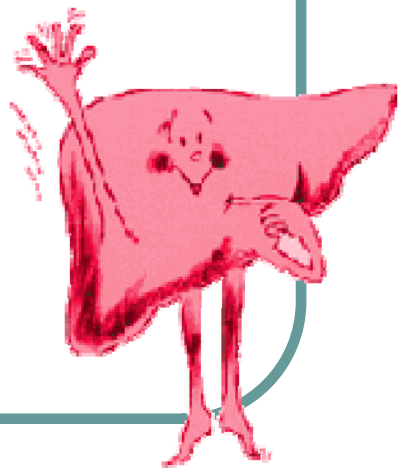
Medicines issues in liver disease

Penny North-Lewis
Paediatric Liver Pharmacist
Leeds General Infirmary
September 2011



Aim

- To illustrate some of the enquiries encountered regarding the use of medicines in patients with liver dysfunction
- To define a strategy for finding solutions to these queries

Plan for session

- Types of liver related MI enquiries
- Why it is so hard to answer them
- Basic hepatology
- Interpreting laboratory tests
- Pharmacokinetics and dynamics
- Pulling together an answer

Types of liver enquiry

- 152 enquiries from Apr 10 to Mar 11
  - 109 choice/dose of drug in a liver pt
  - 20 requests for protocol information
  - 9 for ADR/hepatotoxicity information
  - Others incl. compatability, general background

Types of liver enquiry – choice/dose

- Antimicrobials 34
- Analgesia 11
- Psychotropics 11
- Antiepileptics 6
- Antidepressants 6
- Chemotherapy 6
- Hormones 4
- Others incl. antihistamines, antiemetics

Why the problem?

- Lack of information in regular sources e.g BNF, SPC (misinformation/lack of data)
- Lack of research, small numbers of patients
- No easy equation to use
- Poor understanding of liver dysfunction

Where to start

- Taking in an enquiry
  - Liver Enquiry proforma

LIVER ENQUIRIES - Patient Considerations

Gathering the Information

LFT		Date	Date	Date	Date
	Range				
ALT	<40iu/L				
AST	<40iu/L				
Alk Phos	30-300iu/L				
Bil	3-15 µmol/L				
Alb	34-48g/L				
GGT	0-40iu/L				
INR	0.9-1.2				
PT	9-14.5 secs				
Creat	80-115 µmol/L				

Check enquirers range - ranges may vary, particularly Alk Phos

What is the liver diagnosis?

Over what timescale has this occurred?

Acute - could this be hepatotoxicity?
Chronic - Is the pt cirrhotic?

Any signs or symptoms?

Encephalopathy -present or previous
Jaundice or Pale stools/Dark urine
Ascites - present or previous
Varices - present or previous

Do you have results of any tests?

Ultra Sound Scan

Biopsy

ERCP/HIDA

Endoscopy

Is there known Portal Hypertension

Does the patient have any other conditions or medications that need to be considered?

What is the ideal choice of agent(s)?

Applying the Information

Effect on kinetics/dynamics	Risk factors for side effects	
Ascites (A/D)	Varices	
Cholestasis (A/E)	Coagulopathy or low platelets	
Low albumin (D)	Encephalopathy	
Portal hypertension (M)	Pruritus	
Acute liver failure (M)	Alcoholism	
Cirrhosis - compensated (M)	Ascites	
Cirrhosis - decompensated (M)	Renal impairment/hepatorenal	
Encephalopathy (P)	Cirrhosis	

Key A: Absorption D: Distribution M: Metabolism E: Elimination P: Pharmacodynamics

LIVER ENQUIRIES - Drug Considerations

Pharmacokinetics		**Considerations**
Absorption		Lipid solubilty (Absorption affected by ascites)
Distribution		Water/fat Protein binding % Displaced by bilirubin or displaces bilirubin
Metabolism		First pass effect Hepatocyte dependent Prodrug CYPs Active metabolites Genetics
Elimination		Biliary excretion Alternative mechanisms Enterohepatic recirculation (Renal impairment)

Adverse Effects :

Hepatotoxicity

Does the drug affect LFTs?
What is the incidence of this reaction?
Is this a transient effect?
Is it known how long it will take for the LFTs to recover?

Is the drug associated with causing hepatitis or cholestasis?
What type of reaction does it cause?
What is the incidence of this reaction?
How long does it take to recover from this effect?

Is the drug associated with any more serious or long-term hepatotoxic reactions?
eg hepatic necrosis, vanishing bile duct syndrome?
What is the incidence of this reaction?

Other Relevant Adverse Effects

Dermatological
eg. pruritus and urticaria
What is the incidence of this reaction?
Is it a common, uncommon or rare effect?

Endocrine/Metabolic
eg. fluid & electrolyte imbalance
What is the incidence of this reaction?
Is it a common, uncommon or rare effect?

Gastrointestinal
eg. constipation
What is the incidence of this reaction?
Is it a common, uncommon or rare effect?

Haematological
eg. Thrombocytopenia, effects on clotting, increased risk of bleeding
What is the incidence of this reaction?
Is it a common, uncommon or rare effect?

Neurological
eg.confusion, seizures, sedation
What is the incidence of this reaction?
Is it a common, uncommon or rare effect?

Renal
eg. renal toxicity
What is the incidence of this reaction?
Is it a common, uncommon or rare effect?

Are there any drug interactions or drug-disease interactions that need to be considered?

Why so much information?

