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ALF a primer
Objectives

- Definition
- Classification
- Burden
- Causes
- Specific management
- Local data
ALF

- Acute abnormality of LFT
- INR > 1.5
- Altered level of consciousness due to HE
- Absence of underlying chronic liver disease*
Clinical Features of Acute Liver Failure

- **Brain**
  - Hepatic encephalopathy
  - Cerebral edema
  - Intracranial hypertension

- **Lungs**
  - Acute lung injury
  - Acute respiratory distress syndrome

- **Liver**
  - Loss of metabolic function
  - Decreased:
    - Gluconeogenesis → hypoglycemia
    - Lactate clearance → lactic acidosis
    - Ammonia clearance → hyperammonemia
    - Synthetic capacity → coagulopathy

- **Heart**
  - High output state
  - Frequent subclinical myocardial injury

- **Pancreas**
  - Pancreatitis, particularly in acetaminophen-related disease

- **Adrenal gland**
  - Inadequate glucocorticoid production contributing to hypotension

- **Kidney**
  - Frequent dysfunction or failure

- **Portal hypertension**
  - May be prominent in subacute disease and confused with chronic liver disease

- **Circulating leukocytes**
  - Impaired function, with immunoparesis contributing to high risk of sepsis

- **Systemic inflammatory response**
  - High energy expenditure or rate of catabolism
Incidence

• Rare clinical syndrome
• <10 per million developed world
• USA 2000 cases/yr
• EU?
Classification Systems for Acute Liver Failure

A. O’Grady System

- Hyperacute
- Acute
- Subacute

Weeks from Jaundice to Encephalopathy

B. Bernuau System

- Fulminant
- Subfulminant

Weeks from Jaundice to Encephalopathy

C. Japanese System

- Fulminant
- Late-Onset
- Subclass:
  - Acute
  - Subacute

Weeks from Jaundice to Encephalopathy
Sub-classifications of ALF

- **Hyperacute**
  - Severity of coagulopathy
- **Acute**
  - Severity of jaundice
- **Subacute**
  - Degree of intracranial hypertension
  - Chance of spontaneous recovery
  - Typical cause

<table>
<thead>
<tr>
<th>Sub-classification</th>
<th>Severity of Jaundice</th>
<th>Degree of Intracranial Hypertension</th>
<th>Chance of Spontaneous Recovery</th>
<th>Typical Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>+++</td>
<td>++</td>
<td>+++</td>
<td>+/-</td>
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<td>++</td>
<td>++</td>
<td>++/−</td>
<td>+/-</td>
<td></td>
</tr>
<tr>
<td>Good</td>
<td>Moderate</td>
<td>Poor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paracetamol, HAV, HEV</td>
<td>HBV</td>
<td>Non-paracetamol drug-induced</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

>28 weeks = chronic liver disease
Principal Etiologies of ALF

**Viral**
- Hepatitis B, A, E
  - (less frequent CMV, HSV, VZV, Dengue)

**Toxins**
- *Amanita phalloides*, phosphorus

**Drugs**
- Paracetamol, anti-tuberculous, chemotherapy, statins, NSAIDs, phenytoin, carbamazepine, ecstasy, flucloxacillin

**Vascular**
- Budd–Chiari syndrome
- Hypoxic hepatitis

**Pregnancy**
- Pre-eclamptic liver rupture, HELLP, fatty liver of pregnancy

**Other**
- Wilson disease, autoimmune, lymphoma, malignancy, HLH
Drug induced liver injury

- Antibiotics: amoxicillin-clavulanate, ciprofloxacin, nitrofurantoin, minocycline, dapsone, doxycycline, trimethoprim-sulfamethoxazole, efavirenz, didanosine, abacavir
- Anti-epileptics: valproic acid, phenytoin, carbamazepine
- Anti-tuberculosis drugs: isoniazid, rifampin-isoniazid, pyrazinamide
- Miscellaneous: propylthiouracil, amitryptiline, statins, amiodarone, methotrexate, methyldopa
- NSAID: Diclofenac, ibuprofen, indomethacin, naproxen
- Herbs: ma huang, kava kava, herbalife
Drug induced liver injury
Acetaminophen/Paracetemol

