THE YELLOW PATIENT:
Acutely Presenting Decompensated Chronic Liver Disease

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Topics we'll cover:
- Alcoholic Hepatitis
- Ascites and Spontaneous Bacterial Peritonitis
- Hepatorenal Syndrome
- Hepatic Encephalopathy

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Case

- 51yo unemployed man
- Resident from homeless shelter
- No past medical/drug history or previous admissions
- But heavy alcohol dependence, 60 units/week, many years
- Trying to cut down recently
- Jaundiced and confused

O/E
- Febrile, Tachycardia
- Chest clear, Heart sounds normal
- Tense abdominal distension + lateral dullness to percussion
- 2 cm hepatomegaly
- Tremulous + asterixis
- No focal neurological abnormalities

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Ix

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
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<tbody>
<tr>
<td>BR</td>
<td>220</td>
</tr>
<tr>
<td>Hb</td>
<td>10.8</td>
</tr>
<tr>
<td>Na</td>
<td>129</td>
</tr>
<tr>
<td>ALT</td>
<td>130</td>
</tr>
<tr>
<td>MCV</td>
<td>100</td>
</tr>
<tr>
<td>AST</td>
<td>250</td>
</tr>
<tr>
<td>Plat</td>
<td>90</td>
</tr>
<tr>
<td>Ur</td>
<td>12</td>
</tr>
<tr>
<td>ALP</td>
<td>30</td>
</tr>
<tr>
<td>WCC</td>
<td>17.0</td>
</tr>
<tr>
<td>Creat</td>
<td>89</td>
</tr>
<tr>
<td>GGT</td>
<td>400</td>
</tr>
<tr>
<td>INR</td>
<td>1.9</td>
</tr>
<tr>
<td>CRP</td>
<td>35</td>
</tr>
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- ECG: sinus tachycardia
- Blood/Urine culture: Negative
- CXR: Loss of lung volume, nil focal
- USS - Liver increased in size, coarse edge
  - Diffusely increased echogenicity
  - Free fluid throughout abdomen

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Qs for Discussion:

- What are the main causes of chronic liver disease?
- What specialist investigations would you do next?
Chronic Liver Disease: Screening Investigations

- Chronic Alcohol Abuse (History – collateral)
- Hepatitis B (Viral serology inc. HBcore)
- Hepatitis C (Viral serology)
- Other Liver viruses: Hep A, Hep E, CMV, EBV, HSV
- Autoimmune Hepatitis/Primary Biliary Cirrhosis/Primary Sclerosing Cholangitis (Liver Antibodies Anti-LKM, ANCA, ANA, ASMA, AMA)
- Non-alcoholic Fatty Liver Disease (NASH) (Fasting lipids, glucose)
- Haemochromatosis (Ferritin/Iron Studies, Transferrin satn)
- Wilson’s disease (younger patients) (Serum copper/caeruloplasmin and 24hr urine Copper))
- Alpha1-Antitrypsin Deficiency (Alpha1-AT levels)
- (Cystic fibrosis + other congenital diseases e.g. biliary artesia, glycogen storage disease)

Q for Discussion:
What immediate therapies should be instigated?
- Pabrinex iv
- Vitamin K
- Vitamin B PO
- Thiamine PO
- Chlordiazepoxide PO: reducing dosage
- Address nutrition

Liver Biopsy (TJ) showed
Alcoholic Hepatitis on background of cirrhosis
A clinico-pathological syndrome of Hepatitis (inflammation of liver) due to excessive intake of Alcohol
- EtOH chronic liver disease
- Recently cut down/stopped
- AST > ALT (both usually < 500 IU/L)
- Higher level suggests viral, ischaemic or drug hepatitis (e.g. paracetamol [acetaminophen])
- Fever, hepatomegaly (tender), jaundice, anorexia

Lucey et al. Review. NEJM. 26 June 2009

Alcoholic Hepatitis
- Steroids or Pentoxifylline – reduce mortality in selected cases
- Septic screen important

Discriminant function (Maddrey score):
• $D = (4.6 \times [\text{prothrombin time - control PT}]) + (\text{serum bilirubin})$
• Score > 32 associated with a high short-term mortality
- used to decide treatment
  – Prednisolone 40mg/d for 28 days
  – or Pentoxifylline 400mg tid for 28 days

Q for Discussion:
What important bit of the septic screen don’t we know yet?
- Ascitic tap: 250,000 WC, polymorphs
- Patient is septic with spontaneous bacterial peritonitis
**Ascites**
- A major complication of cirrhosis: 50% over 10y
- 50% mortality in 2 years
- Signifies need to consider liver transplantation

**Causes of Ascites**
- Cirrhosis 75%
- Malignancy 10%
- Heart Failure 3%
- Tuberculosis 2%
- Pancreatitis 1%
- Others 9%