- *Back to first principles*

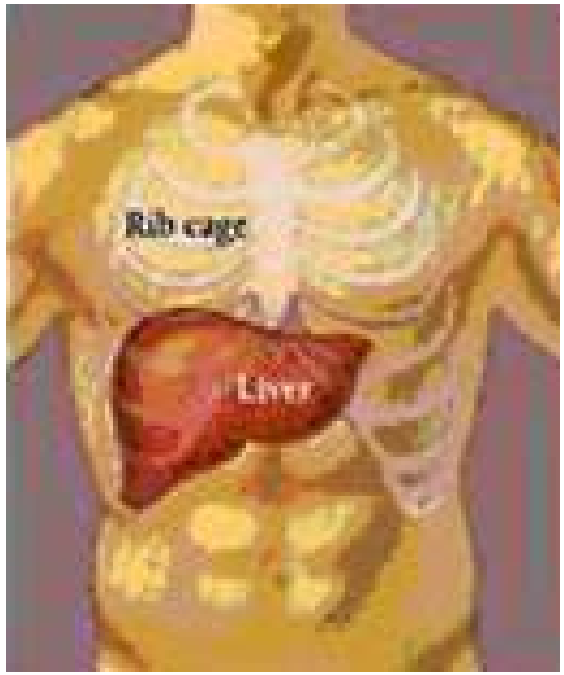
- Identify extent and type of liver dysfunction
- Consider how this will affect drug handling
- Consider how the drug may affect the patient – side effects, pharmacodynamic effects
- Remembering the whole patient

Plan for session

- Types of liver related MI enquiries
- Why it is so hard to answer them
- Basic hepatology
- Interpreting laboratory tests
- Pharmacokinetics and dynamics
- Pulling together an answer

Where is the liver?

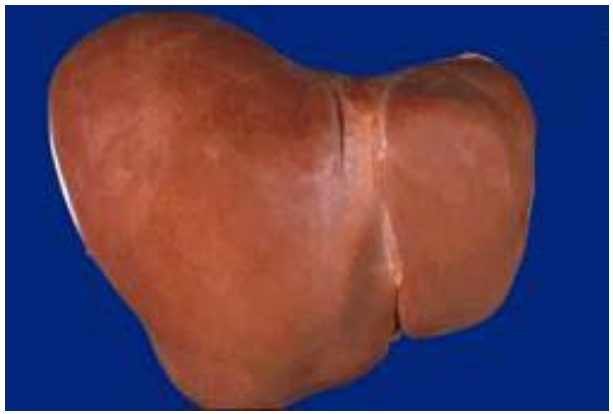
- In a child it can be felt 1-2cm below the ribcage.
- In adults it can only be felt if it is enlarged
- RUQ pain if enlarged



What does the liver do?

Homeostasis
e.g. glucose

Synthesis
(e.g. albumin & clotting factors)



Lipid Metabolism
e.g. cholesterol

Filtration
e.g. antigens

Bile production and secretion

Metabolism e.g drugs, oestrogens, toxic products such as ammonia

Terminology – time frame

- **Acute**

Sudden onset – jaundice to encephalopathy in less than 7 days (hyperacute), 28 days (acute), 6 months (sub-acute)

