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# Prescribing to Patients with Liver Diseases

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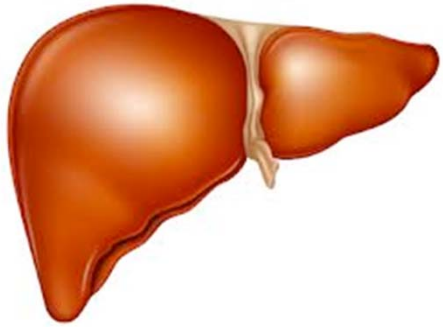
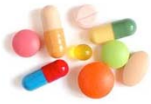
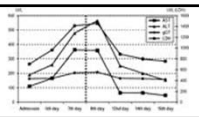
## What you want to know when prescribing to patients with liver diseases

- Effect of the diseased liver on the drugs
- Effect of drugs on the diseased liver
- Put together:
  - Can this drug be used?
  - Any precautions?
  - What dosage?

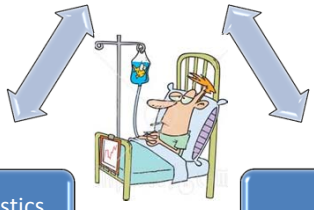
# Liver – primary site of drug metabolism





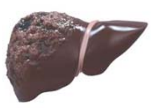


Liver biochemistry



Drug characteristics e.g. pharmacokinetics, side effects

Signs of liver diseases



## Impaired drug handling in liver diseases

- Reduced absorption edematous GI tract in ascites
- Reduced absorption in cholestasis
- Liver cell necrosis
- Shunting of the blood through porto-systemic colaterals
- Reduction in drug-binding proteins
- Abnormal drug volume distribution
- Altered drug elimination
- Altered drug metabolism
- Altered pharmaco-dynamics
- Associated renal failure
- Drug-drug interaction


Amarapurkar DN. Int J Hepatol 2011

## Side effect profiles – special precautions

- Ulcerogenic
- Coagulopathy
- Sedative
- Effects on electrolytes
- Effects on fluid balance
- Renal toxicity

## Drugs to avoided or used with caution

- NSAID / anticoagulations – variceal or ulcer bleeding
- Sedatives – hepatic encephalopathy
- Opiate – constipation and hepatic encephalopathy
- Diuretics – electrolytes disturbance and hepatic encephalopathy

## Prescribing in liver diseases – practical issues

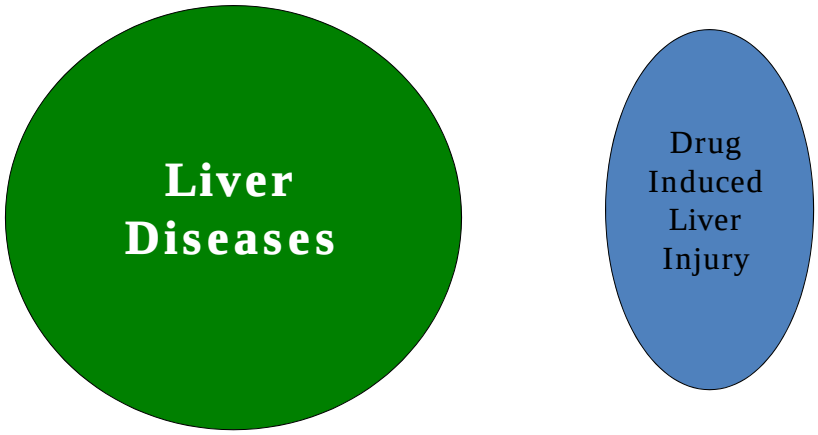
- Pharmacokinetic changes are not predictable
- Liver has amazing capacity even when cirrhotic
- Be careful not to under dose patients for essential therapies e.g. chemotherapy

## Rule of thumb when prescribing in liver diseases

- Avoid or use certain drugs cautiously
- Avoid hepatotoxic drugs if possible
- Use therapeutic levels whenever possible
- Monitor for efficacy e.g. BP, heart rate
- Monitor for toxicity
- Check renal function
- Start with smallest effective dose and titrate accordingly