• Commonest cause of ALF
• Toxic metabolite N-acetyl-p-benzoquinoneimine
• Interval between drug ingestion and treatment with acetylcysteine is closely related to the outcome
• Advanced coma grades do not benefit from NAC and typically require emergency liver transplantation
Acute Hep B-ALF

- 1~4% AHB cases progress ALF
- TB ≥ 5×ULN and HBeAg negative status were the most effective and practicable factors distinguishing ALF from AHB at admission before the onset of encephalopathy.
- Peak PTA < 20% and/or HE grade III-IV were independent predictors of a high probability of death or a need for transplantation.
- Prodromal fever and temp > 38
**Hep A**

- 3% of all cases of ALF
- Worse in older adults
- Prognostication linked to creat, ALT, pressors, intubation

**Hep E**

- 40% of cases in developing countries
- Misdiagnoses DILI
- Mortality 25%
# Alarm causes?

<table>
<thead>
<tr>
<th>Disease group</th>
<th>Hepatic/primary ALF</th>
<th>Extrahepatic/secondary liver failure and ACLF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute liver failure</td>
<td>Drug related</td>
<td>Hypoxic hepatitis (aka ischaemic)</td>
</tr>
<tr>
<td></td>
<td>Acute viral hepatitis</td>
<td>Systemic diseases:</td>
</tr>
<tr>
<td></td>
<td>Toxin-induced ALF</td>
<td>• Haemophagocytic syndromes</td>
</tr>
<tr>
<td></td>
<td>Budd–Chiari syndrome</td>
<td>• Metabolic disease</td>
</tr>
<tr>
<td></td>
<td>Autoimmune</td>
<td>• Infiltrative disease</td>
</tr>
<tr>
<td></td>
<td>Pregnancy related</td>
<td>• Lymphoma</td>
</tr>
<tr>
<td>CLD presenting with a phenotype of</td>
<td>Fulminant presentation of Wilson disease</td>
<td>• Infections (e.g. malaria)</td>
</tr>
<tr>
<td>ALF</td>
<td>Autoimmune liver disease</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Budd–Chiari</td>
<td></td>
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<tr>
<td></td>
<td>HBV reactivation</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Liver resection for either secondary deposits or primary liver</td>
</tr>
<tr>
<td></td>
<td></td>
<td>cancer</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Alcoholic hepatitis</td>
</tr>
</tbody>
</table>
Impact of Liver Transplantation in ALF

- 1-year survival following emergency LTx for ALF is now around 80%
- Selection for LTx depends on:
  - Accurate prediction of survival without transplant
  - Consideration of the survival potential after LTx
  - Consideration of whether a patient is too sick to transplant
Criteria for the Selection of Patients with Acute Liver Failure for Transplantation

<table>
<thead>
<tr>
<th>Factor</th>
<th>King’s College Criteria</th>
<th>Clichy Criteria</th>
<th>Japanese Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age†</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Cause</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Encephalopathy†</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Bilirubin level</td>
<td>Varies</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Coagulopathy†</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

* The King’s College criteria are from O’Grady et al., the Clichy criteria from Bernuau et al., and the Japanese criteria from Mochida et al. Yes indicates that the factor is included as a criterion, and No that the factor is not included; Varies indicates that the criterion is used only in cases not associated with acetaminophen.
† This factor is common to all prognostic models.
Criteria for Emergency Liver Transplantation

<table>
<thead>
<tr>
<th>King’s College criteria</th>
<th>ALF not due to paracetamol</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ALF due to paracetamol</strong></td>
<td><strong>INR &gt;6.5 or</strong></td>
</tr>
<tr>
<td>• Arterial pH &lt;7.3 after resuscitation and</td>
<td>• 3 out of 5 following criteria:</td>
</tr>
<tr>
<td>&gt;24 hours since ingestion</td>
<td>– Aetiology: indeterminate aetiology, hepatitis, drug-induced hepatitis</td>
</tr>
<tr>
<td>• Lactate &gt;3 mmol/L or</td>
<td>– Age &lt;10 years or &gt;40 years</td>
</tr>
<tr>
<td>• The 3 following criteria:</td>
<td>– Interval jaundice encephalopathy &gt;7 days</td>
</tr>
<tr>
<td>– HE &gt;Grade 3</td>
<td>– Bilirubin &gt;300 μmol/L</td>
</tr>
<tr>
<td>– Serum creatinine &gt;300 μmol/L</td>
<td>– INR &gt;3.5</td>
</tr>
<tr>
<td>– INR &gt;6.5</td>
<td></td>
</tr>
</tbody>
</table>