- **Chronic**

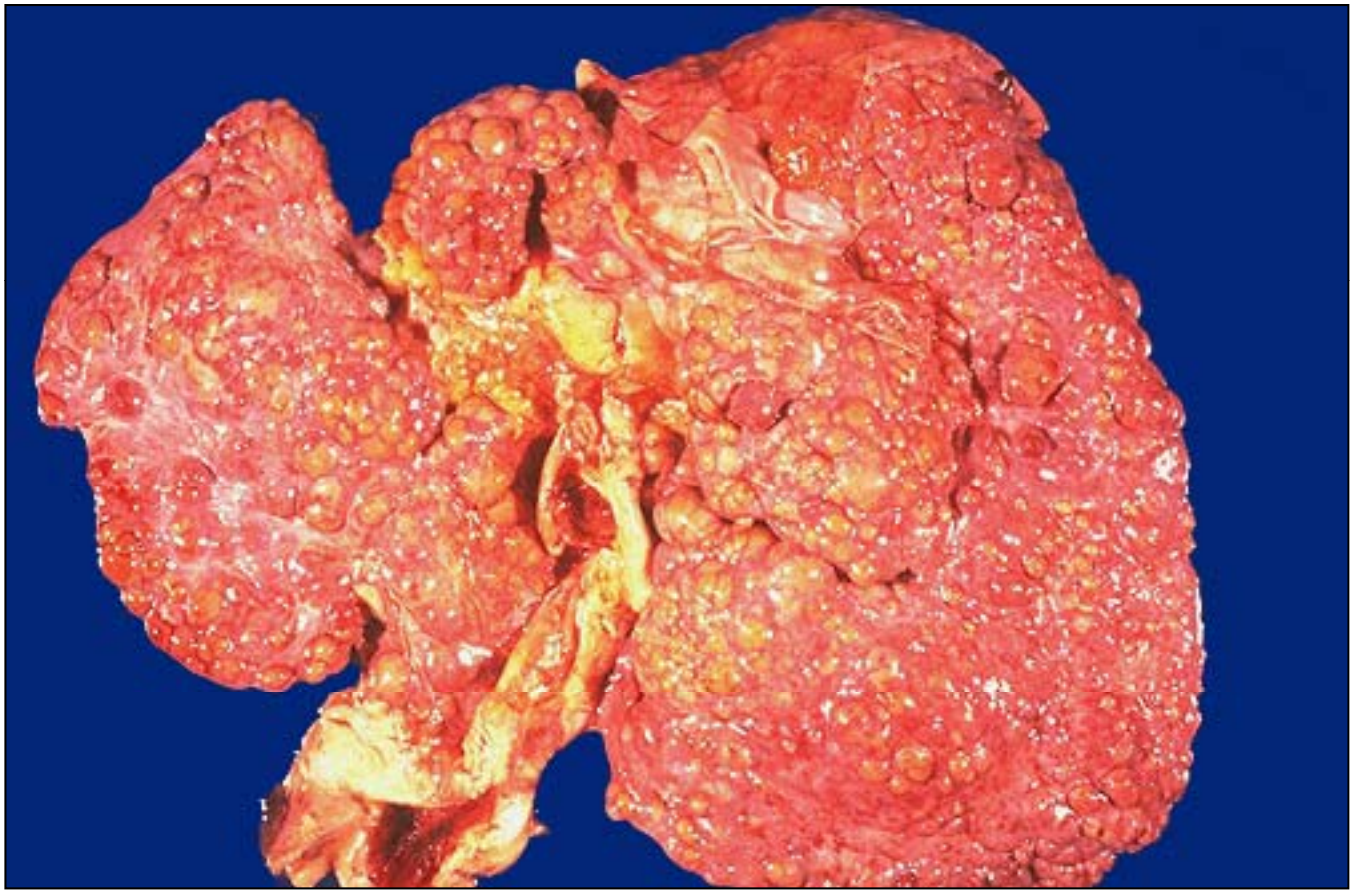
Extended duration – months/years

Terminology – type of picture

- **Hepatocellular**
  - Fatty infiltration (steatosis) e.g. alcohol
  - Inflammation (hepatitis) e.g. viral
  - Cell death (necrosis) e.g. POD
- **Cholestasis**
  - Static bile flow (not specifically bilirubin)

Terminology - Hepatocellular

- **Hepatitis**
  - Inflammation of hepatocytes
- **Fibrosis**
  - An increase in connective tissue in the liver – reversible



