Management of Chronic Liver Disease

Dr Melissa Haines
Gastroenterologist
Waikato Hospital
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

- Alcohol: 50%
- HCV: 30%
- HBV: 5%
- Other: 15%
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

<table>
<thead>
<tr>
<th><strong>Feedback</strong></th>
<th>The nature and extent of alcohol-related problems</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Listen</strong></td>
<td>To patient concerns</td>
</tr>
<tr>
<td><strong>Advise</strong></td>
<td>Patient clearly to reduce consumption</td>
</tr>
<tr>
<td><strong>Goals</strong></td>
<td>Negotiate clinically appropriate goals acceptable to the patient</td>
</tr>
<tr>
<td><strong>Strategies</strong></td>
<td>Specific suggestions to modify drinking</td>
</tr>
</tbody>
</table>
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

- Alcohol: 50%
- HCV: 30%
- HBV: 5%
- Other: 15%

- Alcohol: 40%
- HCV: 5%
- HBV: 50%
- Other: 5%
Estimated 90,000 HBsAg+ living in New Zealand in 2006

Transmission of Hepatitis B Infection

- Transfusion and transplant recipients
- Sexual partners of known chronic carrier
- Healthcare workers
- Newborns of long-term carriers
- Intravenous drug users
- Prisoners and other institutionalised people
They are all healthy carriers!
Chronic hepatitis B has serious long-term consequences.

HBsAg-positive Chronic Hepatitis B

Cirrhosis

Liver Failure

Hepatocellular carcinoma (HCC)

Death

30%

Lok et al 2002
Natural History of Chronic HBV Infection

- **Serology**
  - HBsAg
  - HBeAg
  - Anti-HBe
  - Anti-HBs

- **ALT level**
- **HBV DNA level** (viremia)

- **Disease**: Minimal inflammation, Chronic active hepatitis, Cirrhosis/HCC, Normal to cirrhosis/HCC

- **Chronicity Stage**: Immune tolerant (phase I), Immune Active (phase II), Non-Replicative (phase III), Resolved

- **Years**: 0, 10, 20, 30, 40, 50, 60, 70
Which HBV tests would you order to screen for HBV

- HBeAg
- HBsAB
- HBV DNA
- HBsAg
- HBcAB
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-\(\alpha\)

**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
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

- Intravenous drug use: 74%
- Blood products: 13%
- HCV+ partner: 2%
- Tattoo: 1%
- Other: 2%
- None: 8%
- Intravenous drug use: 74%
Natural History of Hepatitis C

Acute HCV infection
- 70-80% chronic HCV
- 20-30% spontaneous clearance

Chronic hepatitis:
- Minimal-severe inflammation & fibrosis
- Bridging fibrosis

Cirrhosis develops in 10-15% over 20-30yrs

Hepatocellular carcinoma

Liver transplantation

Liver Failure

Liver Failure

Death
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
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

Obesity

NAFLD

Diabetes

Hypertension

Pathophysiology of Nonalcoholic Fatty Liver Disease

1. Insulin resistance
   - Diabetes
   - Obesity
2. Hepatic steatosis (oxidative stress)
3. Inflammatory cytokines
4. Lipid peroxidation
5. NASH

First step:
- Insulin resistance (Diabetes, Obesity) → Hepatic steatosis (oxidative stress)

Second step:
- Hepatic steatosis → Inflammatory cytokines, Lipid peroxidation → NASH
Clinical Course

Natural History of NASH

- **20%** NASH → Cirrhosis → Liver related death
- **30–40%** Sub-acute failure → Cirrhosis → HCC → Post-OLTX recurrence
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

- 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 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 sats 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
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
Differential diagnosis:

- Cirrhosis
- Hepatoma
- TB
- Peritoneal carcinomatosis
- Right heart failure
- Constrictive pericarditis
- Nephrotic syndrome
- Pancreatitis
- Malignant chylous ascites
Pathophysiology of Ascites in Cirrhosis

Portal hypertension
↓
Splanchnic arterial vasodilation
↓
Arterial hypotension
↓
Activation of RAAS and SNS vasoconstrictor systems

- Vasoconstriction in renal and other non-splanchnic circulations
- Sodium and water retention
- Impaired free water excretion

- Hepatorenal syndrome
- Ascites
- Dilutional hyponatraemia

↑ plasma renin
↑ noradrenaline
↑ aldosterone
↑ vasopressin
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

Gines et al, NEJM, 2004
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

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

<table>
<thead>
<tr>
<th>Diuretic type</th>
<th>Name</th>
<th>Dose</th>
<th>SE’s</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distal</td>
<td>Spironolactone</td>
<td>≤ 400 mg/d</td>
<td>Anti-androgenic, Hyperkalaemia, Azotaemia, Renal tubular acidosis</td>
</tr>
<tr>
<td></td>
<td>Amiloride</td>
<td>≤ 30 mg/d</td>
<td>Hyperkalaemia</td>
</tr>
<tr>
<td>Loop</td>
<td>Frusemide</td>
<td>≤ 160 mg/d</td>
<td>Hyponatraemia, Hypokalaemia, Azotamia</td>
</tr>
</tbody>
</table>
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

Predictors of recurrence are serum bilirubin > 70 μmol/L, PT < 45% of control, ascitic [protein] ≤ 1 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

Survive: 50-80%
Die: 20-50%
Re-bleed: 70%
Medical Management of Portal Hypertension

Objectives

- Prevent 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

- **Beta-blockers**
- **Variceal ligation**
- **Sclerotherapy**

Odds ratio (95% CI)

- Treated Better
  - 2
- Treated Worse
  - 0.1, 0.2, 5

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
  - Propanolol 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 – propanolol and norfloxacin
- One week of melaena
- P and BP stable
- No aspirin, NSAIDs

- Refer to emergency department
- Bleeding varix
- Variceal ligation
- IV octreotide or terlipressin
- IV antibiotics
- Secondary prevention with propanolol
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

Survival probability vs. Time (months)

Type 1 and Type 2 survival curves are shown. The survival probability for Type 1 is higher than for Type 2, with a statistically significant difference (P=0.001).

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

- Malabsorption
- Poor dietary intake
  - ↓ protein synthesis
  - ↑ intestinal protein loss
- Catabolic state
- Insulin resistance
  - ↓ substrate utilisation

Malnutrition

- Fatigue
- Infection
- Osteoporosis
- Impaired wound healing

Malnutrition consequences:
- Fatigue
- Impaired wound healing
- Osteoporosis
- Infection
- Insulin resistance
  - Catabolic state
- Malabsorption
  - Poor dietary intake
    - ↓ protein synthesis
    - ↑ intestinal protein loss
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
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
- Propanolol for prevention variceal bleeding
- Lactulose for encephalopathy
- Good nutrition