

Management of..... Chronic Liver Disease

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Outline

- Recognising and diagnosing the patient with chronic liver disease
- Causes of chronic liver disease in NZ
 - Investigations
 - Management
- Complications of end-stage liver disease
 - Management



John

- 54 year old man
- Recently moved to NZ from Australia
- PMHx
 - Type 2 diabetes mellitus 3 yrs
 - Diet-controlled
 - No complications
- No medications



John

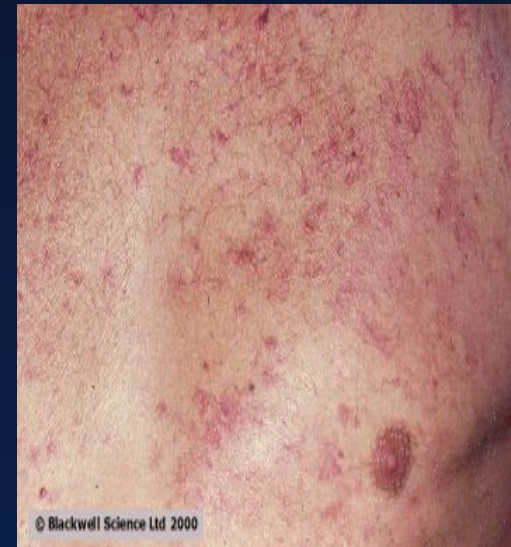
- FHx:
 - No liver disease, viral hepatitis, HCC
- SHx:
 - Lives with parents
 - Unemployed
 - Smoker 30 pk years
 - Alcohol
 - 20+ years heavy alcohol intake
 - Cask wine per day
 - 1L bottle of spirits per week
 - Previous IVDU in Australia
 - Last injected 10 years ago



John

○ Examination

- Palmer erythema, jaundice, muscle wasting, spider naevi, gynaecomastia
- Dupeytren's contracture
- BMI 20
- Abdomen
 - Soft
 - Tender RUQ
 - Hepatomegaly 19cm
 - Splenomegaly
 - No shifting dullness
- No pedal oedema





Chronic Liver Disease



Laboratory Investigations

- Which blood tests are most useful in determining severity of CLD?
 - ALT
 - Platelets
 - Albumin
 - Bilirubin
 - Sodium
 - INR



Laboratory Investigations

- Which blood tests are most useful in determining severity of CLD?
 - ALT
 - Platelets → Hepatic fibrosis and portal HT
 - Albumin → Hepatic synthetic dysfunction
 - Bilirubin → Destruction of liver parenchyma and bile ducts
 - Sodium
 - INR → Hepatic synthetic dysfunction or vitamin K malabsorption



John's results

- Hb 107 (macrocytic), plts 120, WCC 8.5
- Cre 0.1, urea 5.7, Na 128, K 3.5
- INR 1.2, alb 25
- Bili 90, ALT 28, AST 87, GGT 396, ALP 322



John

What are the possible causes
of his chronic liver disease?



Causes of CLD

- Alcohol
- Hepatitis B
- Hepatitis C
- Non-alcoholic steatosis (NASH)
- Autoimmune liver disease
- Genetic or metabolic
- Drugs or toxins



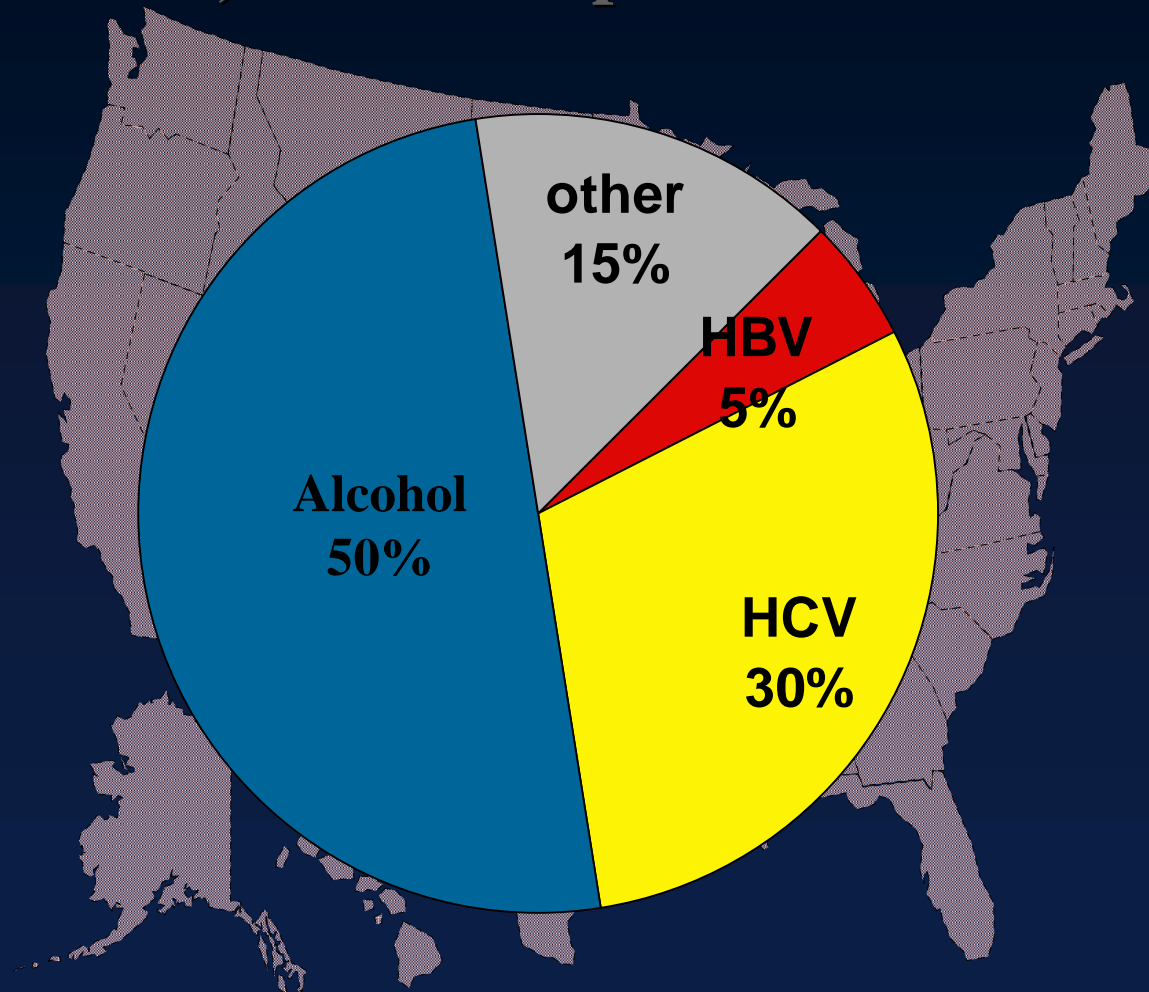
Causes of Chronic Liver Disease

ALCOHOL

● ● ●

End-Stage Liver Disease in USA Liver-Related Mortality

25,000 deaths per annum





Alcoholic Liver Disease

- Recent and past alcohol consumption should be assessed in all cases of liver disease
- Most useful lab marker is GGT
- Fatty liver, hepatitis and cirrhosis
 - 20g/day woman, 40g/day man
- HCV + alcohol = more severe liver disease
- Abstinence from alcohol is the major factor which influences survival



Alcohol Abstinence

- Brief intervention
- Referral to drug and alcohol service
- Helpline
- Counselling
- Pharmacotherapy
 - Acamprosate
 - Naltrexone
 - Disulfiram
- Residential rehabilitation



Brief intervention: FLAGS

Feedback	The nature and extent of alcohol-related problems
Listen	To patient concerns
Advise	Patient clearly to reduce consumption
Goals	Negotiate clinically appropriate goals acceptable to the patient
Strategies	Specific suggestions to modify drinking



Alcoholic Liver Disease

- Thiamine
 - 100mg IM/IV then orally daily until sustained abstinence
- Oral diazepam/oxazepam for withdrawal
 - ? Inpatient