Terminology - Hepatocellular

- **Cirrhosis**

Widespread disorganised nodules in the liver combined with fibrosis

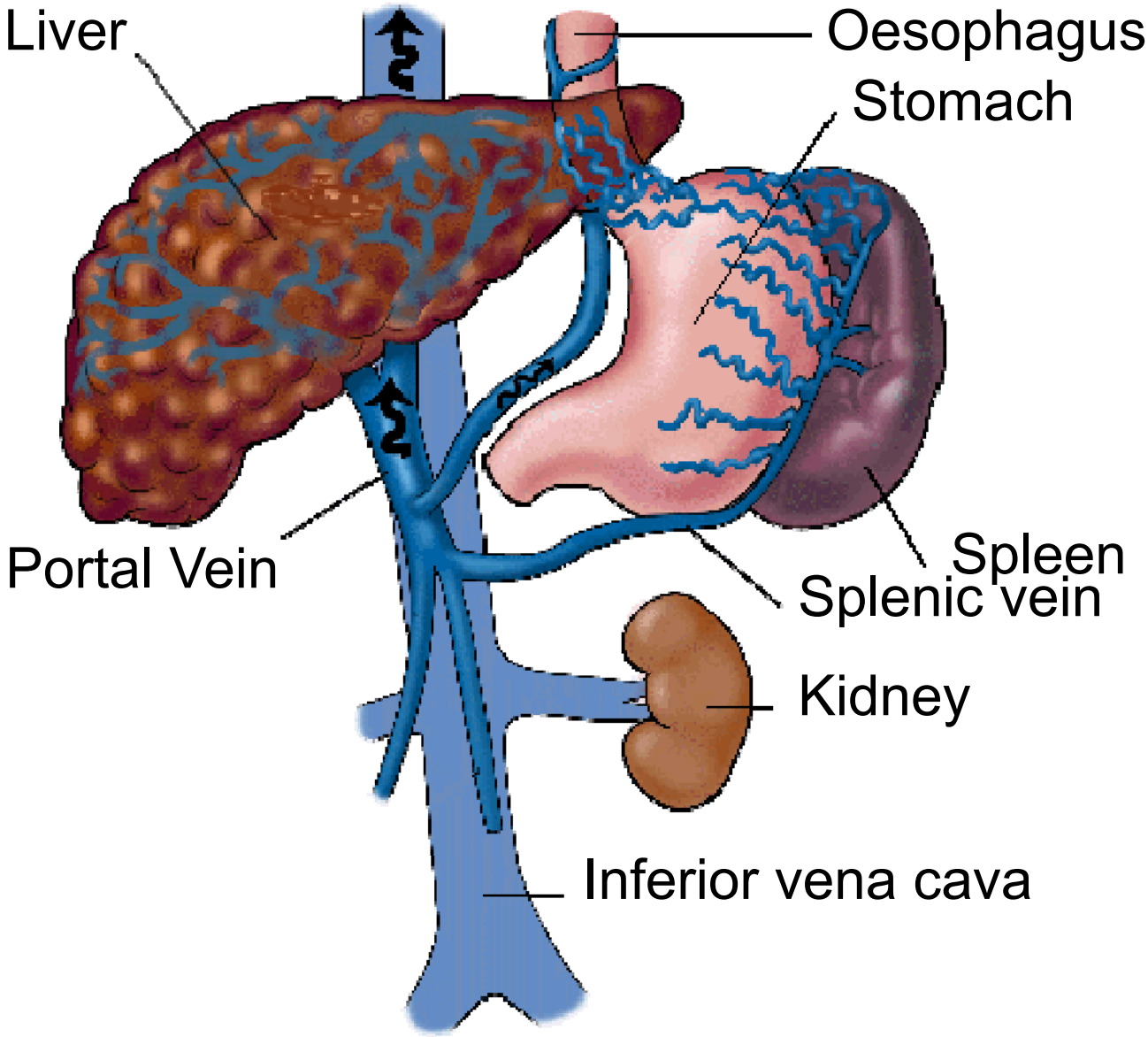
- **Compensated cirrhosis**

When a cirrhotic liver continues to function

- **Decompensated cirrhosis**

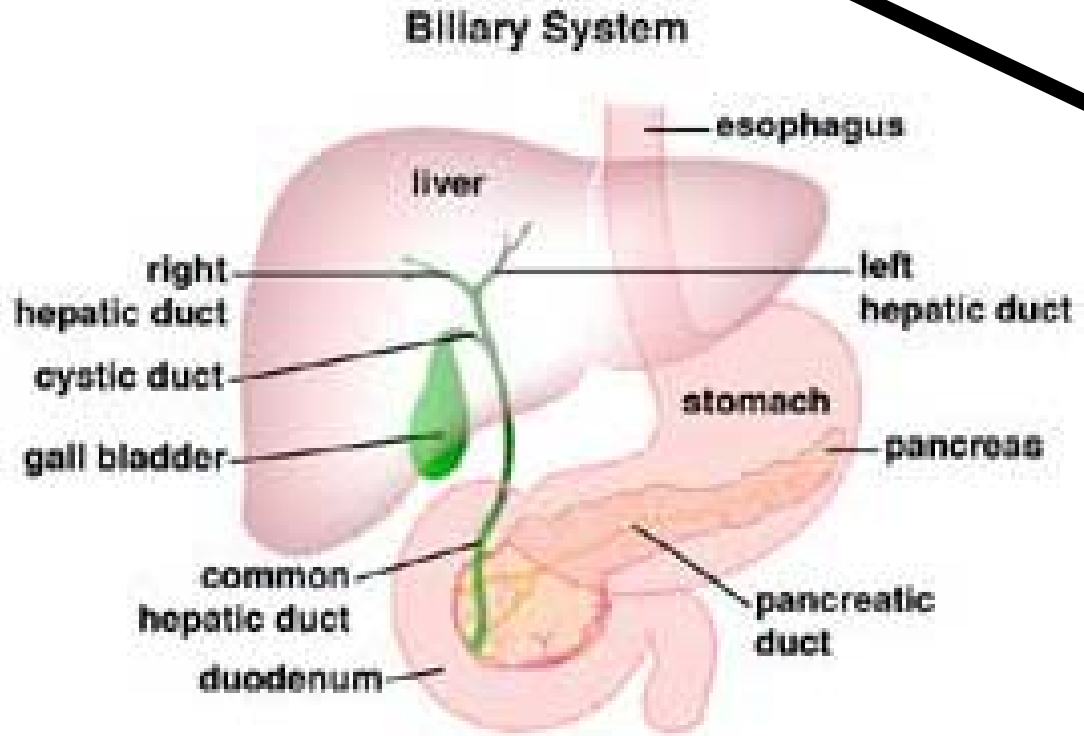
When a cirrhotic liver can no longer function adequately – signs eg coagulopathy occur

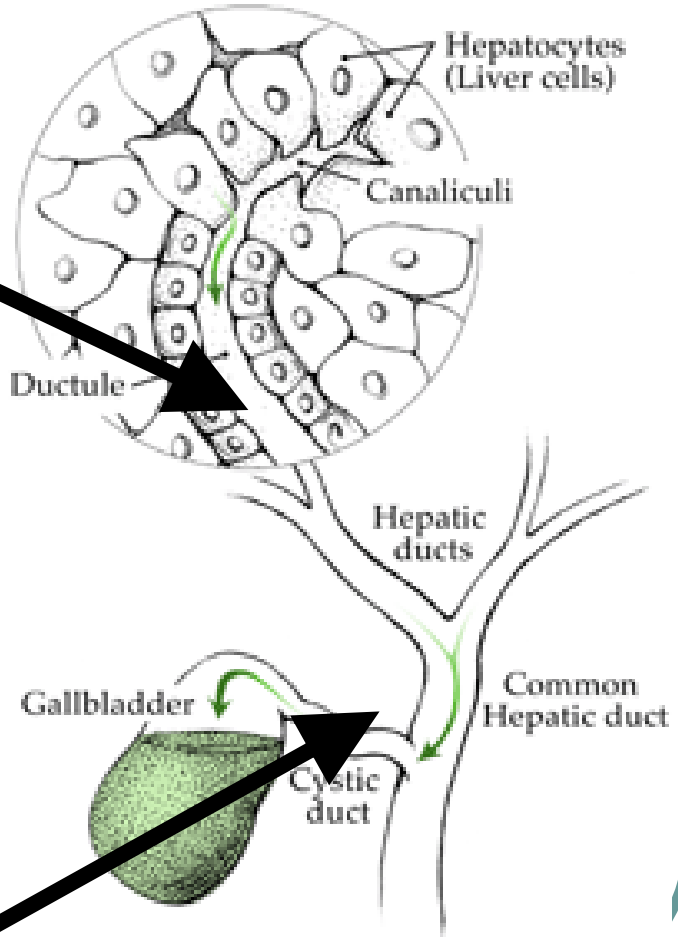
- Portal hypertension



Terminology - Cholestasis

Intrahepatic





Extrahepatic

Causes of liver disease

- Metabolic & inherited – CF, Alagille, tyrosinaemia, Wilson's
- Autoimmune – AIH, PSC, PBC
- Structural – biliary atresia, choledochal cysts
- Infection – hepatitis B, C
- Alcoholic liver disease
- Non-alcoholic fatty liver disease
- Cancer – usually underlying cirrhosis

Causes of liver dysfunction

- Ischaemia
- Infection – H1N1, CMV, EBV, malaria…
- MOF
- Drugs/TPN
- Trauma
- Oncological – metastases
- Gallstones, pancreatitis

Need to know:

- the type of dysfunction your patient has - hepatocellular or cholestatic
- the degree of dysfunction

Why?