## Liver diseases and drug induced liver injury

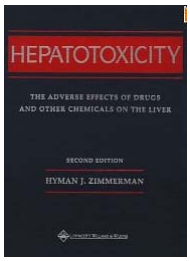
Two conditions seldom overlap



**In *most* cases, risk of hepatotoxicity <u>is not</u> increased when a drug is used in a patient with liver disease**

## But outcome can be worsen

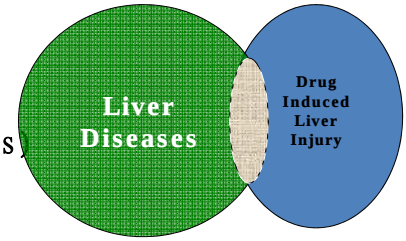
The same degree of liver injury, which is well tolerated in a normal subject, can trigger liver failure, complications and death in patients with an already impaired liver function




Zimmerman HJ: Hepatotoxicity. The Adverse Effect of Drugs and Other Chemicals on the Liver. Lippincott Williams & Wilkins, Philadelphia. 1999

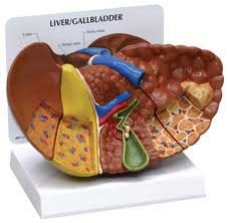
## Agents with increased risk of hepatotoxicity in patients with chronic liver diseases

- Rifampin, INH, pyrazinamide (In HBV & ETOH patients)
- Antiretrovirals (In HCV & HBV patients)
- Methotrexate (in alcoholic & NAFLD)
- Niacin (sustained-release formulation)
- Antiandrogens (flutamide)
- Valproic acid
- Methimazole
- Vitamin A (in large doses)



## Effect of drugs on the diseased liver

- It is safe to prescribe most medications in patients with liver diseases.
- Just pay special attentions to some agents with increased risk of hepatotoxicity in chronic liver diseases.




Zimmerman HJ: Hepatotoxicity. The Adverse Effect of Drugs and Other Chemicals on the Liver. Lippincott Williams & Wilkins, Philadelphia

## Rules for Detecting Hepatotoxicity

- ALT elevation
  - <3x ULN no action needed
  - >3x ULN deserves close attention
  - >5x ULN discontinue the medication


- Hy's Law
  - ALT + bilirubin elevation = **disaster!**

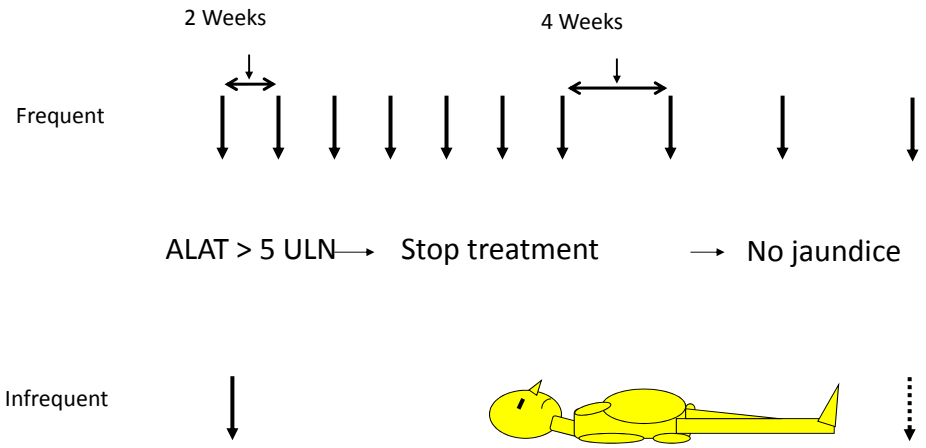
Black M, et al. Gastroenterology 1975;69:289-302
Reuben A, Hepatology 2004;39:574-578

## Hy's rule

by late Hyman Zimmerman 1914-1999

- If both drug-induced hepatocellular injury and jaundice occur at the same time without biliary obstruction, mortality of at least 10% can be expected
- ALT 3xULN and bilirubin 2xULN
- Advocated by FDA as an assessment tool of hepatotoxicity of new drugs

## ALT monitoring – useful or useless ?



Frequent monitoring in high risk cases, OR

Rather than infrequent LFT monitoring, it's best to

WARN THE PATIENT

" Consult and have liver tests performed
if you don't feel well "

"Stop treatment immediately
should you become jaundiced"