Causes of Chronic Liver Disease

Hepatitis B

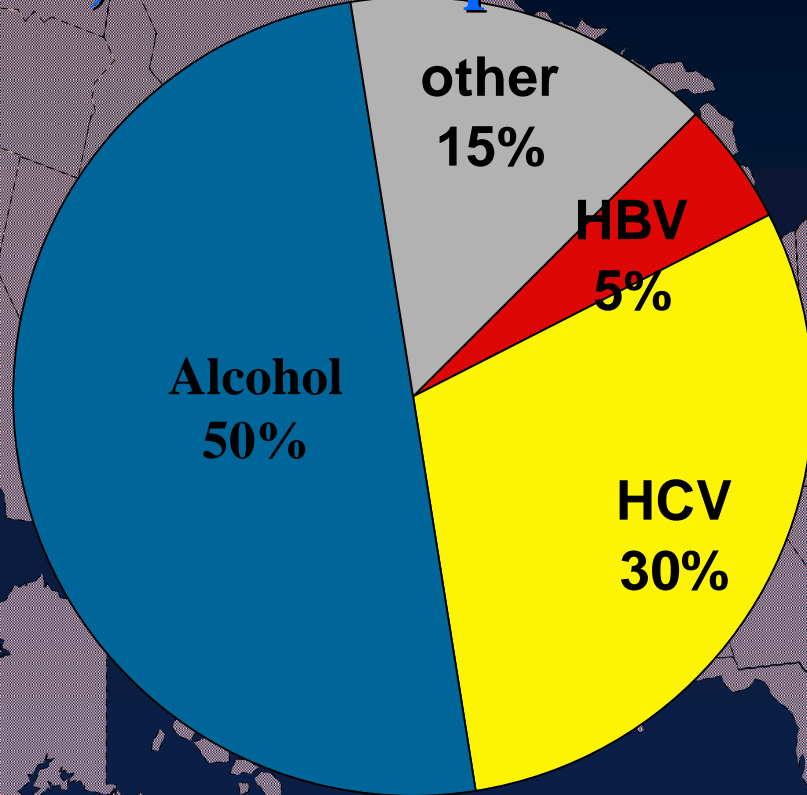
End-Stage Liver Disease in New Zealand

Liver-Related Mortality



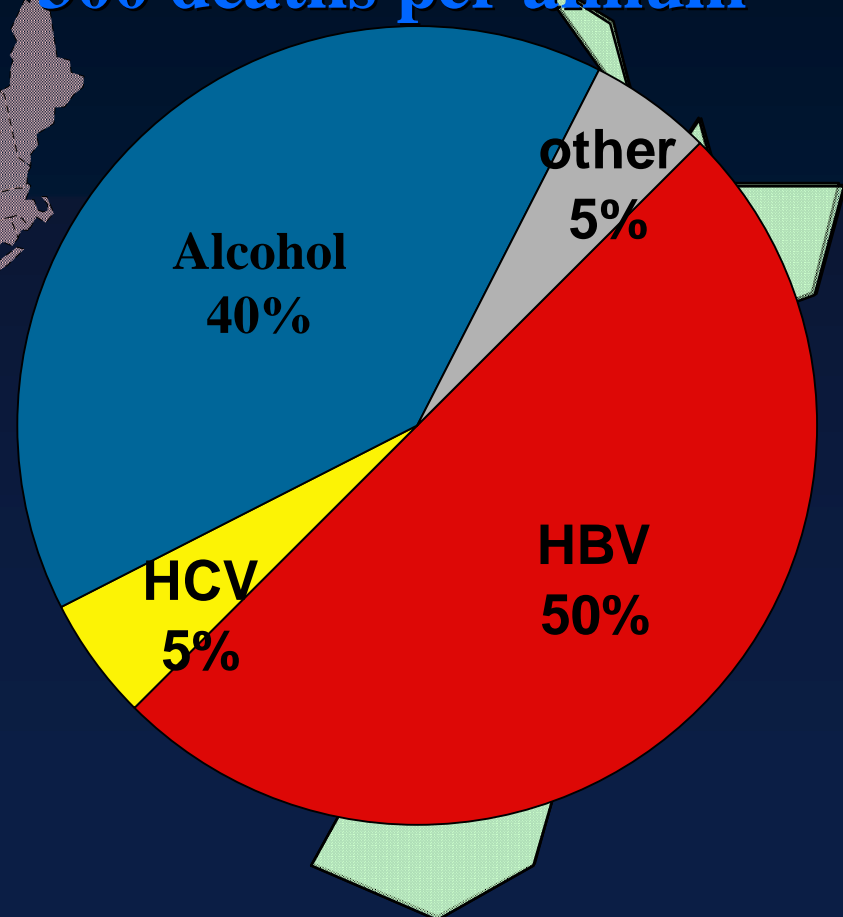
USA

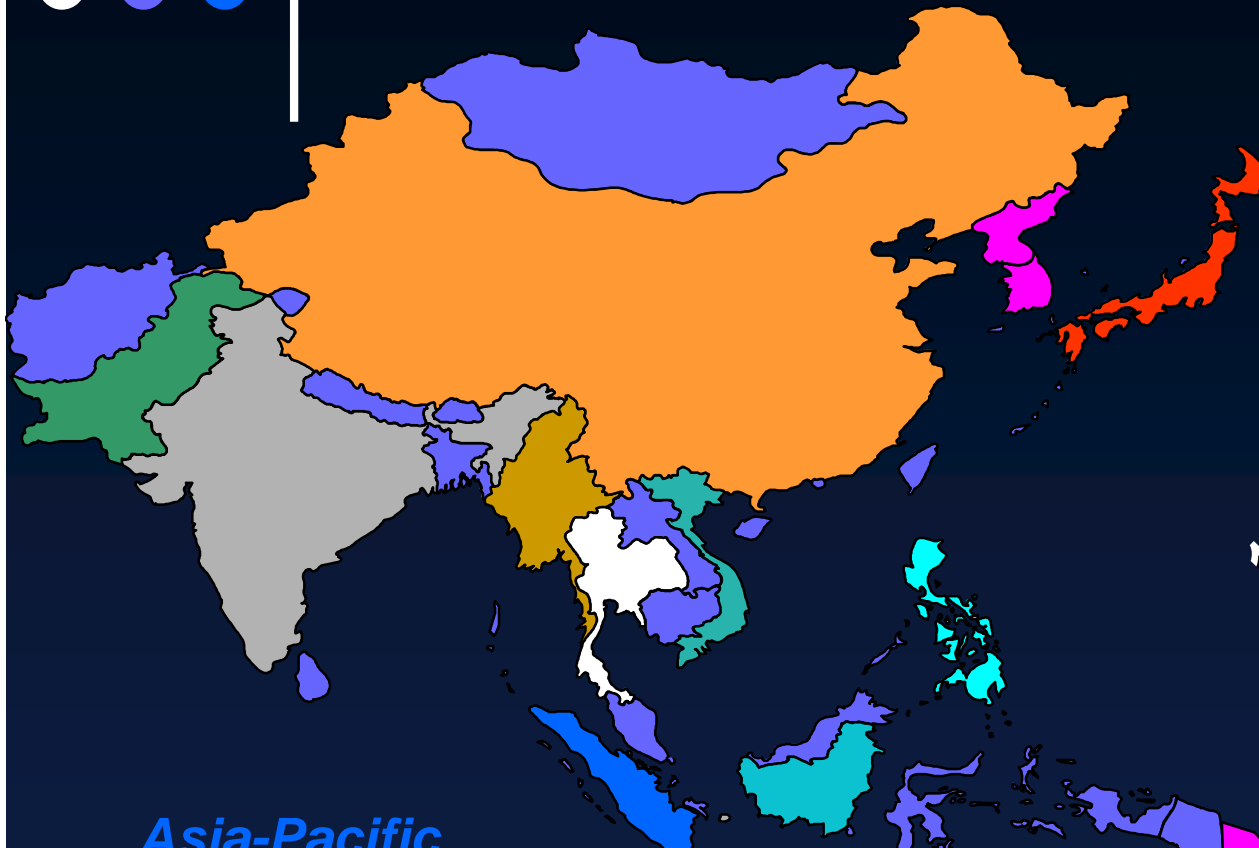
25,000 deaths per annum



New Zealand

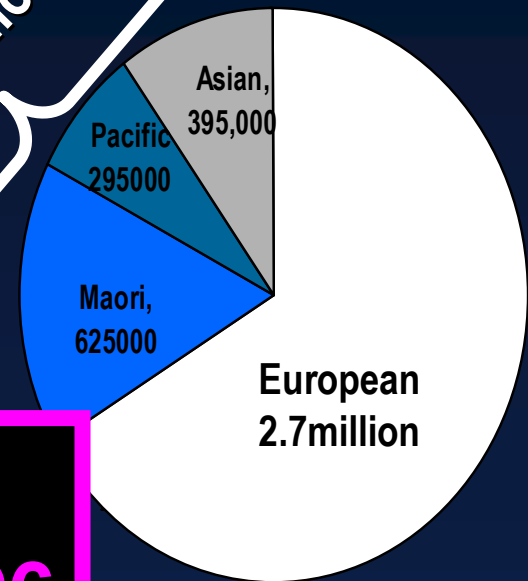
300 deaths per annum





Asia-Pacific

1.2million



Estimated 90,000 HBsAg+ living in New Zealand in 2006

Transmission of Hepatitis B Infection



Transfusion and
transplant recipients

Newborns of long-term
carriers

Sexual partners
of known chronic
carrier

Intravenous
drug users

Healthcare
workers

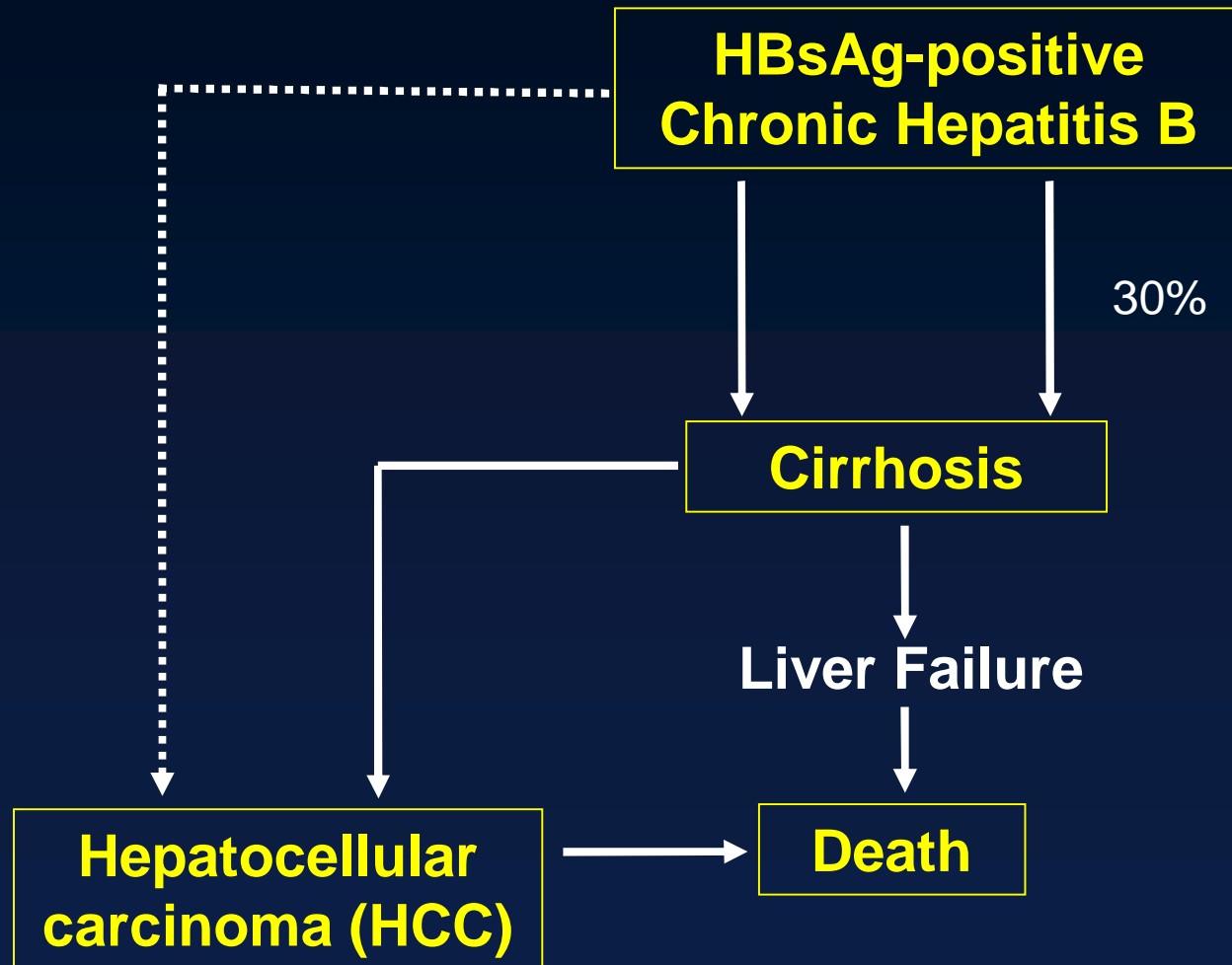
Prisoners and other
institutionalised people