Cholestasis

- Impaired elimination of biliary cleared drugs, malabsorption of fat soluble drugs

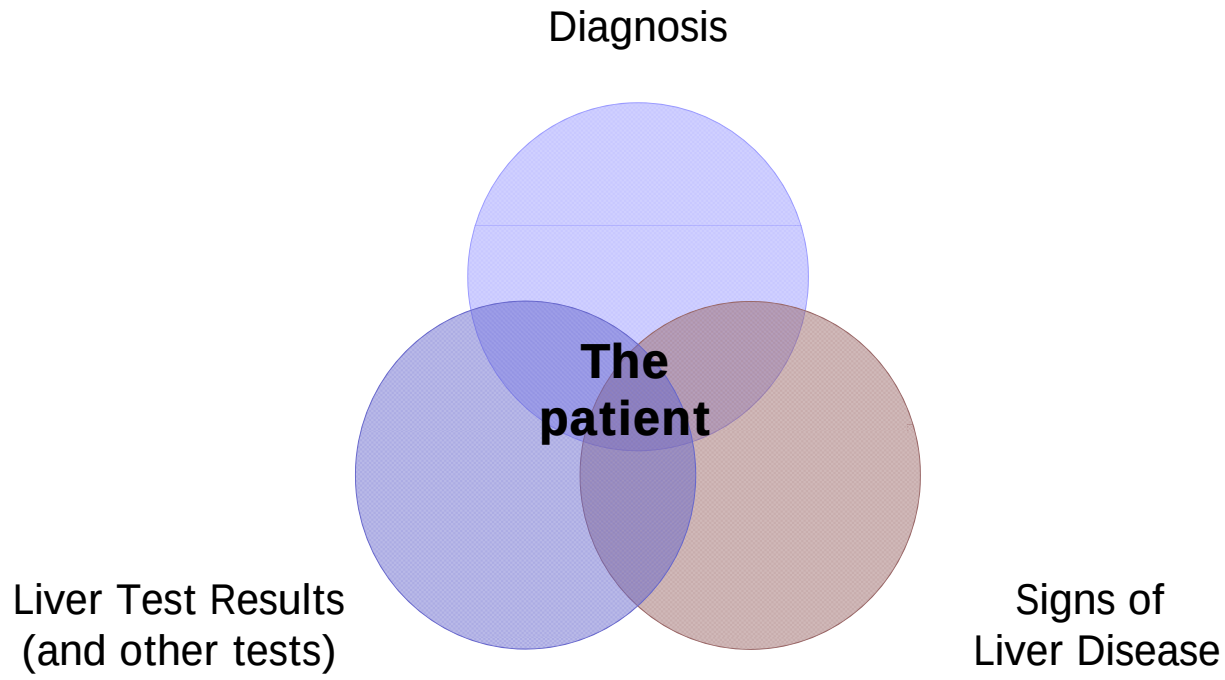
Hepatocellular damage

- Impaired metabolism, reduced protein binding, deranged distribution …

How?

- Diagnosis
  - Gallstones – cholestasis, normal hepatocyte function
  - Tyrosinaemia – hepatocyte damage, normal bile flow
  - Auto-immune hepatitis – hepatitis → fibrosis → cirrhosis → cholestasis → decompensated cirrhosis

Where on the continuum?



Transaminases (0-35iu/L) (ALT & AST)

- Enzyme released from hepatocytes when damaged
- Markers of hepatocellular injury
  - High elevations in acute injury (in several thousands)
  - Can be **normal** in severe chronic liver disease (cirrhosis)
- Also found in heart, muscle and kidney
- ALT more specific to liver than AST

Alkaline Phosphatase
(normal range varies for age and hospital)

- Biliary enzyme – raised with bile duct damage
  - Increased in cholestasis
- Less raised in hepatocellular disease
- Not specific to the liver
  - also found in bone (eg raised in Paget's disease/bone metastases)
  - small quantities in the intestine and placenta

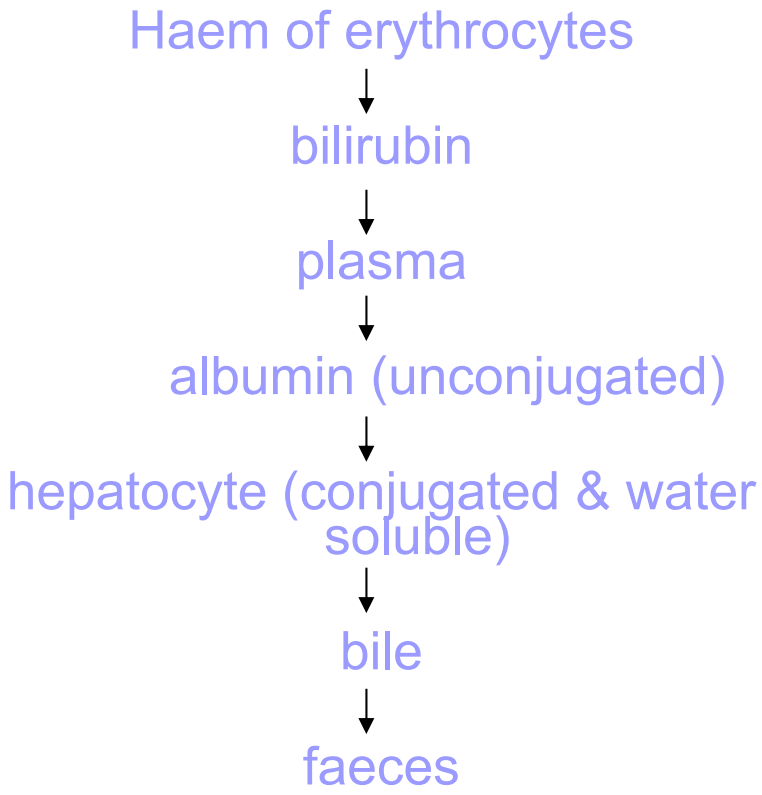
Gamma glutamyl transferase (GGT) (0-30u/l)