## Common examples of using hepatotoxic drugs in liver diseases

**Your Patient's Results**

**Cholesterol – 7.6**
**LDL – 4.4**
**HDL – 0.8**
**Triglycerides – 5.3**
**FBS – 7.8**
AST - 75
ALT – 105

## Can you prescribe a statin?

- **Yes!**
- Dallas Heart Study[1]
  - Statin use:
    - No increased prevalence of elevated ALT
    - No worsening hepatic steatosis
- Histopathological study[2]
  - Statin use:
    - Significant reduction in liver fat
    - Reduced progression to advanced fibrosis

1. Browning JD. Hepatology 2006;44:466-471 2. Ekstedt M et al. J Hepatol 2007:47:135-141

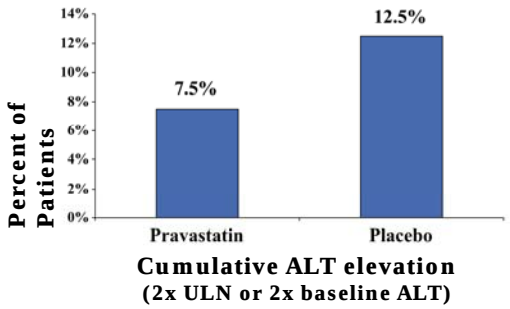
## Statins in patients with elevated liver enzymes

**Predominantly NAFLD patients**

| | Patients With Normal Enzymes Who Took Statins (n = 1437) | Patients With Elevated Enzymes Who Took Statins (n = 342) | Patients With Elevated Enzymes Who Did Not Take Statins (n = 2245) |
|---|---|---|---|
| Mild-moderate elevations in liver biochemistries* | 1.7% | 4.7% | 6.4% |
| | | $P = .002$ | $P = .2$ |
| Severe elevations in liver biochemistries* | 0.2% | 0.6% | 0.4% |
| | | $P = .6$ | $P = .6$ |

Chalasani N, et al. Gastroenterology 2004;128:1287-1292

## High Dose Pravastatin in Liver Disease Patients



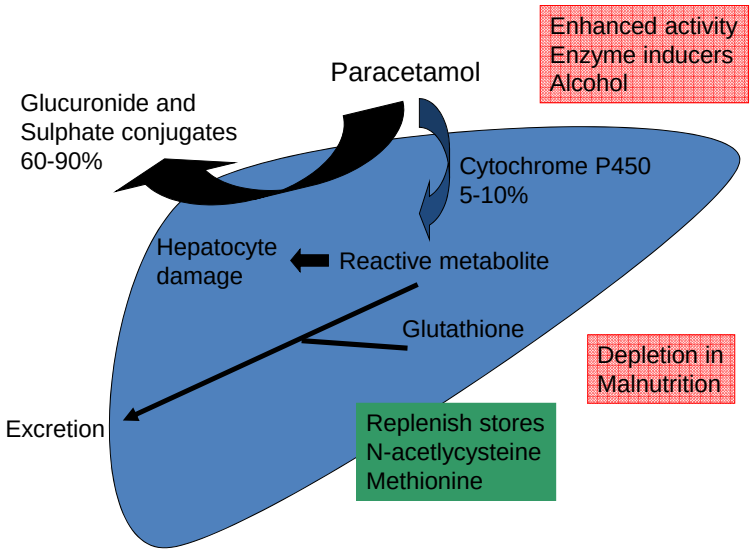

- Similar results for
  - -- Baseline normal vs. elevated ALT
  - -- HCV vs. NAFLD patients