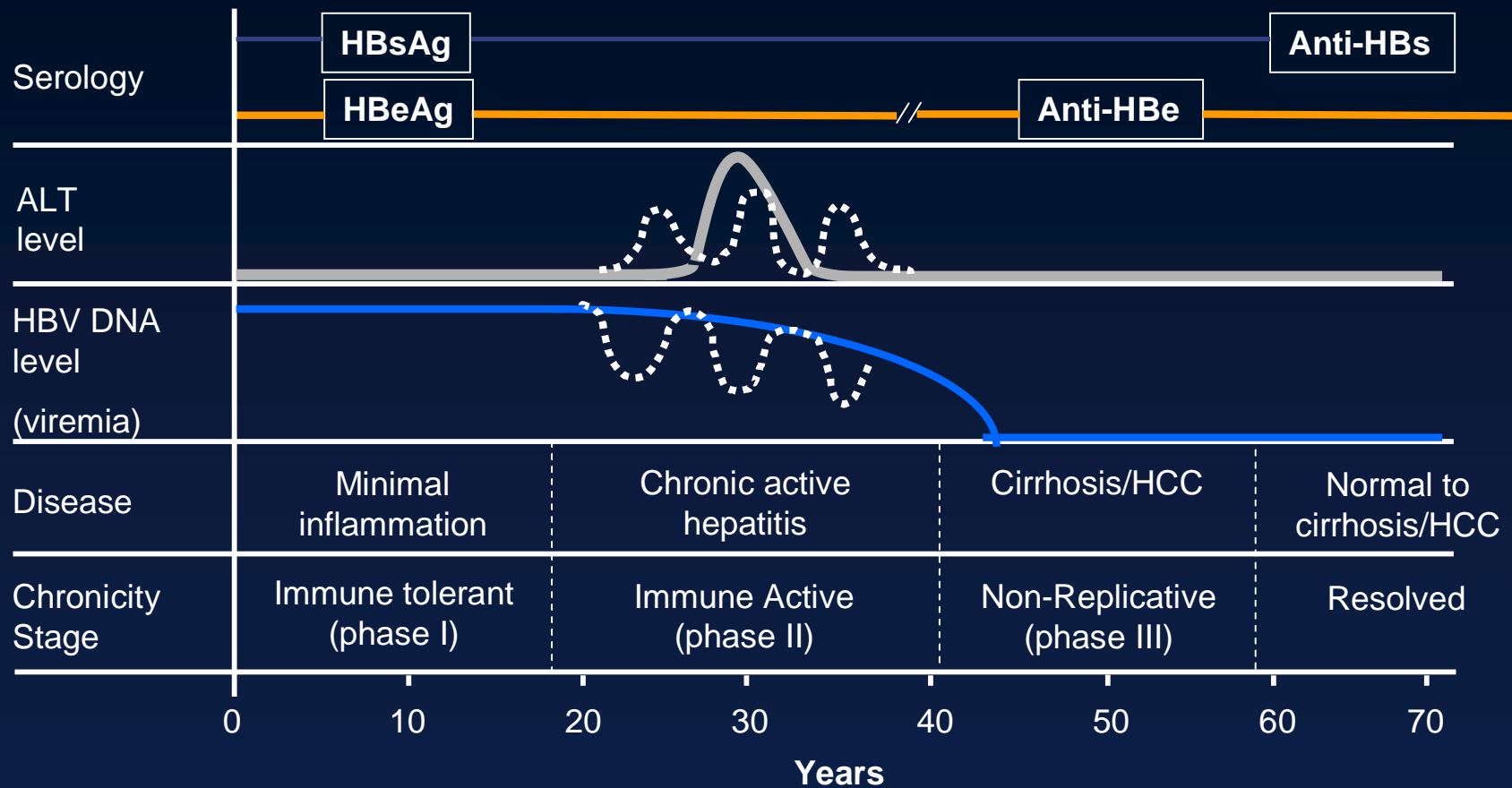


They are all healthy
carriers!

Chronic hepatitis B has serious long-term consequences



Natural History of Chronic HBV Infection





John

- Which HBV tests would you order to screen for HBV
 - HBeAg
 - HBsAB
 - HBV DNA
 - HBsAg
 - HBcAB



John

- Which HBV tests would you order to screen for HBV
 - HBeAg
 - HBsAB
 - HBV DNA
 - HBsAg
 - HBcAB



Is HBV Serology Confusing??



HBV Serology

- sAg determines carrier status / chronic infection
- eAg determines replication and infectivity
- cAb confirms natural infection
- sAb confirms immunity
- HBV DNA (viral load) measures infectivity and replication

● ● ● | Indications for Treatment of Chronic HBV

- Patients with active liver disease:
 - Abnormal liver function tests (AST, ALT)
 - HBeAg positive and $> 10^5$ HBV DNA
 - HBeAg negative and $> 10^4$ HBV DNA
 - Treat if active hepatitis (biochemical or histologic)



Current approaches to treatment of chronic hepatitis B

Drug types

- Anti-viral agents
 - Lamivudine
 - Adefovir dipivoxil*
- Immunomodulators
 - Interferon- α

Treatment duration

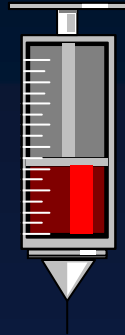
- Continuous long term
- Finite course
- Undefined: dependant on response



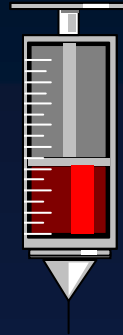
Hepatitis B can be prevented!

If you have never had hepatitis B,
you can get 3 shots . . .

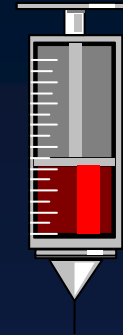
1



2



3



. . . and get long lasting protection.



Causes of Chronic Liver Disease

Hepatitis C

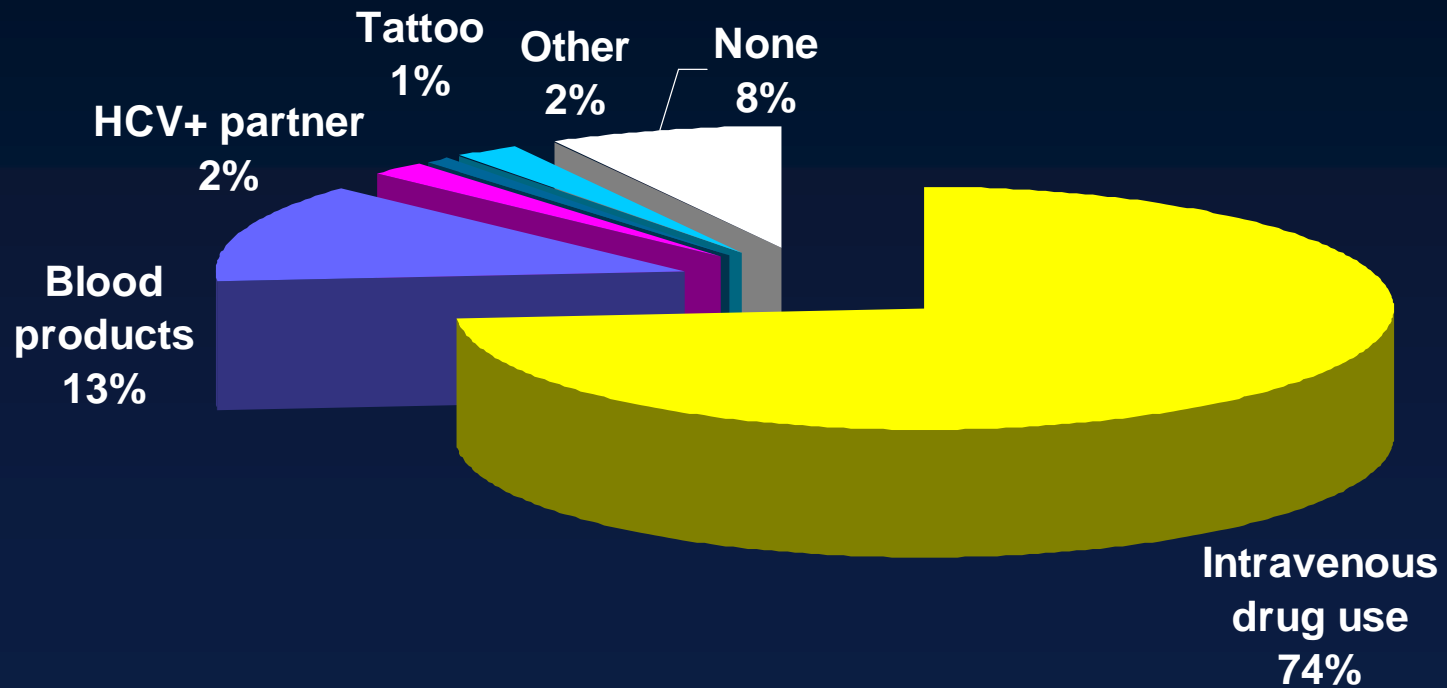


HCV Infection

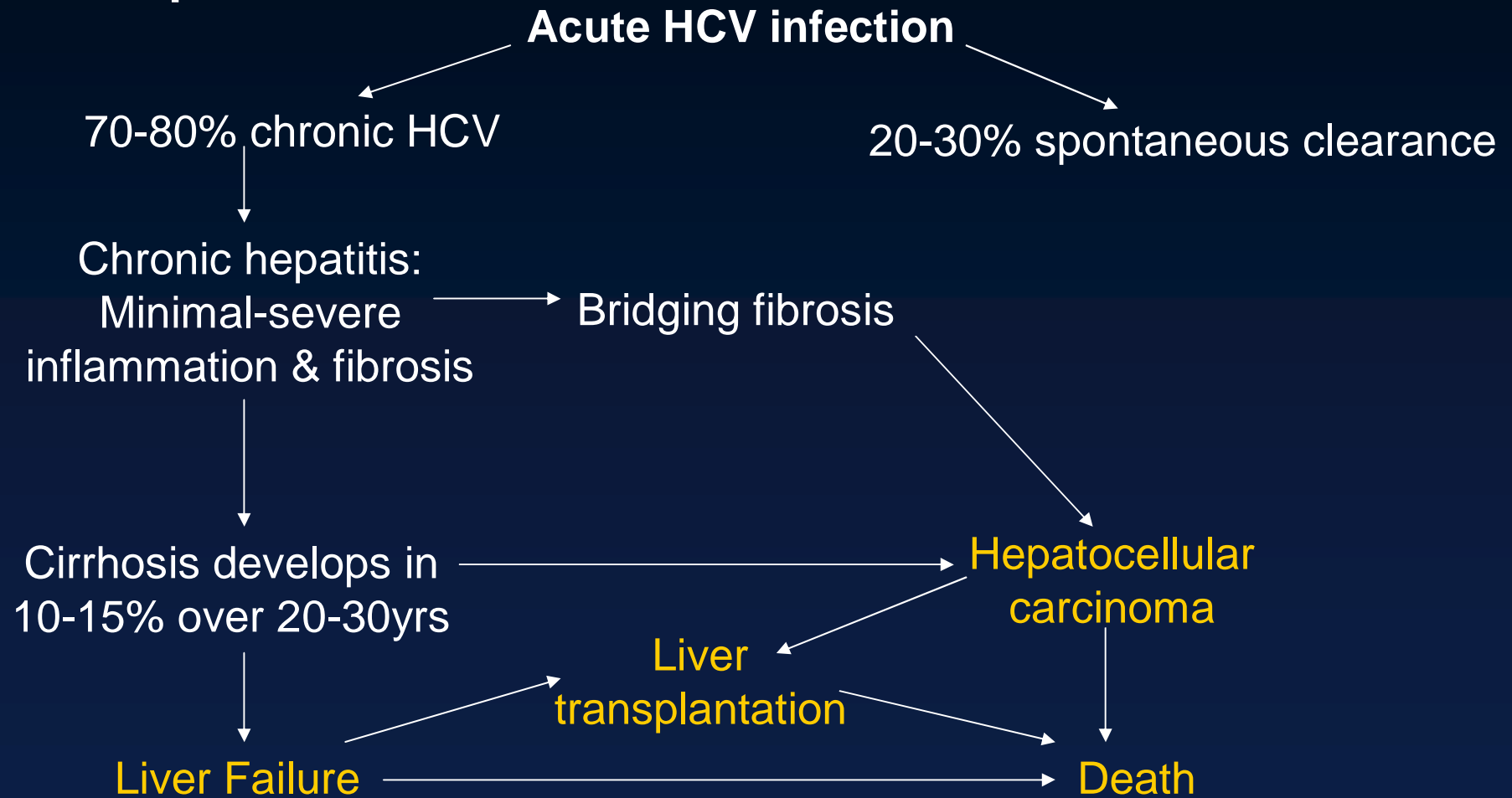
- 30,000 New Zealanders have HCV infection
- Most are young, ex-IVDU
- 9% are cirrhotic at presentation
- ↑↑ referrals to Hepatitis Clinics
 - ↑ detection
 - *awareness of risk factors*
 - ↑ demand for treatment
 - *more effective therapies*
- HBV still main cause of end-stage liver disease in NZ BUT ↑↑ HCV-ESLD over next decade



