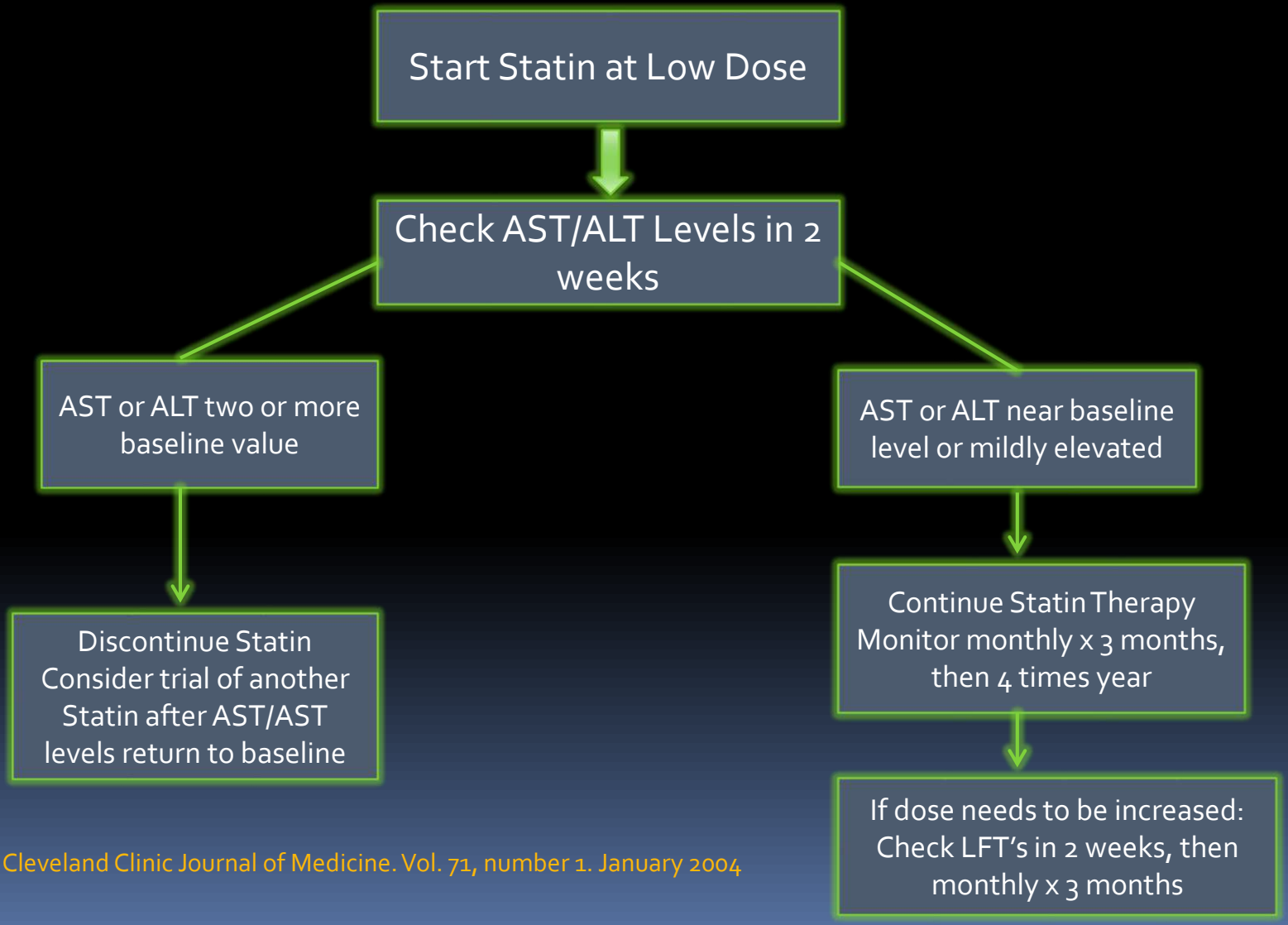


- Statins can and should be prescribed for the same indications in people with chronic liver disease as in those without it
- Statin-induced liver injury is uncommon
- Those with active acute liver disease such as ***acute*** viral hepatitis or alcoholic hepatitis should not receive it until they have recovered

