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Pharmacology in Liver Disease

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NHS Trust

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Objectives

- Outline the drug management for patients with:
  - Ascites
  - Spontaneous Bacterial Peritonitis (SBP)
  - Encephalopathy
  - Bleeding varices
  - Hepatorenal syndrome
  - Pruritus
  - Alcohol withdrawal
- Describe the factors which need to be considered when selecting drugs and dosage regimens in chronic liver disease.

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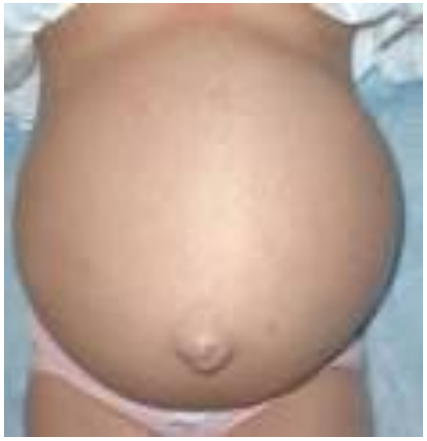
Ascites

- Treatment aim- mobilisation of intra-abdominal fluid
- No added salt diet (80mmol/day)
- Diuretics
- Fluid restriction to 1.5-2L/day
  - (if serum sodium <130mmol/l)
- 90% of patients can be managed as above
- Paracentesis
- TIPSS (transjugular intrahepatic portosystemic shunt)



Drug Choices - Diuretics

- Aldosterone antagonist:
  - Spironolactone 100-400mg od
  - Increased aldosterone due to activation & reduced degradation by liver

Plus/minus

- Loop diuretic:
  - Frusemide (40-160mg od)
  - Bumetanide (1-4mg od)

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Diuretics - side effects

- Hyperkalaemia (spironolactone)
- Hypokalaemia (loop diuretics)
- Hyponatraemia (stop if Na <120mmol/L)
- Nephrotoxicity
- Gynaecomastia (Spironolactone)
- Encephalopathy (electrolyte disturbances)

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Monitoring

- Daily weight
  - aim to lose 0.5kg/day or 1-2kg/day if peripheral oedema
- Dose titrate every 3-5 days
- U&Es
  - Renal function (creatinine, urea)
  - Na, K

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Spontaneous Bacterial Peritonitis

- Start antibiotics whilst awaiting the results of culture of ascitic fluid
  - eg. Piperacillin Tazobactam IV 4.8g 8 hourly (some centres use Cefuroxime, Ciprofloxacin)
- Treat for 5 days- when clinically improved
- Long term prophylaxis
  - Previous episodes of SBP
  - Ascitic protein <10g/l

    =Co-trimoxazole 960mg OD

Encephalopathy

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- Treatment aim: to improve cognitive function

- Events precipitating hepatic encephalopathy:
  - Infection
  - Bleeding e.g. GI
  - Electrolyte imbalance
  - Constipation
  - Drugs
  - Acute liver failure
  - Porto-systemic shunts

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Treatment

- Identify & treat precipitating factors

- Remove causative drugs:
  - Sedating e.g. benzodiazepines
  - Constipating e.g. opioids
  - Diuretics – electrolyte imbalance

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Treatment

- Lactulose 10-50ml bd-tds
  - Laxative effect
  - Broken down in gut leading to acidification of colonic contents and a reduction in absorption of nitrogenous waste
- Side effects of lactulose
  - Flatulence
  - Abdominal pain
  - Diarrhoea
- Enemas
  - If NBM

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Antibiotics for Encephalopathy

- Rifaximin 550mg BD
  - broad antimicrobial spectrum against most of the Gram-positive and negative, aerobic and anaerobic bacteria, including ammonia producing species
  - reducing the production of ammonia and other compounds that are believed to be important to the pathogenesis of hepatic encephalopathy.
- Side effects
  - Nausea
  - Anaemia
  - Ascites
  - Peripheral Oedema

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Monitoring

- Stool chart
  - Aim to produce 2-3 loose stools a day
- Temperature if infection
- Cognitive improvement
  - Number connection tests
  - Serial sevens

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Bleeding Varices

- Aims of Treatment
  - Resuscitate (blood/FFP/colloids)
  - Control bleeding (medical & endoscopic treatment)
  - Prevent complications
  - Prevent re-bleeding

Stop bleeding

- Drug therapy: Terlipressin, Octreotide

Plus 1 of:

- Sclerotherapy
- Endoscopic Oesophageal Banding
- Adhesives e.g. Histoacryl glue for gastric varices
- TIPSS (transjugular intrahepatic portosystemic shunt)

Octreotide & Terlipressin

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- Reduce portal pressure by causing splanchic vasoconstriction
- Reduce re-bleeding rates

- Terlipressin (reduced mortality)
  - 1-2mg IV bolus 4-6 hourly (usually 2mg qds)
- Octreotide (unlicensed use)
  - Continuous IV infusion - 50mcg/hour