Risk factors for HCV exposure



Natural History of Hepatitis C





Management of HCV

- Diagnosis
 - HCV IgG antibody positive
 - HCV RNA positive
- Determine genotype
 - 1 & 4 'hard to treat': 12 months, 55% cure rate
 - 2 & 3 'easy to treat': 6 months, 80% cure rate
- Treatment
 - Pegylated interferon + ribavirin



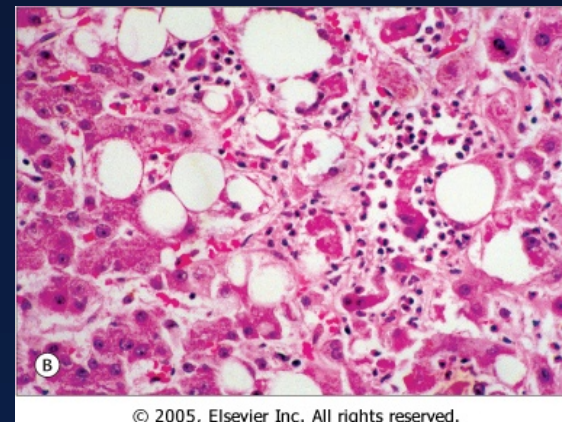
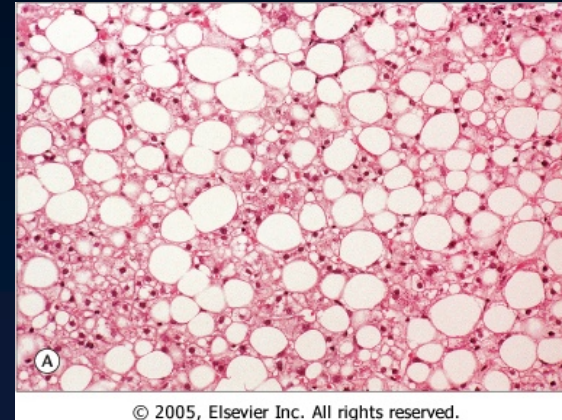
Causes of Chronic Liver Disease

NASH



Definition

- Liver biopsy
 - Macrovesicular fatty change
 - Inflammation
 - With or without fibrosis or cirrhosis
- Negligible alcohol consumption
 - <40g/wk
- Absence HBV or HCV



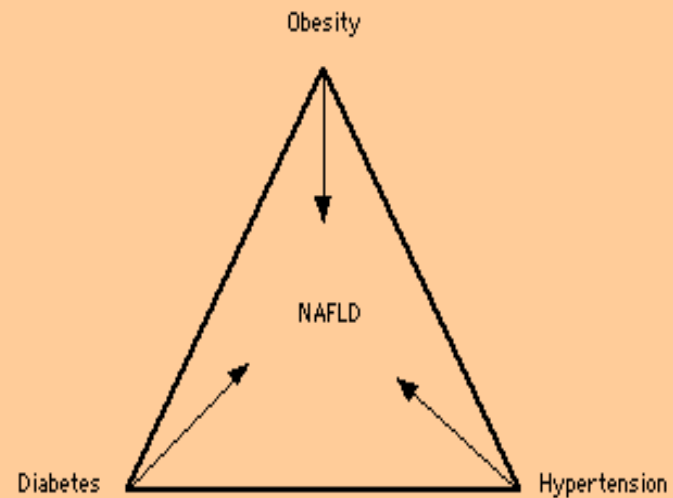


Epidemiology

- Worldwide prevalence not determined
- Most common liver disease in the Western world and increasing
- Affects all racial and ethnic groups
 - No age or sex predilection
- Aetiology of NASH unknown

Association with Metabolic Syndrome

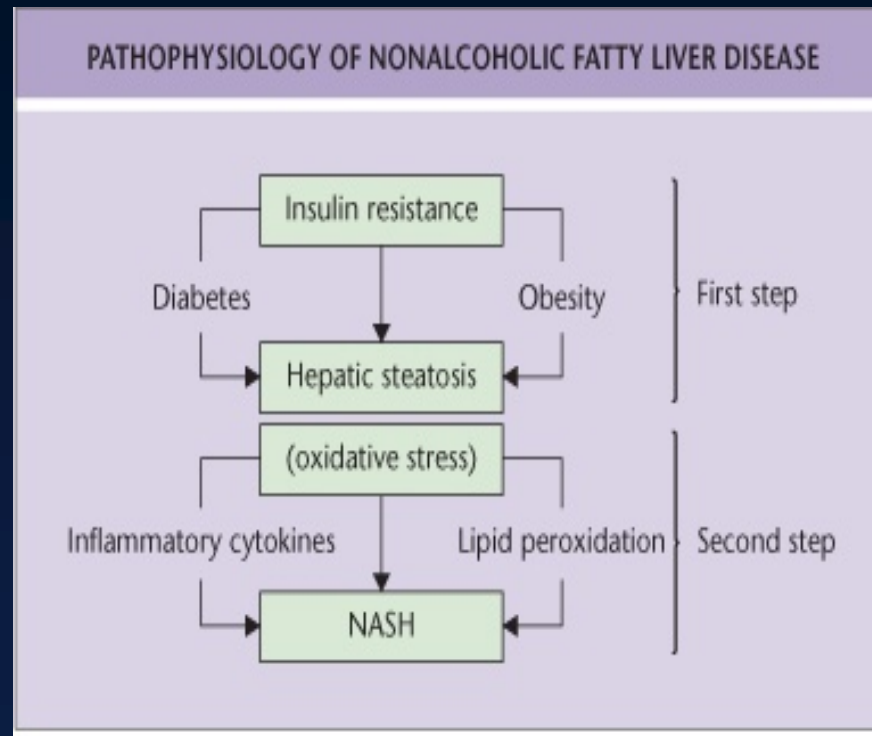
NAFLD as a Manifestation of Syndrome-X†



†Reproduced with permission from the American Gastroenterological Association. Sanyal, AJ. AGA technical review on nonalcoholic fatty liver disease. *Gastroenterology* 2002; 123:1705.

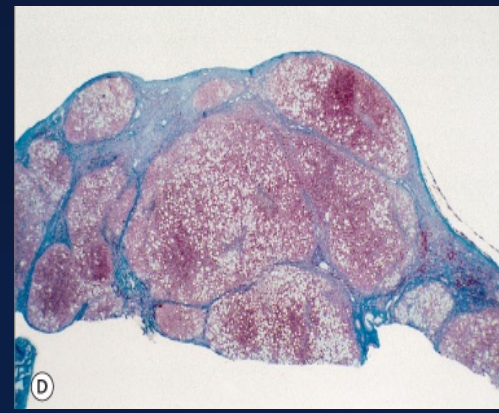
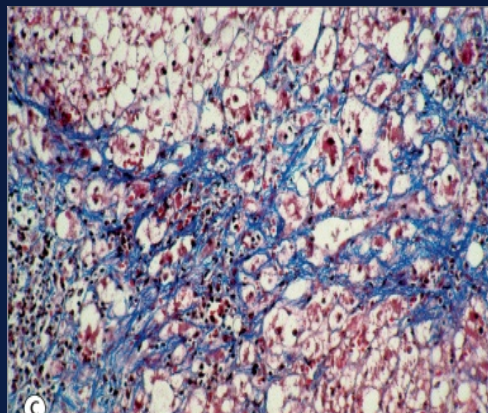
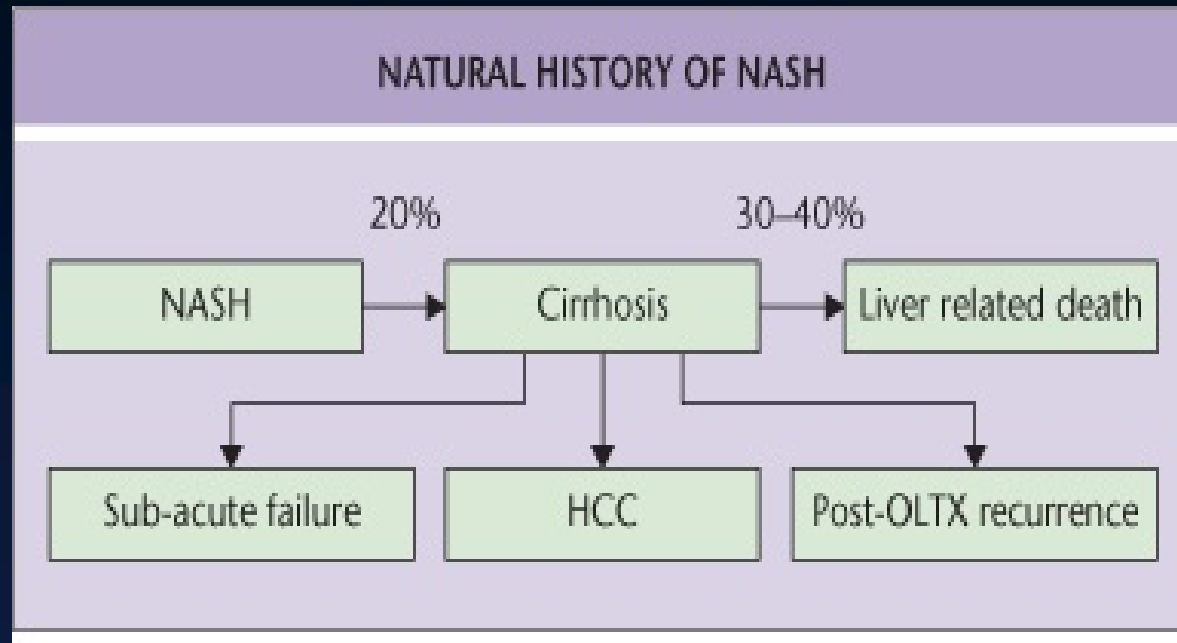