Statins and CLD

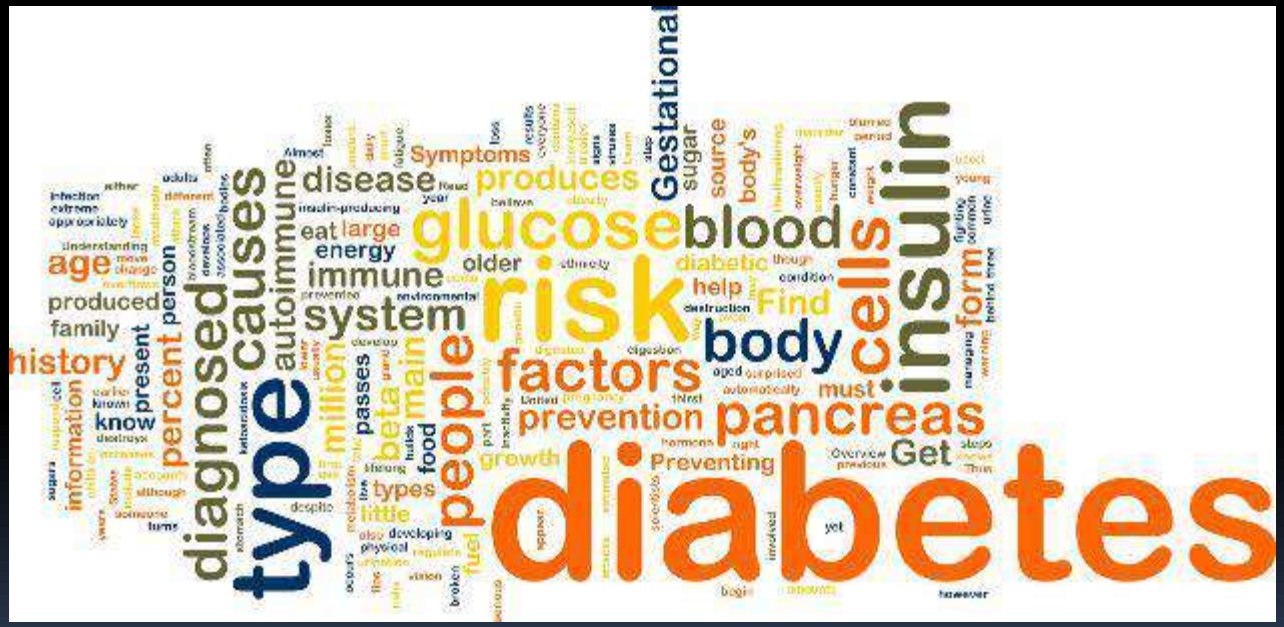
- 20% of the population has elevated enzymes due to fatty liver disease (NAFLD) ↘
- Statins rarely cause fibrosis
- Statins are under-prescribed
- Statins are used after liver transplantation to treat hyperlipidemia safely

Statins Therapy in patients with CLD:



Cleveland Clinic Journal of Medicine. Vol. 71, number 1. January 2004

How about diabetes medications??



Diabetes medications

- Glucophage
  - Very safe but…
  - Careful in alcoholics or renal insufficiency
- Sulfonylureas/Meglitinides
  - Metabolized in the liver and highly protein bound
  - Avoid in severe CLD/renal insufficiency
- Insulins
- Newer agents
  - SGLT2 inhibitors, DPP4 inhibitors, GLP-1 agonists

Natural/Herbal Medicines

- High risk for hepatotoxicity
- Determine the need
- Assess for drug-drug interactions
  - Search the LiverTox Database from the NIH
    - https://livertox.nlm.nih.gov/
- Careful with "proprietary blends"

