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University of Edinburgh

Hepatology Highlights for the Healthcare Specialist
Tuesday 17 April 2019 • Pentland Suite, Level 2, Edinburgh International Conference Centre
Acute liver failure

BHIVA meeting, April 2018
No disclosures relevant to this presentation
ALF DEFINITIONS

Trey and Davidson, 1970

Potentially a reversible condition that is the consequence of severe liver injury, in which the onset of hepatic encephalopathy occurs within 8 weeks of first symptoms of illness in the absence of pre-existing liver disease.
# Aetiology of ALF

## Drug Causes
- Halothane
- Paracetamol with or without enzyme inducers
- Anti-TB medication (rifampicin, isoniazid, pyrazinamide)
- MAOI
- NSAIDS
- Anticonvulsants (valproate, phenytoin, lamotrigine)
- Antibiotics (cotrimoxazole, ketoconazole)
- Illegal drugs

## Non-drug Causes
- Viral; HAV, HBV, HCV (?), HDV, HEV, CMV, Coxsackie.
- Autoimmune hepatitis
- Pregnancy; AFLP, HELLP.
- Ischaemia.
- Budd-Chiari.
- Malignancy.
- Wilsons Disease.
- *Amanita phalloides*
Paracetamol Poisoning - Epidemiology

- Commonest discharge diagnosis for overdose
- Slight reduction in discharges to 100 per 100,000 population since 1998 in Scotland
- Commonest cause of acute liver failure in the UK and US
- Legislation changes led to reduction in admissions with severe overdose by 30% in England
Paracetamol toxicity

- Approx 10-15 gm of paracetamol is sufficient to induce hepatotoxicity
- Related to metabolic activation of paracetamol
- Toxic metabolite identified as N-acetyl-p-benzoquinoneimine
- Glutathione binds NAPQI and limits toxicity
- N-acetylcysteine is an effective antidote within the therapeutic window
Severity of liver damage

- ALT markedly increased - not good marker
- Prothrombin time best marker
- Often early acidosis before fluid resuscitation
- Hypoglycaemia
Predictors of severity

- Quantity of paracetamol
- Time to NAC
- Age
- Chronic alcohol misuse
Initial Management

• Clear history of time of overdose and any additional tablets
• If around 12 hours or unclear start NAC
• Monitor blood glucose
• Routine bloods including PT and paracetamol level
• Intravenous fluids- 5% dextrose and N-saline
Progress

- Monitor prothrombin time and creatinine
- Monitor neurological state
- Psychiatric evaluation as early as possible
- If PT rising rapidly SLTU contacted and transferred early-if PT =hrs post OD-50% risk of FHF
On transfer

• Main thrust initially to ascertain suitability for transplantation
• Psychiatric evaluation
• Contact with GP and family
• Continue intravenous fluids and monitoring PT, creatinine and glucose
Acute Liver Failure admitted to SLTU (n=621)
Referrals ALF to SLTU

Number of Patients


POD  Non-POD  Total

0 10 20 30 40 50 60 70 80
KCH criteria-paracetamol

- pH < 7.30 after fluid resuscitation

- or all 3 of following: PT >100s creat>300 grade 3 encephalopathy
Bernal et al. Lancet 2002

- Arterial lactate >3.5 mmol/l before resuscitation
- Arterial lactate >3.0 mmol/l following resuscitation

As good as KCH as indicating poor prognosis in ALF.
Clinical Progress

- Encephalopathy worsens
- Patient becomes agitated and difficult to manage
- Oligoanuric
- Require ITU assessment
MEDICAL CONTRAINDICATIONS TO TRANSPLANTATION

- Untreated or progressive infection
- Clinically apparent extrahepatic or metastatic malignancy
- Progressive hypotension, resistant to vasopressor support
- Clinically significant ARDS, FiO2 > 0.8
- Fixed dilated pupils > 1 hour in the absence of thiopentone
- Severe coexistent cardiopulmonary disease, AIDS
PSYCHIATRIC CONTRAINDICATIONS TO TRANSPLANTATION

- Multiple episodes of self harm (>5) within an established pattern of behaviour (esp. if non-drug methods used)
- Consistently stated wish to die, in the absence of established mental illness
- Chronic refractory schizophrenia or other mental illness, resistant to therapy
- Incapacitating dementia or mental retardation
- Active intravenous drug abuse or oral polydrug use
- Alcohol dependence or abuse
- Established pattern of non-compliance with treatment
Clinical problems in acute liver failure

- Encephalopathy
- Cerebral oedema
- Cardiovascular disturbance
- Deranged coagulation
- Renal failure
- Gut failure