Pathophysiology





Clinical Course





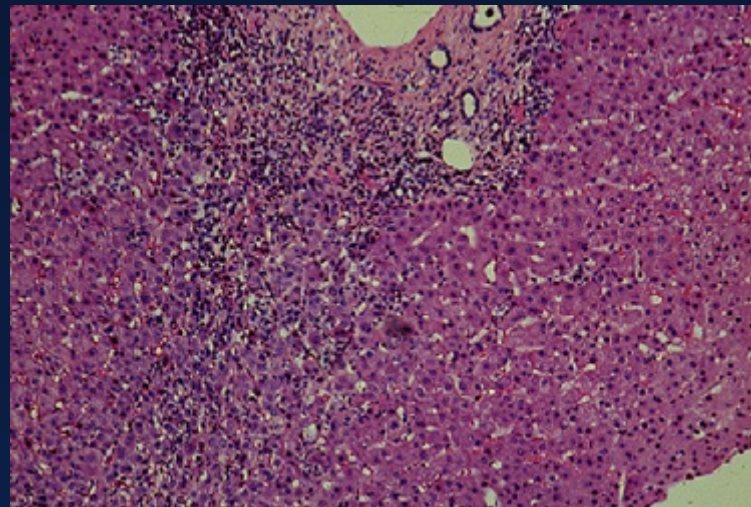
Treatment

- No proven effective treatment for NASH
- Modification of risk factors recommended
 - Obesity
 - Hyperlipidaemia
 - Poor diabetic control
- Weight loss and increased physical activity lead to improvement in:
 - Liver enzymes
 - Histology
 - Serum insulin levels
 - Quality of life (Hickman 2004, Dixon 2004, Peterson 2005)
- Several potential treatments not routinely used in clinical practice



Causes of Chronic Liver Disease

Autoimmune Liver Disease





Autoimmune Liver Disease

- Autoimmune hepatitis
 - Globulins (IgG)
 - Anti-nuclear antibody (ANA)
 - ± Anti-smooth muscle antibody (SMA)
 - ± Antibodies to liver-kidney microsome type 1 (anti-LKM-1)
 - Rx: steroids, azathioprine
- Primary biliary cirrhosis
 - Anti-mitochondrial AB positive
 - Rx: ursodeoxycholic acid
- Primary sclerosing cholangitis



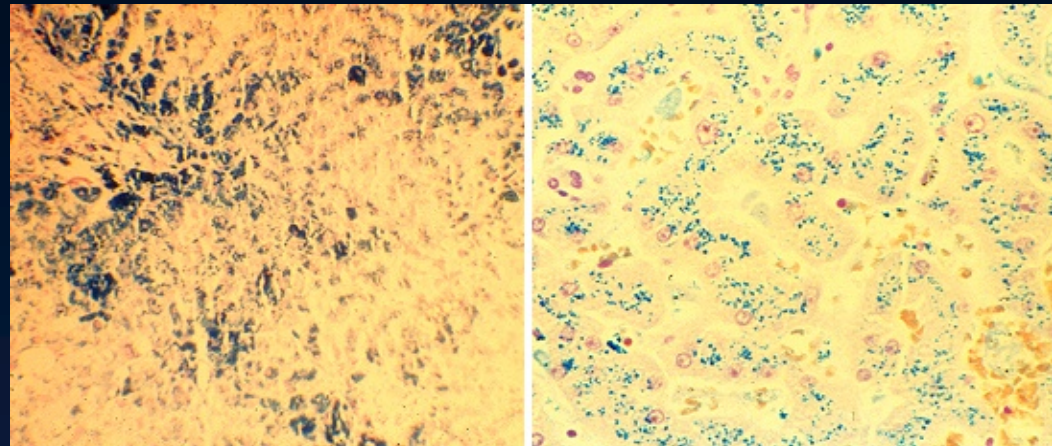
Causes of Chronic Liver Disease

Genetic/Metabolic Disease



Genetic/Metabolic Disease

- Genetic haemochromatosis



- Alpha1 antitrypsin deficiency

- Wilson's disease



Haemochromatosis

- HFE gene positive: autosomal recessive
 - C282Y homozygous
 - C282Y/H63D compound heterozygote
- Clinical
 - Asymptomatic
 - Arthralgias
 - Chronic liver disease
- Elevated transferrin saturation and ferritin
 - Note: raised in inflammation, chronic liver disease
- Rx: phlebotomy, avoid alcohol
- Screen relatives



John's results

- HBsAg neg, HBsAB neg, HCV neg
- Fe studies normal
- Autoimmune screen negative



What would you do ?

- Refer to gastroenterology unit
- Arrange screening for HCC
 - USS
 - Tumour marker
 - ? CEA
 - ? CA19-9
 - ? AFP
- Vaccinate against HBV



What would you do?

- Refer to gastroenterology unit **Yes**
- Arrange screening for HCC **Yes**
 - Which tumour marker
 - CEA
 - CA19-9
 - **AFP**
 - **USS**
- Vaccinate against HBV **Yes**



John

- Diazepam for withdrawal
- Parenteral thiamine initially (100mg IM), then oral until sustained abstinence
- IV vitamin K 10mg then orally for 3-5 days
- Vaccinate against HBV
- Referred to gastroenterology service

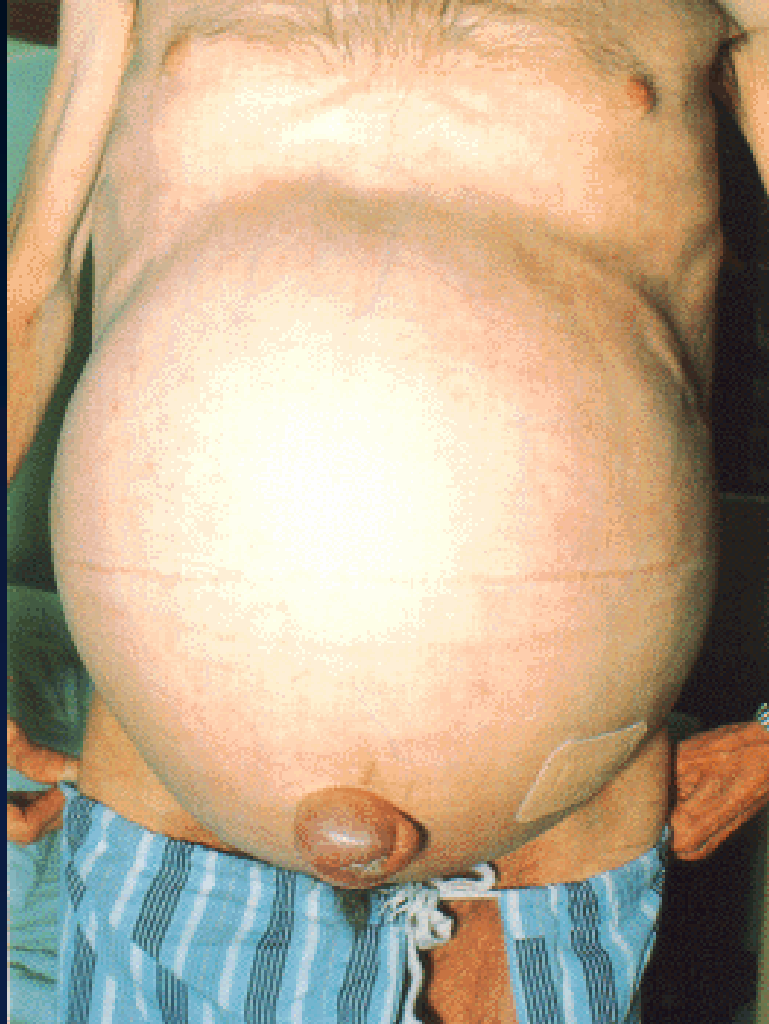
-meanwhile John presents with leg oedema, increased abdominal girth, shifting dullness, Na 124



Portal Hypertension

- Most common and life-threatening complications of CLD
- Responsible for the most common complications:
 - Variceal bleeding
 - Ascites
 - Peripheral oedema
 - Hepatorenal syndrome (HRS)
 - Dilutional hyponatraemia
 - Encephalopathy