- Usually discontinued 2 days after bleeding stopped (terlipressin licensed for 72 hrs)

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Terlipressin side effects

- Abdominal cramps
- Headache
- Increased blood pressure

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Monitoring: Terlipressin/ Octreotide

- Bleeding
- Blood Pressure
- Length of treatment course

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Antibiotics in Variceal Bleed

- Reduce bacteraemia: SBP
- Reduce short term mortality
- Local policy
  - Piperacillin-Tazobactam 4.5g IV for 48 hours

Prevention of recurrent variceal bleeding

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- Non-selective beta-blockers e.g. Propranolol or Nadolol
  - Reduce portal pressure by decreasing splanchnic blood flow and the hyperdynamic circulation associated with cirrhosis
  - Starting dose: propranolol 20-40mg bd up to 80mg bd
  - Reduce mortality

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Beta blocker side effects

- Bronchospasm (CI in asthma)
- Bradycardia
- Hypotension
- Peripheral vasoconstriction
- Fatigue
- Impotence

Beta blocker monitoring

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- BP

  - Aim for >100mmHg systolic (some patients may tolerate lower)

- Heart rate
  - Aim of treatment is to reduce HR to 25% less than baseline (above 55bpm)- this is the maximum tolerated dose)

Hepatorenal Syndrome (HRS)

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- Renal impairment associated with liver disease
- Low arterial pressure, reduced renal perfusion
- Aim to increase renal perfusion and renal function
- Vasoconstrictors constrict splanchic bed and increase renal perfusion
- Poor prognosis

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Treatment of HRS

- Terlipressin IV used most frequently
  - Unlicensed use
  - Range of doses in studies from 0.5mg bd to 2mg 6 times a day
  - In practice, St James's liver unit use 1mg qds
  - In combination with 20% HAS

**Remove any nephrotoxic medications

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Pruritus in liver disease

- Cause?
- Subjective; varies from patient to patient
- Can be all over body, in eyes, ears etc or isolated areas
- Often worse at night and when hot
- Can be debilitating
- Can be indication for liver transplant
- Efficacy of treatment can be monitored by visual analogue scale

Pruritis – Treatment options

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- Topical preparations
  - E.g. menthol 1% in aqueous cream
  - Do not apply on broken skin
  - Short term, immediate relief
  - May not be useful for patients with generalised all over itch

- Antihistamines
  - non-sedating (e.g. cetirizine)- ? ineffective
  - sedating (e.g.chlorpheniramine)
  - Sedating drugs can be useful at night to aid sleep

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Cholestyramine (Questran®)

- Anion exchange resin; forms insoluble complexes with bile acids in the intestine and excreted in faeces (prevents their absorption).
- Initiate at 4g od or bd
- May take 48hours to take effect
- Reduces absorption of other drugs - give other drugs 1 hour before or 4-6 hours after colestyramine
- Can mix in drinks / incorporate into recipes

Cholestyramine side effects

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- Not absorbed therefore no systemic side effects:

- Unpleasant taste
- Constipation
- Occasionally, diarrhoea
- Nausea & vomiting
- Can cause depletion of fat soluble vitamins long term

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Ursodeoxycholic acid

- Naturally occurring bile acid; displaces toxic bile acids from enterohepatic pool, protects cells from toxic bile acids and stimulates bile excretion.
  - "displacement theory"
- Dose: 10-15mg/kg/day
- Can be given in divided doses or single dose
- Can take up to 2 weeks to take effect
- May worsen itch!

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Other options for Pruritis

- Rifampicin / Phenobarbitone
- Induce hepatic enzymes
- Not licensed for this indication
- Rifampicin 150mg bd, increase to 300mg bd
- Takes 48 to 72 hours to work
- Interacts with lots of drugs (not ideal post transplant)
- Colours urine red

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- Ondansetron
- Not licensed for this indication
- 5HT3 antagonist
- Inhibits perception of itch
- Anecdotal reports suggest IV has been effective (within 1 hour)
- If effective after stat IV dose, give oral 4mg bd increasing to 8mg bd

- Opioid antagonists; Work quickly but patients become tolerant, therefore regular dose increases necessary
  - Naloxone – continuous infusion
  - Naltrexone orally 25-50mg daily

- Serotonin Selective Reuptake Inhibitors eg Sertraline

- Gabapentin

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Alcohol Withdrawal

- Anxiety, tremor, sweating, nausea, tachycardia, hypertension, hallucinations

- Chlordiazepoxide (regular and prn)
  - Initially chlordiazepoxide ~20-30mg qds + 5-10 mg prn
  - A maximum daily dose of 120mg
  - Reducing course over ~ 7 days