Pathogenesis of ascites in liver disease – Appendix 1

**Ascites: Basic Investigations**

**Serum Albumin – Ascitic Albumin Gradient**

<table>
<thead>
<tr>
<th>High &gt; 11g/L</th>
<th>Low &lt; 11g/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cirrhosis</td>
<td>Peritoneal carcinoma</td>
</tr>
<tr>
<td>Heart Failure</td>
<td>Peritoneal tuberculosis</td>
</tr>
<tr>
<td>Massive Liver metastases</td>
<td>Pancreatitis</td>
</tr>
<tr>
<td>Fulminant Liver Failure</td>
<td>Biliary leak</td>
</tr>
<tr>
<td>Vascular Occlusion</td>
<td>Nephrotic syndrome</td>
</tr>
<tr>
<td>Alcoholic Hepatitis</td>
<td>Serositis</td>
</tr>
<tr>
<td>Acute Fatty Liver of Pregnancy</td>
<td>Bowel infarction/perforation</td>
</tr>
<tr>
<td>Myxoedema</td>
<td></td>
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</tbody>
</table>

**Ascites: Basic Investigations – WCC**

**Spontaneous Bacterial Peritonitis (SBP)**
- Ascitic neutrophil count >250 cells/mm³
- 15% in-patients with ascites
- SBP develops in 25% patients within 1 year
- Subsequent prognosis < 40% at 1 year

**Other ls**
Ascitic fluid Cytology and Amylase

**Management of Ascites**

**Dietary Salt Restriction to 90mM/day (5.2g)**
- Lower diuretic requirement
- Faster resolution of ascites
- Shorter hospital stay

Achievable by:
- no-added salt
- avoid pre-prepared food

**Management of Ascites: Diuretics**

**Diuretics and Regular Weights**
- Spironolactone
  - Initially; aldosterone antagonist; distal tubules
  - 100-400mg/d; 3-5 day lag before natriuresis (urine Na > K)
- Then add loop diuretic (Frusenid 40 – 160mg/d)

**Management of Ascites: Hyponatraemia**

**Hyponatraemia - Poor prognostic indicator**

<table>
<thead>
<tr>
<th>Na &gt; 125mmol/l</th>
<th>Na &lt; 125mmol/l</th>
</tr>
</thead>
<tbody>
<tr>
<td>no need for H2O restriction</td>
<td>consider stopping diuretics esp if Na &lt; 121mmol/l</td>
</tr>
<tr>
<td>continue diuretics if renal function stable</td>
<td>if creatinine rising (&gt;150μmol/l), volume expansion</td>
</tr>
<tr>
<td>maintaining renal function crucial</td>
<td></td>
</tr>
</tbody>
</table>

Pathogenesis of ascites in liver disease – Appendix 1
Management of Ascites: Therapeutic Paracentesis

- 8g albumin iv/L ascites after 5L removed
- Failure to volume expand risks circulatory dysfunction + renal failure
- Albumin better > artificial plasma expanders, which activate RAA more
- Ascites recurs in 90% pts if diuretics not begun; in 20% despite diuretics
- Do NOT leave drain in situ overnight

Management of Ascites: Transjugular Intrahepatic Portosystemic Shunt - TIPS

- For refractory ascites and hepatic hydrothorax
- 25% risk encephalopathy
- May PPT heart failure (consider ECHO)

Management of Ascites: Spontaneous Bacterial Peritonitis (SBP)

- 70% due to
  - E. coli
  - Gram positive cocci (mainly strep)
  - Enterococci
- Tazocin/3rd gen cephalosporins cover 95% flora isolated from ascites
- If asymptomatic, oral ciprofloxacin or augmentin
- Albumin (1.5g/kg for 6h then 1g/kg on d3)
  - reduces mortality (41% to 22%, 3m)
  - decreases renal impairment: 33% to 10% (Sort et al., NEJM 1999)

Management of Ascites: Spontaneous Bacterial Peritonitis (SBP)

- Those who survive SBP
  - 70% recurrence at 1 year
  - Prophylactic norfloxacin or ciprofloxacin reduces SBP recurrence to 20%
  - Consider transplantation

Patient given Tazocin, Spironolactone, Frusemide and undergoes Paracentesis

LFTs better, sepsis settling, less confused

BUT renal function going off

Na 129—124
K 3.7—5.6
Ur 12—25
Creat 89—180

Urine output 30mls/hour

Hepatorenal Syndrome (HRS)

- Acute renal failure in patient with cirrhosis, severe alcoholic hepatitis, or hepatic failure from any cause
- HRS represents the end-stage of a sequence of reductions in renal perfusion
**Hepatorenal Syndrome (HRS)**

- Ascites and Hyponatraemia are harbingers of doom......
- 40% of patients with cirrhosis and ascites develop HRS during the natural history of their disease.
- Type 1
  - rapid and progressive renal impairment
  - most commonly precipitated by SBP (25% of patients)
  - characterized by diuretic resistant ascites
  - most patients die within 10 weeks
- Type 2
  - Moderate and stable reduction in the GFR
  - median survival of 3-6 months