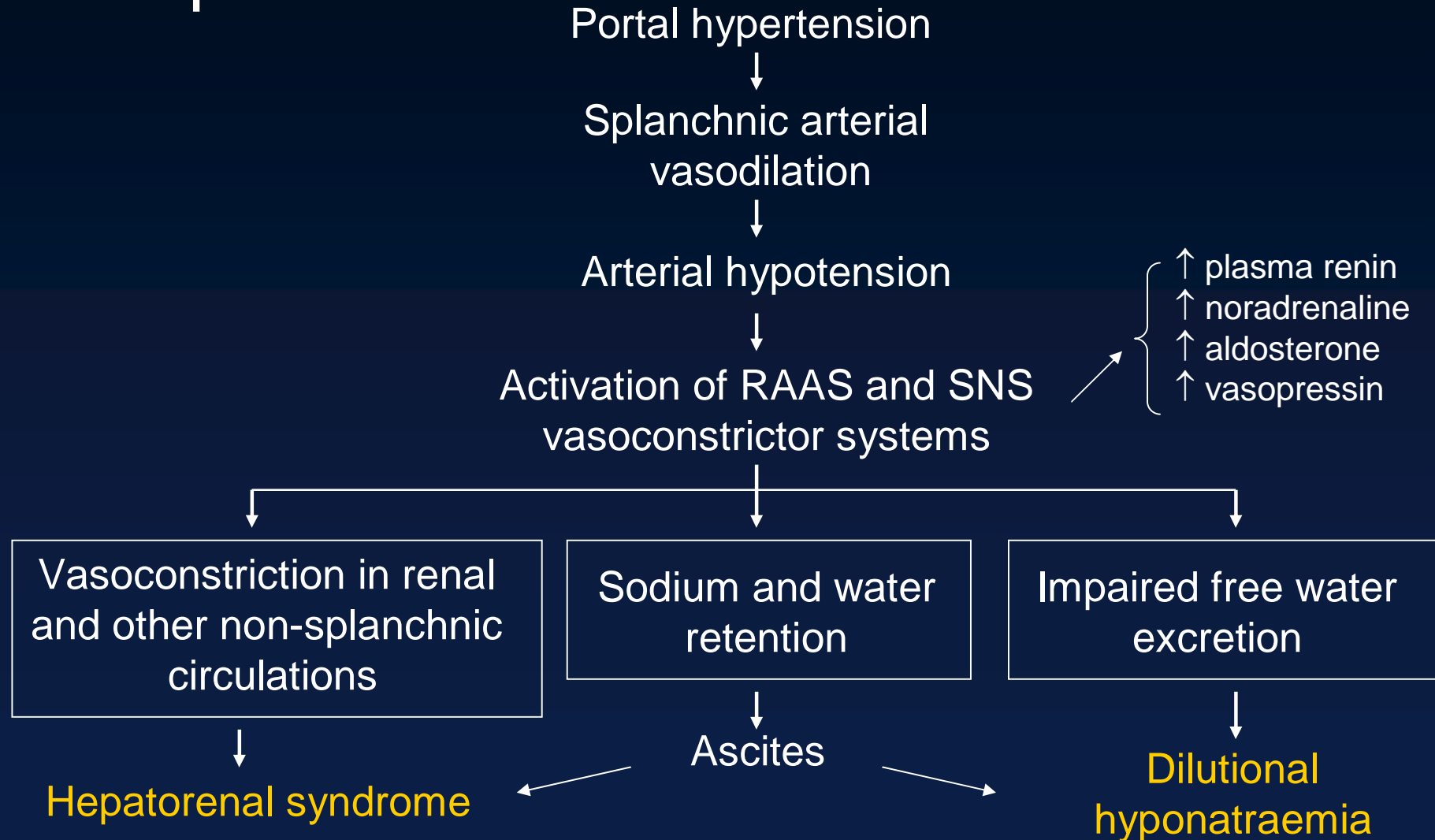
Ascites in Liver Cirrhosis



Differential diagnosis:

- ✓ Cirrhosis
- ✓ Hepatoma
- ✓ TB
- ✓ Peritoneal carcinomatosis
- ✓ Right heart failure
- ✓ Constrictive pericarditis
- ✓ Nephrotic syndrome
- ✓ Pancreatitis
- ✓ Malignant chylous ascites

Pathophysiology of Ascites in Cirrhosis





Cirrhotic Ascites

Patient evaluation

- Evaluate renal and circulatory function
 - Serum urea, creatinine and electrolytes
 - Ur protein (24 hr urine)
 - Ur Na⁺ (24 hr urine)
 - Arterial BP
- Ascitic fluid analysis
 - Cell count
 - Bacterial culture
 - Total protein
 - Albumin
 - Cytology
 - Other tests as needed



John's results

- Serum creatinine 0.1
- Serum albumin 24
- Negative urinary protein
- Ascites
 - Albumin 3
 - Polymorph count 200
- Cytology pending



What is the aetiology of John's ascites?

- Malignancy
- Infection
- Portal Hypertension



Ascitic Fluid Analysis

- Serum-ascitic albumin gradient
 - > 11 g/L suggestive of cirrhotic rather than malignant ascites
 - John: serum albumin 24, ascitic albumin 3
 - $24 - 3 = 21$
- Polymorph count >250 suggests spontaneous bacterial peritonitis



Management of Ascites

- What strategies would you use?
 - Fluid restriction
 - Sodium restriction
 - Frusemide
 - Spironolactone
 - Refer for therapeutic large volume paracentesis



Management of Ascites

o What strategies would you use?

- Fluid restriction
- Sodium restriction
- Frusemide
- Spironolactone
- Refer for therapeutic large volume paracentesis



Sodium and Water Restriction

- In patients with moderate ascites dietary restriction of Na^+ :
 - Facilitates elimination of ascites
 - Delays re-accumulation
 - Oral Na <88mmol/day
- Fluid restriction
 - Serum Na <120 mmol/L



Diuretics

Indications

- Mild to moderate ascites
- Oedema without ascites
- Prevention of ascites recurrence post-LVP



Management of Cirrhotic Ascites

Diuretics

Diuretic type	Name	Dose	SE's
Distal	Spironolactone	≤ 400 mg/d	Anti-androgenic Hyperkalaemia Azotaemia Renal tubular acidosis
	Amiloride	≤ 30 mg/d	Hyperkalaemia
Loop	Frusemide	≤ 160 mg/d	Hyponatraemia Hypokalaemia Azotamia



Refractory Ascites in Cirrhosis: Definition

- Inability to mobilise ascites despite sodium restriction and max tolerable doses of diuretics
 - 400mg/d spironolactone 160mg/d frusemide
- Development of diuretic-related complications
 - Renal impairment
 - Hepatic encephalopathy
 - Electrolyte imbalance
- Treated with therapeutic large volume paracentesis



John

- Comes back to see you one month later
 - Fever, mild abdominal pain
- Chest clear, dipstick urine NAD, no other source of infection identified
- Diagnostic tap (if available)
 - Polymorphs 750
 - Culture pending



Question

- What is the diagnosis?
- What should you do?
- How should he be treated?
- Does he need long-term treatment?

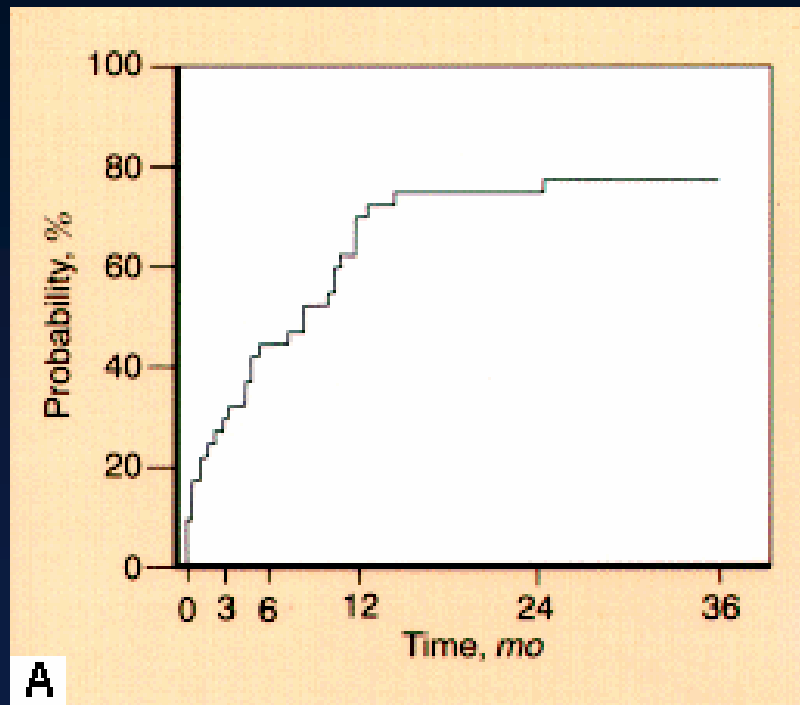


Question

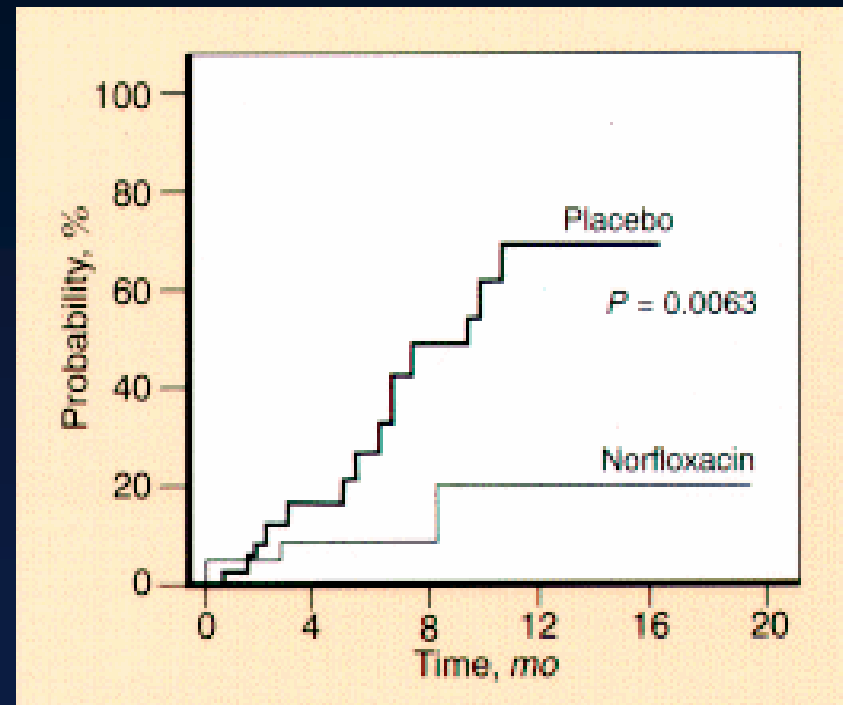
- What is the diagnosis?
 - SPONTANEOUS BACTERIAL PERITONITIS
 - Presence of > 250 neutrophils/ml diagnostic
- What is the most likely organism?
 - Aerobic GN 70% (E coli, enterococcus)
- What should you do?
 - Refer to hospital
- How should he be treated?
 - Treatment 3rd generation cephalosporin for 10 days
- Does he need long-term Abs?
 - Yes: norfloxacin, co-trimoxazole

SBP Recurrence

Recurrence rate



Norfloxacin prophylaxis

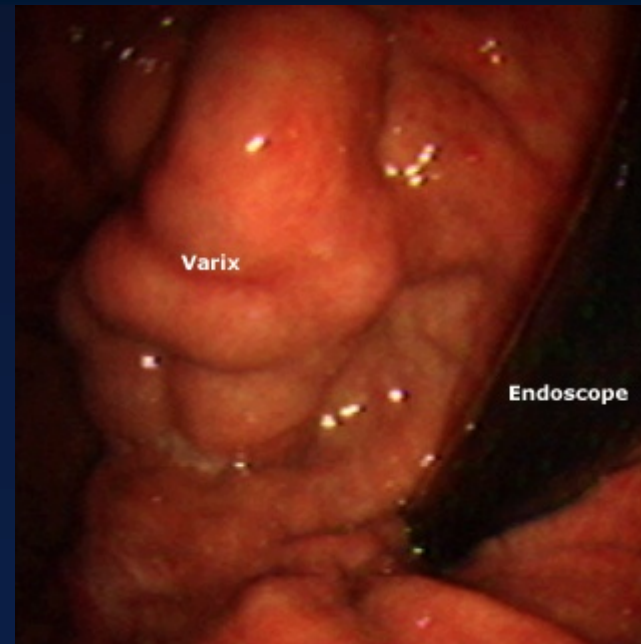
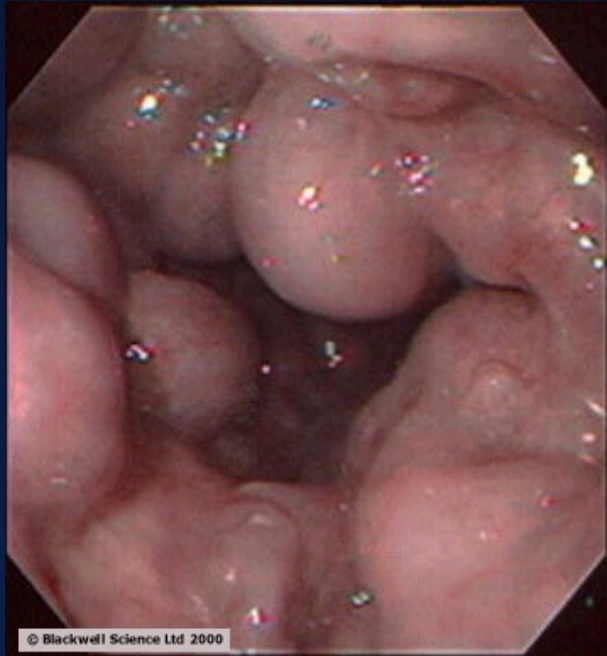