- Enzyme in biliary tract
  - Increased in cholestasis
- Increased by enzyme inducing drugs

  e.g. rifampicin and alcohol
- Useful to determine if isolated raised alkaline phosphatase is liver related

Bilirubin (3-17 micromol/l)

- **Unconjugated**
  - Increased production (haemolysis)
  - Decreased conjugation (Gilberts, neonate, cirrhosis)
- **Conjugated**
  - Intrahepatic cholestasis
  - Extrahepatic cholestasis (gall stones, BA)



Albumin (37-49g/l)

- Synthesised in liver
- Half-life approx 20 days
- Good indicator of chronic liver disease
- Low specificity
  - Decreased intake e.g. malnutrition
  - Increased loss e.g. enteropathy

Prothrombin Time (~13 secs) or INR (0.9-1.2)

- Decreased synthesis of clotting factors (cirrhosis)

OR

- Vitamin K malabsorption (in cholestasis)

- Elevation > 3 seconds significant
- Prolonged in acute & chronic liver disease
- Useful prognostic indicator of impending liver failure e.g. acute liver failure or decompensated chronic liver disease

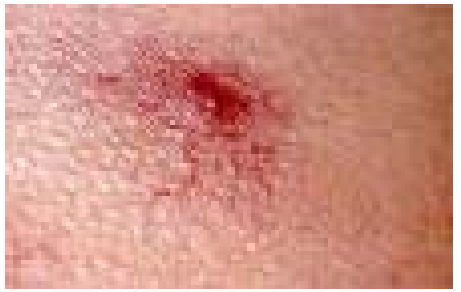
Other useful tests

- Ultrasound – liver texture, dopplers for blood flow in hepatic artery, portal vein
- Liver biopsy – fibrosis, cirrhosis, intrahepatic cholestasis
- OGD – varices
- HIDA – bile flow (cholestasis)
- Blood glucose, creatinine

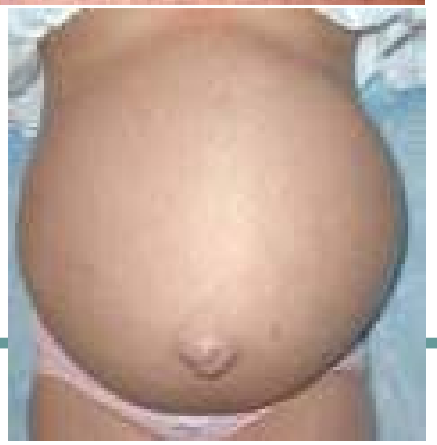
Signs of liver dysfunction

- Jaundice
- Pale stools/dark urine
- Palmar erythema
- White nails
- Gynaecomastia/testicular atrophy
- Spider naevi
- Ascites
- Bruising and bleeding
- Splenomegaly
- Oesphageal and gastric varices
- Encephalopathy

Jaundice



“Spiders”



Ascites

Symptoms of liver dysfunction

- Pruritus
- Lethargy
- Abdominal pain
- Bruising and bleeding
- Anorexia

Problem with specificity

ALT **25 (5-40u/l)**
Bilirubin **28 (5-17μmoles/l)**

1. Alk Phos 499 (30-300u/l)
   ⇒ normal liver function; Pagets disease

2. Alk Phos 499 (30-300u/l)
   ⇒ itch, liver biopsy; primary biliary cirrhosis

3. Albumin 21 (35-50g/l)
   ⇒ normal liver function; malnourished

ALT 25 (5-40u/l)
Bilirubin 28 (5-17μmoles/l)

4. INR 1.9, prothrombin time 21 (12-16sec)

⇒ normal liver function; on warfarin

5. Alk Phos 499 (30-300u/l)
Albumin 21 (35-50g/l)
INR 1.9 (PT 21 secs)

⇒ a. combination of any of above diagnoses

⇒ b. ascites, encephalopathy, varices;
end stage chronic liver disease

- Helps to decide how to modify drug therapy and to categorise patient into one of the following types:
  - Hepatitis
  - Cholestasis
  - Cirrhosis – compensated
  - Cirrhosis – decompensated
  - Acute liver failure

LIVER ENQUIRIES - Patient Considerations

Gathering the Information

LFT		Date	Date	Date	Date
	Range				
ALT	<40iu/L				
AST	<40iu/L				
Alk Phos	30-300iu/L				
Bil	3-15 µmol/L				
Alb	34-48g/L				
GGT	0-40iu/L				
INR	0.9-1.2				
PT	9-14.5 secs				
Creat	80-115 µmol/L				

Check enquirers range - ranges may vary, particularly Alk Phos

What is the liver diagnosis?

Over what timescale has this occurred?

Acute - could this be hepatotoxicity?
Chronic - Is the pt cirrhotic?

Any signs or symptoms?

Encephalopathy -present or previous
Jaundice or Pale stools/Dark urine
Ascites - present or previous
Varices - present or previous

Do you have results of any tests?

Ultra Sound Scan

Biopsy

ERCP/HIDA

Endoscopy

Is there known Portal Hypertension

Does the patient have any other conditions or medications that need to be considered?

What is the ideal choice of agent(s)?