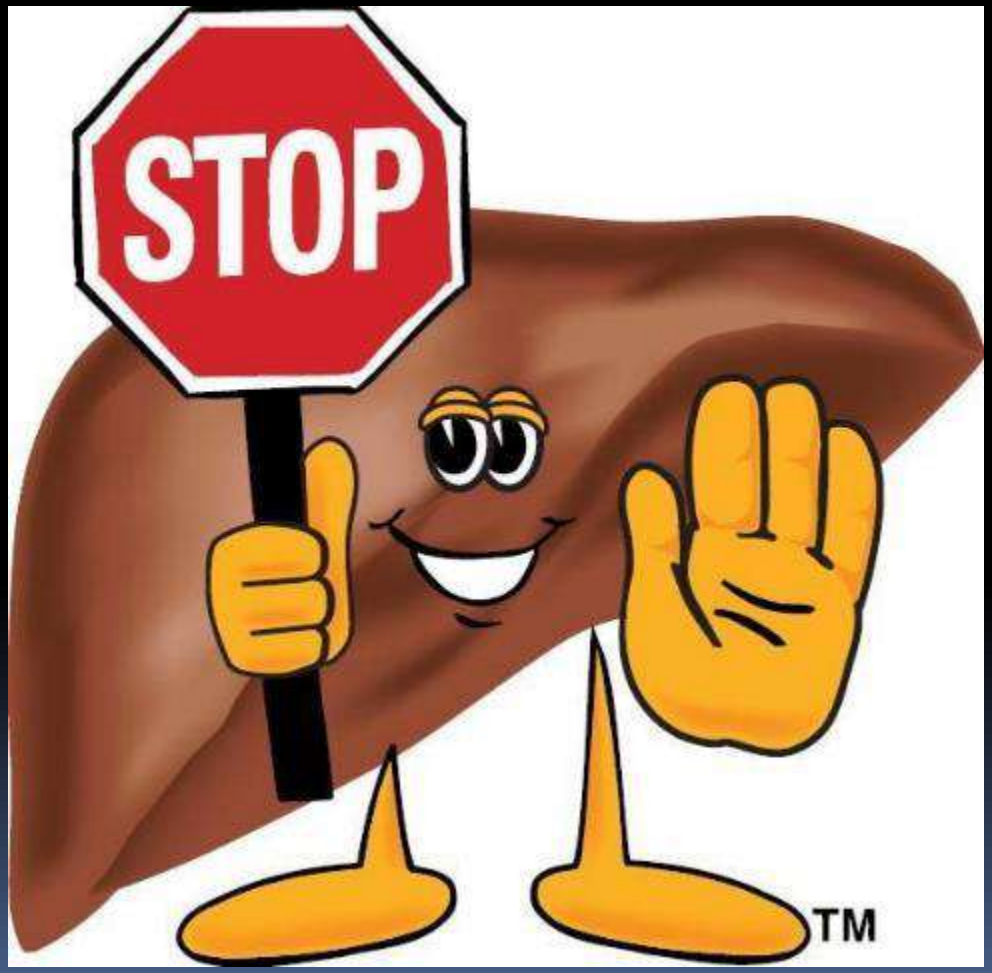
COVID 19 PEARLS

- Remdesivir
  - No dose adjustments
  - Monitor liver enzymes while on therapy
- Hydroxychloroquine (Plaquenil)
  - QTc prolongation
- Tocilizumab (Actemra)
- Siltuximab (Sylvant)
- REGEN-COV
  - Safe in cirrhosis
- Dexamethasone
- Ivermectin
- Immunosuppressive agents in OLT

Conclusion

- Liver disease can enhance the risk of adverse reactions of medications
- No test can determine drug dosing in patients with hepatic impairment
- Most drugs can be used safely
- Drug prescribing should be carefully done in patients with severe liver disease (cirrhosis), especially dose with jaundice, ascites or encephalopathy

…THANK YOU!!!!



References

1. Amarapurkar DN. Prescribing medications in patients with decompensated liver cirrhosis. *Intl J Hepatology* 2011; doi:10.4061/2011/519526: pp1-5.
2. S.I. Sokol, et al, "Cardiovascular drug therapy in patients with hepatic diseases and congestive heart failure," *Journal of Clinical Pharmacology,* vol. 40, no. 1, pp 11-30, 2000
3. R.K. Tandon,"Prescribing in patients with liver disease," *Medicine Update 2012*, vol. 22, pp. 494-497, 2012
4. Verbeeck RK. Pharmacokinetics and dosage adjustment in patients with hepatic dysfunction. *Eur J Clin Pharmacol* (2008) 64: 1147-1161