Predictors of recurrence are serum bilirubin $> 70 \mu\text{mol/L}$, PT $< 45\%$ of control, ascitic [protein] $\leq 1 \text{ gm/dL}$

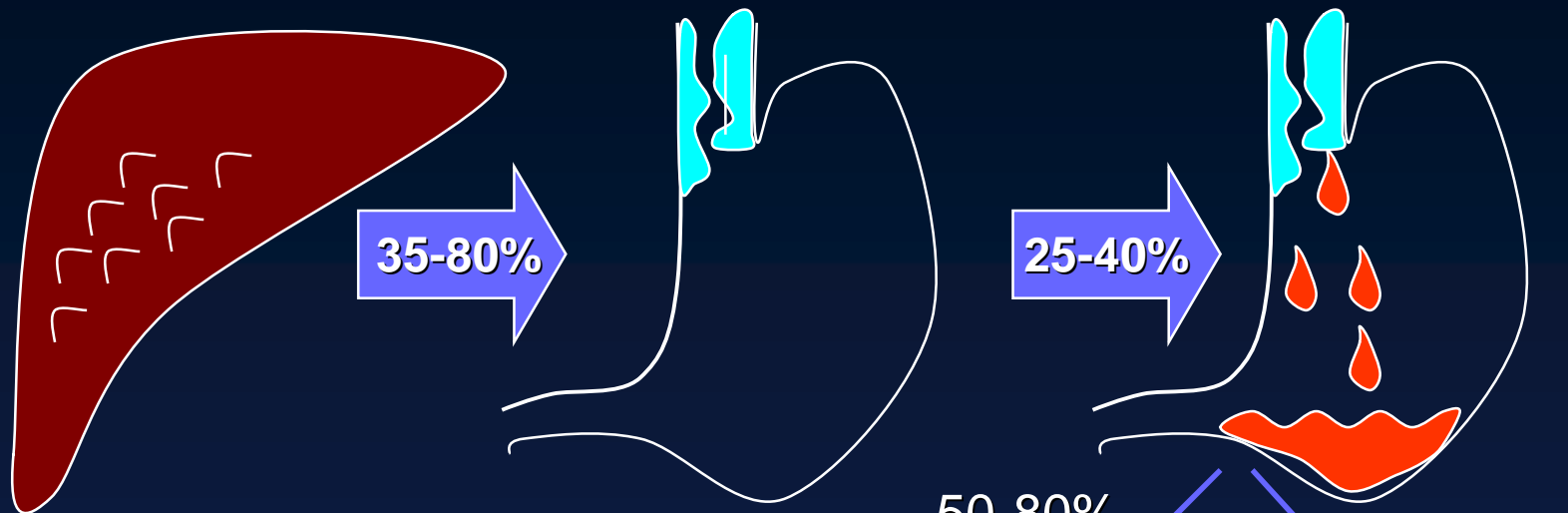


John

- Finally sees gastroenterologist
- Has gastroscopy



Complications of Portal Hypertension Oesophageal Varices



- ✓ Varices form at rate of 4-5% per year
- ✓ Develop when HVPG > 10 mmHg
- ✓ Varices increase from small to large in 12% patients per year in first 2 years





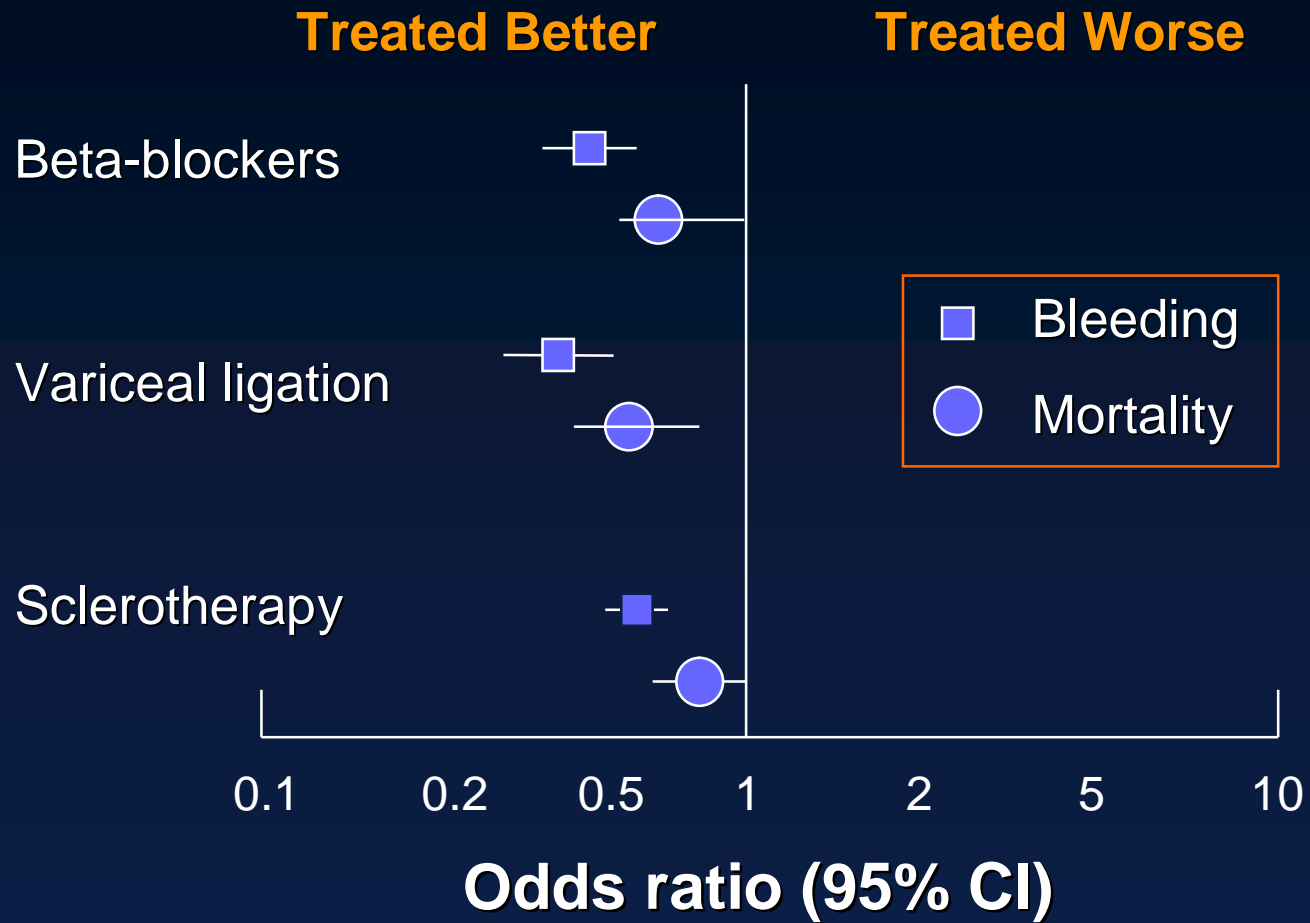
Medical Management of Portal Hypertension

○ Objectives

- Prevent of development of varices
- Prevent and control gastrointestinal bleeding and rebleeding
- Improve survival without impairment to quality of life



Primary Prevention of Variceal Bleeding Treatment options



D'Amico *et al.* Hepatology 1995



Prevention of Variceal Bleeding Beta-Blocker Therapy

- What are the objectives of treatment?
 - 25% reduction in HR or pulse < 60 bpm
- Which beta-blocker and dose
 - Propranolol 20-40mg
- Risk of initial bleed reduced 50%
- Usage limited by:
 - Contraindications (15-20%)
 - Side-effects



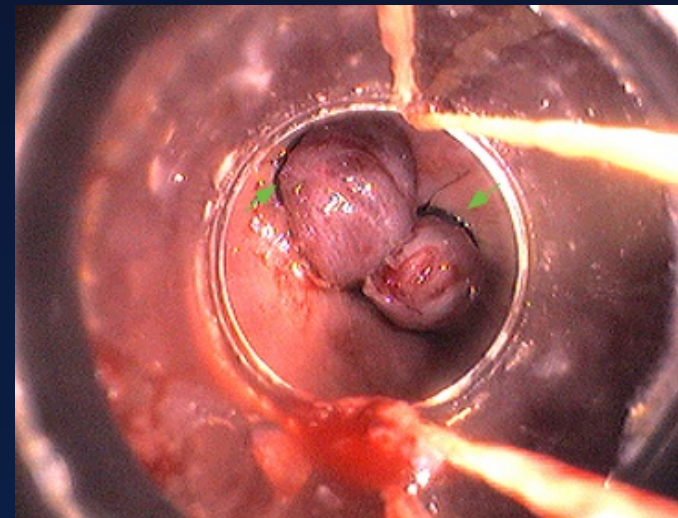
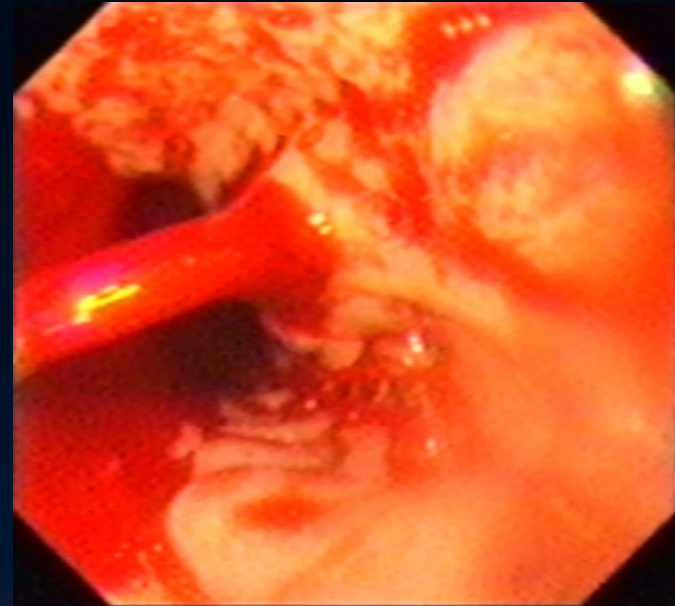
John