Wernicke's encphalopathy

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- Vitamin B deficiency
- Thiamine -100mg tds
- Vitamin B Co. strong- 2 tabs tds
- High risk
  - Pabrinex IV 1 pair Daily for 3-5 days
  - Anaphylaxis risk– give over >10mins
- Treatment (1 or more signs present)
  - Pabrinex IV 2 pairs tds for 2 days followed by 1 pair twice a day until improvement ceases

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- How to determine a patient's liver function and how it effects drug handling……
- There isn't a book that gives dosing of drugs in liver impairment
- No way of measuring directly the liver's ability to metabolise drugs
- Effects of liver impairment on the way drugs are handled in the body not consistent & predictable
- Limited published information available (which maybe misleading e.g. from manufacturers)

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References

- “Drugs and the Liver”
- A guide to drug handling in liver dysfunction
- Edited by Penny North-Lewis
  - Paediactric Liver Pharmacist, SJUH

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Need to consider lots of factors…..

- LFTs
- Clotting function
- Signs
- Diagnosis
- Other investigations e.g. biopsy, ultrasound
- The drug

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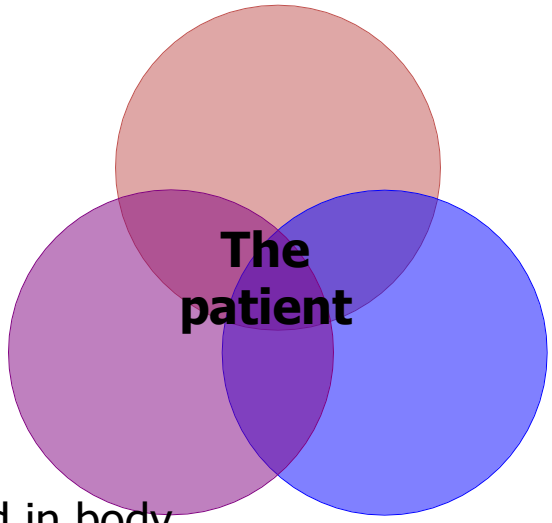
Drug handling in particular patient

Liver Test Results



Drug Characteristics
e.g. how drug is handled in body and side effects

Signs of Liver Disease

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The drug

- Absorption
- Distribution
- Metabolism
- Elimination
- Side Effect profile
- Hepatotoxicity

Absorption of drugs

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- Absorption of some drugs may be affected by oedema in ascites (e.g. frusemide?- less absorption in gut wall)
- Fat soluble drugs have reduced absorption in cholestasis (e.g. fat soluble vitamins)
- The effect of fat soluble drugs may be increased in Cachetic patients

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Distribution

- Fat soluble drugs are not affected by ascites

- Water soluble drugs will distribute into ascitic fluid which may lead to lower serum concentration and reduce efficacy
  - May need to increase dose

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Distribution

- Reduced albumin levels
  - If highly protein bound drugn (ie binds to albumin); Increased free drug available= toxic
  - E.g phenytoin (90%), warfarin (99%)

**May need to reduce dose

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Metabolism

- Reduced number of hepatocytes may lead to reduced metabolism of drugs (to active/ inactive form)

- Reduced hepatic flow in portal hypertension/ cirrhosis leads to increased systemic availability (reduced first pass metabolism)

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Elimination

- Accumulation may occur in cholestatic patients if the drug undergoes biliary excretion
  - a problem if active/toxic metabolites are produced
  - alternative routes of elimination? e.g. kidneys

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Side Effect Profile

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

- Sedation
- Constipation
- Coagulopathy
- Effects on electrolytes
- Effects on fluid balance
- Renal toxicity
- GI ulceration

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Drugs to avoid/use cautiously

- **NSAIDs/ Anticoagulants**
  - In cirrhotics – risk of varices/bleeding abnormalities
- **Sedatives**
  - In cirrhotics/encephalopathics – sedatives mask/precipitate encephalopathy.
- **Constipating drugs**
  - Risk of encephalopathy with constipation
- **Diuretics**
  - Electrolyte imbalance can precipitate encephalopathy
- **Sodium containing drugs e.g. IV or effervescent preparations**
  - May worsen ascites

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Important Points to Consider

- Avoid or use certain drugs cautiously
- Avoid hepatotoxic drugs if possible
- Use therapeutic levels, where possible
- Monitor for efficacy eg BP, HR
- Monitor for toxicity
- Check renal function
- Use the smallest effective dose at the greatest interval and titrate according to response
- Take Care: not to under dose!

Drug Choice in liver disease

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- Analgesics
  - Paracetamol – normal doses
  - Opiates – small doses, titrate slowly – care with constipation/sedation (encephalopathy)
- Antidepressants
  - SSRI's e.g Fluoxetine, venlafaxine over older sedating drugs e.g. amitriptyline (tricyclic antidepressant)
- Anti-emetics
  - Ondasetron
- Benzodiazepines
  - Short acting

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Any Questions?

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