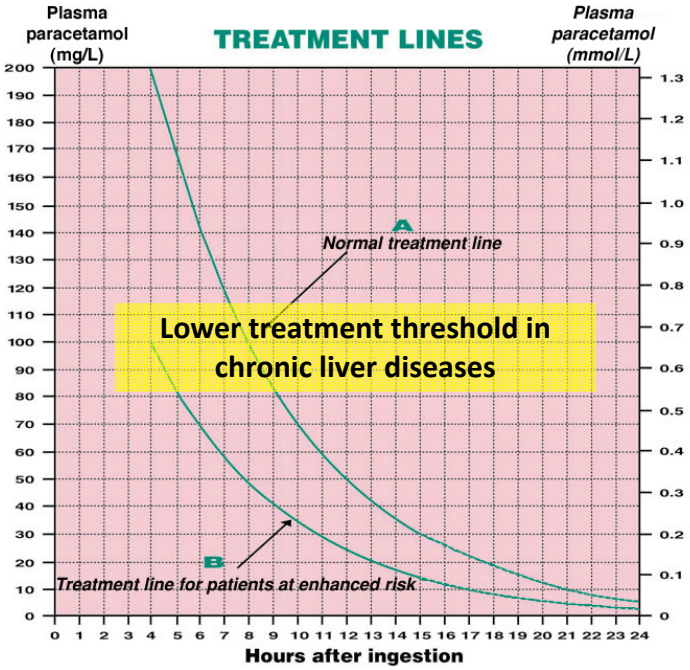
Lewis JH, et al. Hepatology 2007;46:1453-63

## Analgesics in liver disease

- Paracetamol
  - – Safe in small quantities
  - – Probably the safest analgesic for liver patients
  - – Reduce maximum daily intake and avoid regular dosing for >5 days)
    - ie 500mg QID prn (max 2g daily)

# Metabolism of paracetamol



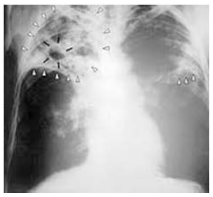
# Analgesics in chronic liver disease

- NSAIDs
  - **NEVER**! Variceal haemorhage, renal failure
- Codeine/Tramadol
  - Risk of encephalopathy
  - Need to balance risk versus need for analgesia
  - Co-prescribe lactulose
  - Use lower doses, avoid regular dosing
- Stronger opiate
  - Never without consultation with specialist
  - High risk of over-sedation and encephalopathy
  - Effects may be delayed/prolonged



# TB Treatment and Liver Disease

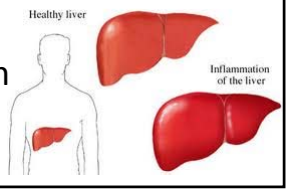
- Use standard short-course regimen for patients without clinical evidence of chronic liver disease but history of:
  - Viral hepatitis (acute or chronic)
  - Excessive alcohol consumption



- Use a liver-sparing regimen for patients with established chronic liver disease
  - 2SHRE/6HR or 2SHE/10 HE

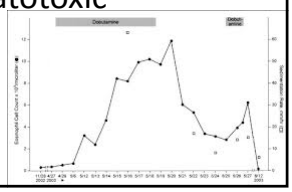
## TB Treatment and Hepatitis

- Asymptomatic elevation ALT occurs in 20% patients on 4 drugs
- Drug induced hepatitis = ↑ ALT ≥3xULN with symptoms OR ↑ >5 times if asymptomatic
- INH, PZA and RIF can all cause hepatotoxicity
  - INH: age related
  - PZA: dose related
  - RIF: unpredictable and less common




## TB Treatment and Hepatitis - Management

- If ↑ ≥3x normal with symptoms or >5x normal without symptoms:
  - stop all anti-TB medications and evaluate patient
  - try to rule out other causes of acute liver disease
  - if severely ill, may start 3 non-hepatotoxic drugs
  - after ALT <2xULN — rechallenge drugs one-by-one starting with drugs that are not hepatotoxic



## Antibiotics to be avoided in liver diseases

- Chloramphenicol—higher risk of bone marrow suppression (markedly increased half life)
- Erythromycin estolate: causes cholestasis
- Tetracycline—dose related hepatotoxicity
- Griseofulvin—contraindicated
- Nitrofurantoin prolonged use

## Antibiotics to be used with cautions

- Piperacillin
- Ceftazidime
- Ceftriaxone
- Cefoperazone +/- Sulbactam
- Erythromycin
- Azithromycin
- Tetracycline
- Cotrimoxazole + Trimethoprim
- Metronidazole
- Ketoconazole & other fluconozoles

# Conclusions

- Most drugs are safe in liver diseases
- Use certain drugs cautiously
- Avoid hepatotoxic drugs if possible (or close monitoring if deem necessary)
- Immediate stop suspected drugs with deteriorated LFT (hopefully before development of jaundice)