Applying the Information

Effect on kinetics/dynamics	Risk factors for side effects	
Ascites (A/D)	Varices	
Cholestasis (A/E)	Coagulopathy or low platelets	
Low albumin (D)	Encephalopathy	
Portal hypertension (M)	Pruritus	
Acute liver failure (M)	Alcoholism	
Cirrhosis - compensated (M)	Ascites	
Cirrhosis - decompensated (M)	Renal impairment/hepatorenal	
Encephalopathy (P)	Cirrhosis	

Key A: Absorption D: Distribution M: Metabolism E: Elimination P: Pharmacodynamics

Next stage - drug

- PK
- PD
- ADRs

Absorption

- **Ascites** may impair absorption e.g. diuretics
  - Bigger doses or IV
- **Cholestasis** may impair absorption of fat soluble drugs e.g. fat soluble vitamins
  - Bigger doses

Distribution

- **Ascites** will increase volume of distribution for water soluble drugs
  - Bigger doses *per kg*
- **Low albumin** will alter amount of free drug if highly protein bound
  - Reduced doses

Metabolism

- **Decompensated cirrhosis** - reduced number of functioning hepatocytes
  - Reduce dose or increase interval
- **Portal hypertension** - reduced first pass metabolism if highly extracted drug e.g. propranolol, lidocaine
  - Reduce dose

Metabolism

- Prodrugs that need to be metabolised to the active form in the liver may need bigger doses! E.g. enalapril

Elimination

- **Cholestasis** – biliary cleared drugs may accumulate
  - Caution if active/toxic metabolites are produced, possibly not important if inactive
  - Compensatory pathways e.g. renal if reduced biliary clearance?

Pharmacodynamcis

- Increased receptor sensitivity
  - More permeable BBB
  - Increased respiratory depression with opioids

Side Effect Profile

Drugs with the following side effects may need to be avoided/used with caution:

- GI ulceration – *varices, coagulopathy*
- Constipation – *cirrhosis, encephalopathy*
- Pruritus - *cholestasis*
- Sedation – *encephalopathy, cirrhosis*
- Coagulation defects - *coagulopathy*
- Effects on electrolytes – *cirrhosis, encephalopathy*
- Effects on fluid balance – *ascites, cirrhosis*
- Renal toxicity - *cirrhosis*

Hepatotoxicity

- Dose dependent (intrinsic e.g. paracetamol, methotrexate)
- Dose independent (idiosyncratic)
- Usually acute, can be chronic
- Acute is usually in 5 to 90 days of starting drug
- Can occur after stopping causative drug
- Existing liver dysfunction does not increase risk of hepatotoxic reaction

LIVER ENQUIRIES - Drug Considerations

Pharmacokinetics		**Considerations**
Absorption		Lipid solubilty (Absorption affected by ascites)
Distribution		Water/fat Protein binding % Displaced by bilirubin or displaces bilirubin
Metabolism		First pass effect Hepatocyte dependent Prodrug CYPs Active metabolites Genetics
Elimination		Biliary excretion Alternative mechanisms Enterohepatic recirculation (Renal impairment)

Adverse Effects :

Hepatotoxicity

Does the drug affect LFTs?
What is the incidence of this reaction?
Is this a transient effect?
Is it known how long it will take for the LFTs to recover?

Is the drug associated with causing hepatitis or cholestasis?
What type of reaction does it cause?
What is the incidence of this reaction?
How long does it take to recover from this effect?

Is the drug associated with any more serious or long-term hepatotoxic reactions?
eg hepatic necrosis, vanishing bile duct syndrome?
What is the incidence of this reaction?

Other Relevant Adverse Effects

Dermatological
eg. pruritus and urticaria
What is the incidence of this reaction?
Is it a common, uncommon or rare effect?

Endocrine/Metabolic
eg. fluid & electrolyte imbalance
What is the incidence of this reaction?
Is it a common, uncommon or rare effect?

Gastrointestinal
eg. constipation
What is the incidence of this reaction?
Is it a common, uncommon or rare effect?

Haematological
eg. Thrombocytopenia, effects on clotting, increased risk of bleeding
What is the incidence of this reaction?
Is it a common, uncommon or rare effect?

Neurological
eg.confusion, seizures, sedation
What is the incidence of this reaction?
Is it a common, uncommon or rare effect?

Renal
eg. renal toxicity
What is the incidence of this reaction?
Is it a common, uncommon or rare effect?

Are there any drug interactions or drug-disease interactions that need to be considered?

Key messages – when to worry

- Cirrhosis, esp decompensated – encephalopathy, coagulopathy
- Varices – risk of bleeding, effect on first pass metabolism
- Ascites – Na content, fluid retention
- Cholestasis – if drug biliary cleared
- Low albumin – if highly protein bound >90%

Drugs to avoid/use cautiously!!

- NSAIDs
- Opioids
- Tricyclic antidepressants
- Benzodiazepines
- Antipsychotics
- Antimuscarinics
- Anticholinergics
- Long acting drugs unless carefully titrated and pt stable

Which analgesic can you use in a patient with liver disease?

a) Paracetamol
b) Ibuprofen
c) Morphine
d) Don’t know
e) Need more information

Review of common analgesics

Analgesia

- Paracetamol
- Ibuprofen
- Morphine

Drug Considerations **Drug ……**

Pharmacokinetics

		Considerations
Absorption		Lipid solubilty (Absorption affected by ascites)
Distribution		Water/fat Protein binding % Displaced by bilirubin or displaces bilirubin
Metabolism		First pass effect Hepatocyte dependent Prodrug CYPs Active metabolites Genetics
Elimination		Biliary excretion Alternative mechanisms Enterohepatic recirculation (Renal impairment)

Side effects
Consider – GI ulceration, sedation, coagulopathy, platelet effects, effects on fluid balance, effect on electrolytes, biliary sludging, renal impairment, constipation