(Respiratory problems)

SEPSIS
## Hepatic encephalopathy

<table>
<thead>
<tr>
<th>Grade</th>
<th>Conscious level</th>
<th>Personality</th>
<th>Neurological signs</th>
<th>EEG</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Sleep reversal</td>
<td>Forgetful</td>
<td>Tremour</td>
<td>Triphasic waves (5Hz)</td>
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<tr>
<td></td>
<td>Restless</td>
<td>Agitated</td>
<td>Apraxia</td>
<td></td>
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<td></td>
<td></td>
<td>Irritable</td>
<td>Incoordination</td>
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<td></td>
<td></td>
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<td>Impaired handwriting</td>
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<tr>
<td>2</td>
<td>Lethargy</td>
<td>Disorientated</td>
<td>Asterixis</td>
<td>Triphasic waves (5Hz)</td>
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<tr>
<td></td>
<td>Slowed</td>
<td>Loss of inhibition</td>
<td>Dysarthria</td>
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<td></td>
<td></td>
<td>Inappropriate behaviour</td>
<td>Ataxia</td>
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<td></td>
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<td></td>
<td>Hyporeflexes</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Sleepy</td>
<td>Disorientation</td>
<td>Asterixis</td>
<td>Triphasic waves (5Hz)</td>
</tr>
<tr>
<td></td>
<td>Confused</td>
<td>Aggressive</td>
<td>Muscular rigidity</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Extensor planters</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Hyperreactive reflexes</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Coma</td>
<td>None</td>
<td>Decerebration</td>
<td>Delta slow waves</td>
</tr>
</tbody>
</table>
Clinical problems in acute liver failure

- Encephalopathy
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- Cardiovascular disturbance
- Deranged coagulation
- Renal failure
- Gut failure
- (Respiratory problems)
- SEPSIS
Cause of cerebral oedema

Multifactorial

Cytotoxic problem rather than disruption of blood-brain barrier

1. Ammonia metabolism to glutamine in astrocytes
   - osmotic effect

2. Cerebral hyperaemia

3. Inflammatory mechanism
Management of cerebral oedema

Basic measures:

- patient position, venous drainage, adequate sedation,
- adequate ventilation, hypervent

Osmotic agents

Hypothermia

Hepatectomy

?Barbiturate coma

Detoxification using liver support system
Treatment objectives

- Cerebral perfusion pressure = mean arterial pressure – intracranial pressure
- Cerebral oedema increases ICP therefore aim to reduce ICP
- Other manoeuvres to increase MAP
- Aim for CPP>50mmHg
Hypothermia and ICP

[Graphs showing intracranial pressure in patients who did and did not undergo OLT]
Clinical problems in acute liver failure

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- **Cardiovascular disturbance**
- Deranged coagulation
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- SEPSIS
Cardiovascular support

Hyperdynamic circulation

Hypotension, vasodilatation, elevated cardiac output, low SVRI

- resuscitation
- use of N-acetylcysteine
- norepinephrine
Clinical problems in acute liver failure

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- **SEPSIS**
Coagulopathy

Coagulation disturbance vs bleeding

Invasive procedures and coagulopathy

Bleeding unusual complication

Thromboelastography helpful at operation
Clinical problems in acute liver failure

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(Respiratory problems)

SEPSIS
Renal support

Haemofiltration vs haemodialysis

Nutritional support
Enteral / jejunal feeding?
Clinical problems in acute liver failure

- Encephalopathy
- Cerebral oedema
- Cardiovascular disturbance
- Deranged coagulation
- Renal failure
- Gut failure
- Respiratory problems
- Sepsis
Respiratory Problems

- Common
- Pneumonia, aspiration
- Atelectasis
- Ventilation related
- ARDS
SEPSIS

Incidence- common (80%)

Organisms- gram positive in 70% of cases;
  fungal infection in up to 30%

Time course- often cause of late death

Antibiotic and anti-fungal prophylaxis is given when patients ventilated
LIVER SUPPORT SYSTEMS
Cell mass

90% of liver mass is hepatocytes

Approximately 20% of liver mass is required in patients undergoing hepatic resection

100g – 400g hepatocytes required

- may allow improved function of native liver
Randomised controlled trials have shown no benefit in FHF
HepatAssist

Porcine cryopreserved cells

No published randomised trials
MARS
No hepatocytes

Uncertain role in FHF
MARS liver support
Conclusions

• Paracetamol poisoning is common
• Acute liver failure has reduced in England but not Scotland
• Mortality is high and transplantation may be indicated
• Liver support devices may improve outcome