Contraindicated in ascites

- (NSAIDs)
  - high risk of developing further sodium retention, hyponatremia, and renal failure (Level A1).
- Drugs that decrease arterial pressure or renal blood flow
  - ACE-inhibitors, angiotensin II antagonists, or a1-adrenergic receptor blockers (Level A1).
- Aminoglycosides
  - reserved for patients with bacterial infections that cannot be treated with other antibiotics (Level A1).
- In patients with ascites without renal failure,
  - the use of contrast media does not appear to be associated with an increased risk of renal impairment (Level B1).
  - Contrast media should be used with caution and the use of general preventive measures of renal impairment is recommended (Level C1).

Types of Drug-Induced Liver Injury

- Indirect
  - caused by the action of the drug (what it does) rather than by its toxic or idiosyncratic properties (what it is)
  - induction of a new liver condition
  - exacerbation of a preexisting condition
    - induction of immune-mediated hepatitis
    - worsening of hepatitis B or C

Drug induced liver injury (DILI)

- The diagnosis is challenging.
  - based largely on exclusion of other causes
- Timing of the onset of injury after the implicated agent has been started (latency)
- Resolution after the agent is stopped (dechallenge)
- Recurrence on re-exposure (rechallenge)
- Knowledge of the agent's potential for hepatotoxicity (likelihood)
- Clinical features (phenotype)

DILI

- There are no specific diagnostic markers for drug-induced liver injury
- Special tests
  - liver biopsy, imaging, and testing for serologic markers
  - helpful mostly in ruling out other causes of liver injury

Types of Drug-Induced Liver Injury

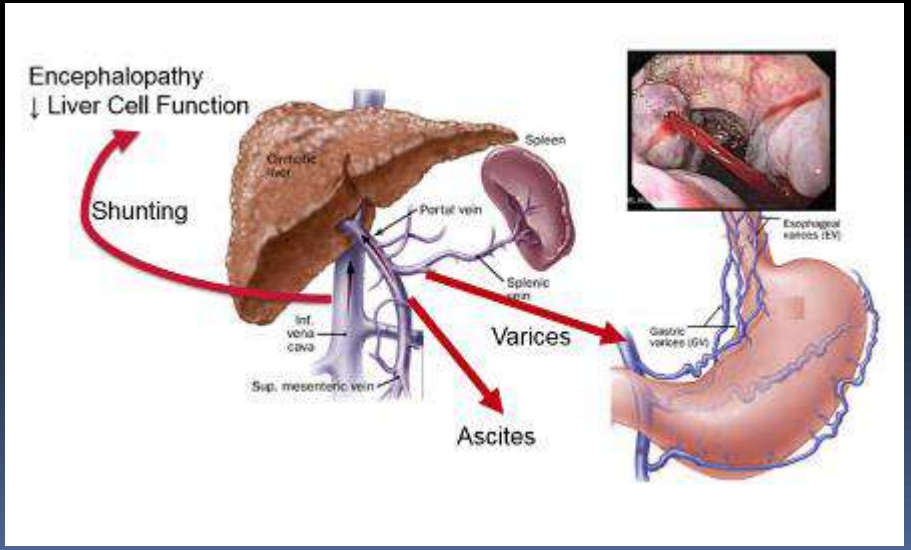
- Direct
  - caused by agents that are intrinsically toxic to the liver.
  - is common, predictable, dose-dependent, and reproducible in animal models.

Types of Drug-Induced Liver Injury

- Idiosyncratic
  - caused by agents that have little or no intrinsic toxicity and that cause liver injury only in rare cases
  - is unpredictable, not dose-dependent, and not reproducible in animal models.

Hepatic Pathophysiology

- Drug biotransformation in the liver is dependent on two factors:
  1. Hepatic blood flow
  2. Metabolic capacity of the liver



In patients with liver cirrhosis, impaired drug handling is due to:

1. Liver cell necrosis
2. Shunting of the blood through porto- systemic collaterals
3. Reduction in the concentration of drug binding protein
4. Abnormal drug volume distribution
5. Altered drug elimination
6. Altered drug metabolism
7. Associated renal failure
8. Drug-drug interactions