- Comes to see you because of tiredness
- Didn't like taking his medication –
propranolol and norfloxacin
- One week of melaena
- P and BP stable
- No aspirin, NSAIDs
- **Refer to emergency department**



Endoscopy

- Bleeding varix
- Variceal ligation
- IV octreotide or terlipressin
- IV antibiotics
- Secondary prevention with propranolol



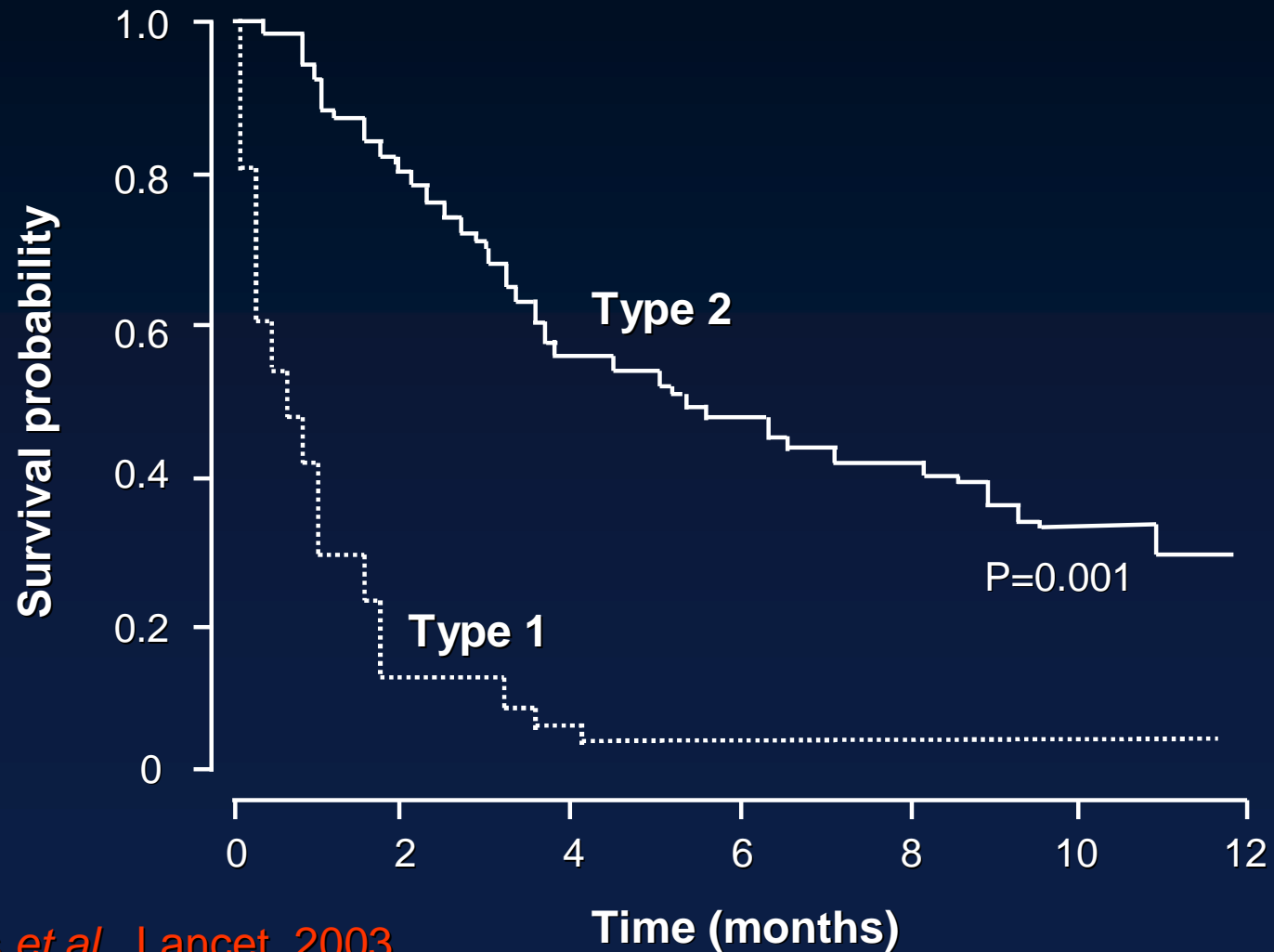


Hepatorenal Syndrome (HRS)

- Defined as development of renal failure in patients with severe liver disease in the absence of other identifiable renal pathology
- Annual incidence in patients with ascites is 8% or 40% risk over 5 years



Patient Survival After Diagnosis of HRS



Gines *et al.* Lancet 2003



John

- Neighbour brings John in to see you
- Forgetful, muddled sentences, confused
- Alert
- Hepatic fetor
- Hepatic flap
- Afebrile

- What's the diagnosis??



Hepatic Encephalopathy

- Acute or chronic
- Search for precipitants
 - Infection
 - Renal impairment
 - Hyponatraemia
 - Dehydration
 - Constipation
 - GI bleed



Hepatic Encephalopathy

- Grade 1
 - Subjective changes (personality, dressing apraxia)
 - Point charts (star, join the dots)
- Grade 2 and 3
 - Confusion (increased reflexes)
 - Agitation
 - Decreased LOC (depressed reflexes)
- Grade 4
 - Comatose



John

- How would you treat this?
 - Neomycin antibiotic
 - Protein restriction
 - Lactulose 20ml QID
 - Lactulose 20ml daily
 - Diazepam

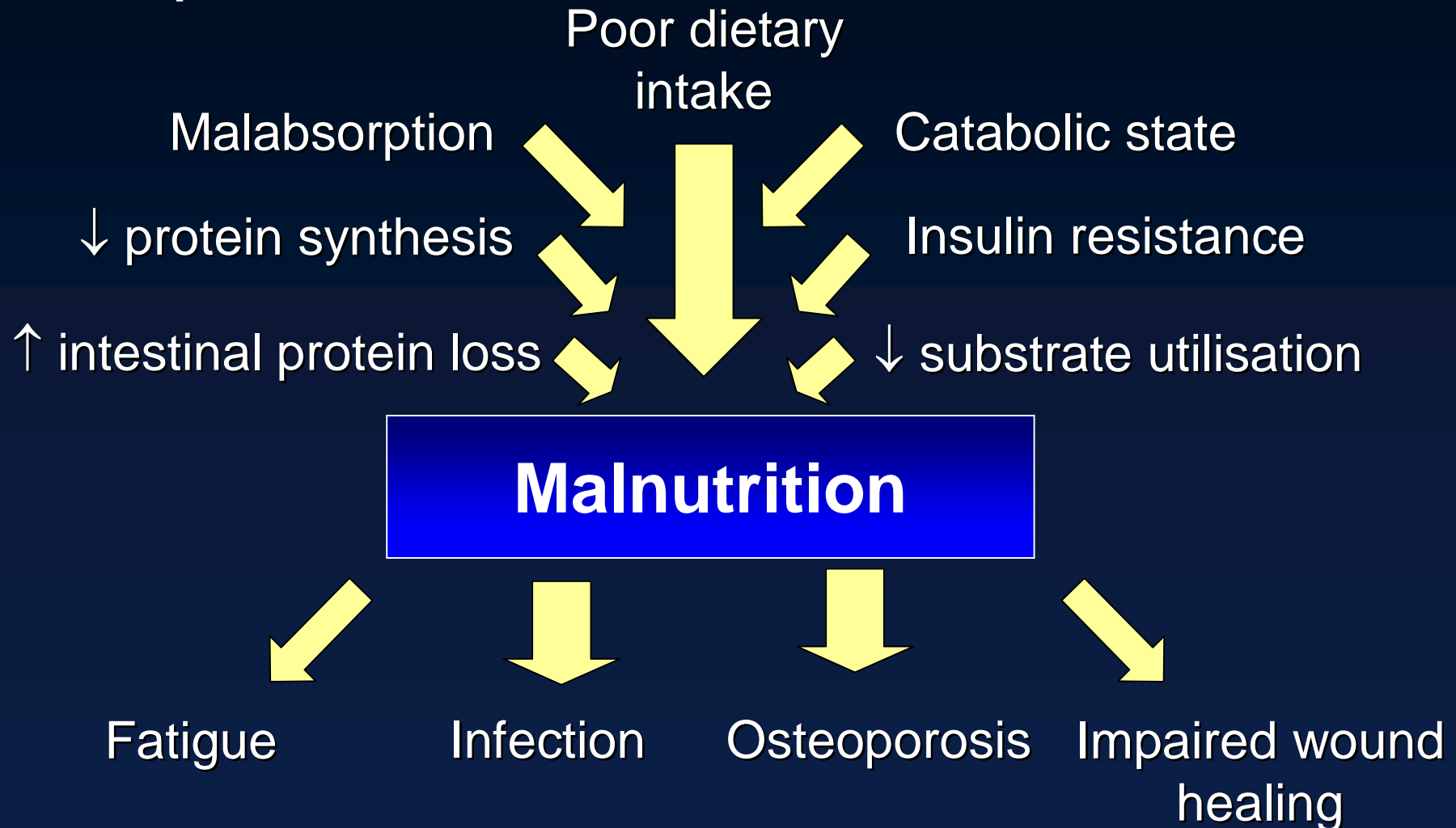


John

- How would you treat this?
 - Neomycin antibiotic
 - Protein restriction
 - Lactulose 20ml QID
 - Lactulose 20ml daily
 - Diazepam



Malnutrition in Liver Cirrhosis





Clinical failure: malnutrition

- High calorie diet
- No protein restriction
- Frequent small meals
- Dietary supplements
- Ensure adequate calcium and vitamin D
- Pro-kinetic agents
- May need to use NG feeding



Key Points Chronic Liver Disease

- John: recognising and diagnosing CLD
 - Important investigations in CLD
 - Albumin, INR, platelets, bilirubin
 - Causes
 - Alcohol, viral hepatitis, NASH, autoimmune liver disease, haemochromatosis
 - Viral serology, iron studies, autoimmune screen
- **Treat underlying disease early (prevention)**
- **All cirrhotic patients referred for evaluation**



Key Points Complications

- HBV vaccination
- Increase surveillance and clinical suspicion
- Sodium restriction and spironolactone for ascites
- Melaena needs urgent assessment
- Propranolol for prevention variceal bleeding
- Lactulose for encephalopathy
- Good nutrition