Hepatotoxicity - known hepatotoxin/type

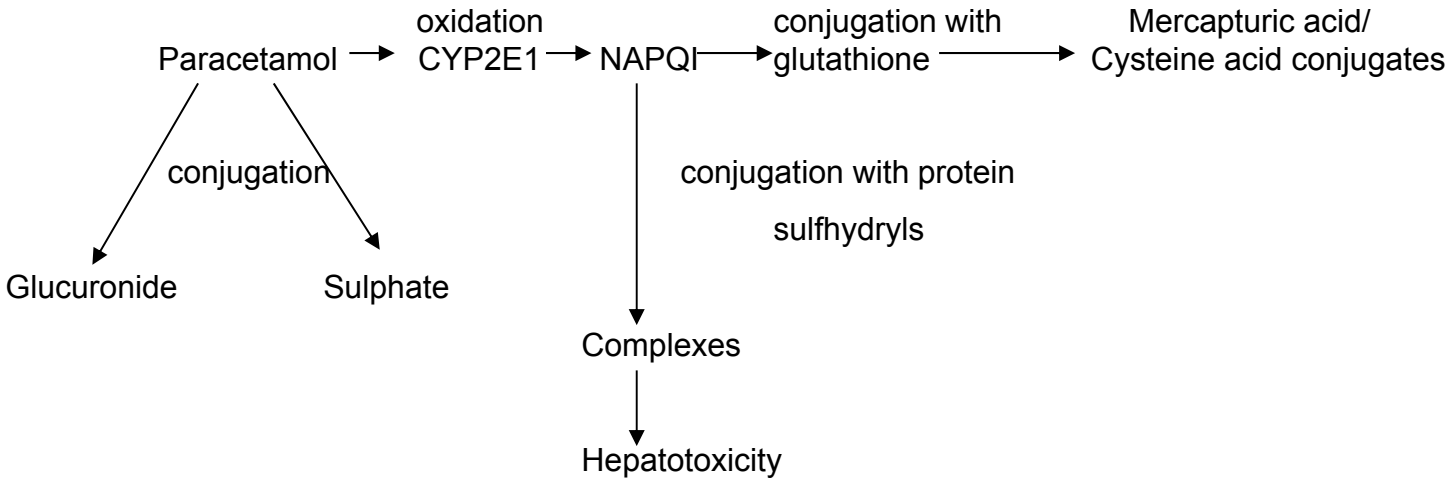
Published information in specific liver diseases/clinical studies
BNF/SPC

Effect of drug on liver patient

- Hepatitis
  - Mild, normal INR and no chronic liver disease
- Cholestasis
  - Normal hepatocyte function
- Cirrhosis
  - Compensated but only just – INR 1.3-1.4, albumin 32, known varices, no encephalopathy

Paracetamol

- Hepatic metabolism (multiple pathways)
  - Need glutathione – stores may be reduced in the severely malnourished
- Hepatotoxic in overdose



Choice of analgesic? Paracetamol

- Use in mild hepatitis?
  - Yes *(caution alcoholics)*
- In cholestasis?
  - Yes
- In cirrhosis?
  - Yes
  - Reduce to TDS in severe decompensated cirrhosis
- In acute liver failure?
  - Yes – possibly reduce to TDS
  - Not if cause of ALF is POD!

Choice of analgesic? Ibuprofen

- Lipid soluble
- 99% protein binding
- Extensive hepatic metabolism
- Side effects?
  - GI ulceration
  - Inhibition of platelet aggregation
  - Renal impairment
  - Fluid retention and electrolyte abnormalities
  - Hepatotoxicity

Choice of analgesic? Ibuprofen

- Use in mild hepatitis?
  - Yes – normal dose but monitor for hepatotoxicity
- In cholestasis?
  - Possible impaired oral absorption (lipid soluble drug)
  - May displace bilirubin from protein binding sites or v.v.
  - Caution if pt has raised INR due to vit K malabsorption
  - Prefer avoid but could use with careful consideration
- In cirrhosis?
  - Poor metabolism, accumulation
  - Bleeding risk, renal toxicity, fluid and electrolyte disturbance
  - AVOID

Morphine

- Low protein binding
- Extensive hepatic metabolism, first pass >50%
- Biliary excretion and enterohepatic recirculation
- Half life 1-5 hrs
- Side effects
  - Sedation, respiratory depression
  - Constipation
  - Pruritus

Morphine

- Use in mild hepatitis?
  - Yes – normal dose
- In cholestasis?
  - Possible impaired excretion
  - Pruritus, bile duct spasm
  - Yes – normal dose but monitor and use prn
- In cirrhosis?
  - Poor metabolism, accumulation. Varices may affect 1st pass
  - Sedation, resp depression – encephalopathy
  - Caution reduce dose (to 25-50%) and frequency

- Paracetamol is OK

Summary

- Work out what is wrong with your patient's liver and how bad it is
- See if the pharmacokinetics of the drug you want to use could be affected
- Check the drug doesn't have side effects which could harm the patient

Advise accordingly

Sources of further information

- Medicines Q&As on NELM
- Drug PK data – Dollery, micromedex, SPC
- Drugs and the Liver!

- Caution with interpreting references

Child-Pugh score – cirrhosis only

Score	**1**	**2**	**3**
SBr	<34	34-51	>51
Albumin	>35	30-35	<30
INR	<1.7	1.7-2.3	>2.3
Ascites	None	Easily controlled	Poorly controlled
Encephalopathy	None	Minimal	Advanced

A = 5-6 *(mild)*, B = 7-9 *(moderate)*, C ≥ 10 *(severe)*