**HRS Diagnosis**

- Creatinine > 130 µmol/L that progresses: days to weeks
- Absence of another cause for renal disease, inc:
  - shock
  - sepsis
  - acute tubular necrosis and other causes of pre-renal disease
  - nephrotoxic drugs
  - absence of obstruction
  - no known parenchymal renal disease
- No improvement in renal function after volume expansion with i.v. albumin for at least 2d and withdrawal of diuretics
- Must exclude spontaneous bacterial peritonitis, which is complicated by acute renal failure that may be reversible in 30% cases

*Gines P & Schrier R. Renal Failure in Cirrhosis. NEJM Sep 2009*

**HRS therapy**

- Terlipressin (iv 1-2g qds) and human albumin solution (40g/day)
- superior to placebo for HRS reversal (34% vs 13%, p=0.008)

Further Reading:

- Ascites
- Spontaneous Bacterial Peritonitis
- Hepatorenal Syndrome

EASL PRACTICE GUIDELINES; J Hepatology September 2010

**Hepatic Encephalopathy (HE)**

- Spectrum of potentially reversible neuropsychiatric abnormalities in patients with liver dysfunction after exclusion of unrelated neurologic and/or metabolic abnormalities.
- Reversibility of symptoms after improvement of liver function considered to proof of causal relation to liver disease.
- HE Grading: Appendix 2

**Precipitating factors**

- Sepsis
- SBP Rx fluids ++
- Albumin
- Avoid renal failure
- CNS active drugs
- Electrolyte abnormalities
- Diuretics: over use
- Gastrointestinal bleeding
Hepatic Encephalopathy in CLD

- Not usually a cause of death … if airway is managed
- Treat precipitating cause e.g. antibiotics, bleeding, fluids
- CT head rules out bleeding
- EEG may help if diagnosis unclear
- Lactulose and Enemas
  - Sharma et al., Gastroenterology 2009; RCT
  - Lactulose effective in 2ndary prevention of overt HE
  - 125 patients, median follow-up 14 months
  - HE episodes: lactulose group 20% vs. placebo group 47% (p=0.001)

L-ornithine L-aspartate

- Ammonia removed by formation of urea and by synthesis of glutamine from glutamate in hepatocytes
- Ornithine + Aspartate increase ammonia removal by stimulating glutamine synthesis
- Decreasing ammonia therapies: L-ornithine L-aspartate
  - Ineffective in acute liver failure (RCT; Gastroenterol. June 2009)
  - Improves overt encephalopathy in chronic liver disease

Rifaximin

- Minimally absorbed broad spectrum antimicrobial
- Concentrates in GI tract
- Reduces ammonia-producing enteric bacteria
- Bass et al., NEJM 25th March 2010
  - Double blind, Placebo-controlled RCT
  - 299 patients in remission from recurrent HE
  - Randomised to Rifaximin or placebo for 6 months
  - HE recurrence: 22% in Rifaximin group vs. 46% in placebo group
  - Hospitalization for HE: 14% vs. 23%

Q for Discussion:
What important issues need to be addressed post-discharge?

- Support to prevent alcohol relapse
- Variceal screening (OGD)
- Hepatocellular screening (6-monthly AFP + liver USS)
- Vitamin D levels
- Early follow-up: consider liver transplant assessment

Appendix 1: Pathogenesis of Ascites in Liver Failure

1. Portal (sinusoidal) Hypertension
   - Abnormal Na + Water Retention
   - Systemic/Splanchnic Vasodilatation
     - key step in renal dysfunction + Na retention
     - NO, prostacyclin results in effective arterial blood volume + hyperdynamic circulation
   - Renal v/constriction to systemic vasodilatation is partly a homeostatic response:
     - renal sympathetic activity
     - activation of renin-angiotensin system to maintain BP
   - hydrostatic press in hepatic sinusoids
   - this favours transudation of fluid in peritoneal cavity
   - renal blood flow \( \Rightarrow \) GFR, delivery and fractional excretion of Na
   - Na reabsorption in distal tubule (hyperaldosteronism): Total Body Na High

2. Abnormal Na + Water Retention
   - Portal (sinusoidal) Hypertension

Appendix 2: Grades of Encephalopathy

<table>
<thead>
<tr>
<th>Grade</th>
<th>Symptoms</th>
<th>Signs</th>
<th>GCS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Short attention span</td>
<td>Tremor Ataxia Incoordination</td>
<td>15</td>
</tr>
<tr>
<td>2</td>
<td>Lethargy</td>
<td>Disorientation Personality change</td>
<td>Asterixis Ataxia Dysarthria</td>
</tr>
<tr>
<td>3</td>
<td>Confusion Somnolence</td>
<td>Asterixis Ataxia</td>
<td>8-11</td>
</tr>
<tr>
<td>4</td>
<td>Coma</td>
<td>Decerebration</td>
<td>&lt;8</td>
</tr>
</tbody>
</table>

Seizures can occur at any grade