Beaujon-Paul Brousse criteria (Clichy)

- Confusion or coma (HE stage 3 or 4)
- Factor V <20% of normal if age <30 years or
- Factor V <30% if age >30 years
Comparison of traditional criteria for emergency liver transplantation compared with new alternatives

<table>
<thead>
<tr>
<th>Prognostic variable</th>
<th>Aetiology</th>
<th>Predictor of poor prognostic outcome</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>KCC</td>
<td>All</td>
<td>See previous slide</td>
<td>69</td>
<td>92</td>
</tr>
<tr>
<td>Clichy criteria</td>
<td>All</td>
<td>HE + Factor V &lt;20% (age &lt;30 yr) or &lt;30% (age &gt;30 yr) Grade 3–4 HE + Factor V &lt;20%</td>
<td>-</td>
<td>86</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>76</td>
</tr>
<tr>
<td>Factor V; Factor VIII/V ratio</td>
<td>Paracetamol</td>
<td>Factor VIII/V ratio &gt;30 Factor V &lt;10%</td>
<td>91</td>
<td>91</td>
</tr>
<tr>
<td>Phosphate</td>
<td>Paracetamol</td>
<td>Phosphate &gt;1.2 mmol/L on Day 2 or 3 post overdose</td>
<td>89</td>
<td>100</td>
</tr>
<tr>
<td>APACHE II</td>
<td>All</td>
<td>APACHE II &gt;19</td>
<td>68</td>
<td>87</td>
</tr>
<tr>
<td>Gc-globulin*</td>
<td>All</td>
<td>Gc-globulin &lt;100 mg/L Paracetamol Non-paracetamol</td>
<td>73</td>
<td>68</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>30</td>
<td>100</td>
</tr>
<tr>
<td>Lactate</td>
<td>Paracetamol</td>
<td>Admission arterial lactate &gt;3.5 mmol/L or &gt;3.0 mmol/L after fluid resuscitation</td>
<td>81</td>
<td>95</td>
</tr>
<tr>
<td>α-fetoprotein</td>
<td>Paracetamol</td>
<td>AFP &lt;3.9 μg/L 24 hours post peak ALT</td>
<td>100</td>
<td>74</td>
</tr>
<tr>
<td>MELD</td>
<td>Paracetamol</td>
<td>MELD &gt; 33 at onset of HE</td>
<td>60</td>
<td>69</td>
</tr>
<tr>
<td></td>
<td>Non-paracetamol</td>
<td>MELD &gt; 32</td>
<td>76</td>
<td>67</td>
</tr>
</tbody>
</table>
Worldwide Causes of Acute Liver Failure

- **Bangladesh**: HEV 75%, HBV 13%, Unknown 6%
- **India**: HEV 44%, Unknown 31%, HBV 15%
- **Sudan**: Unknown 38%, Other causes* 27%, HBV 22%
- **Germany**: Other causes* 28%, Unknown 21%, HBV 18%
- **Japan**: HBV 42%, Unknown 34%, Other drugs 9%
- **UK**: Paracetamol 57%, Unknown 17%, Other drugs 11%
- **USA**: Paracetamol 39%, Other causes* 19%, Unknown 18%
Local Data

- 01/04/2012 to 01/05/2018
- 25 pts
- Median age 31yrs
- F=20
- 18 African, 5 Caucasian, 2 Asian

- 13 DILI
- 4 viral
- AIH 2
- Wilsons 2
- Unknown 4

- Kings College Criteria 14/15 transplanted patients.

- Overall survival rate 44% (11/25)
- 66.67% (10/15) in post-transplant patients.
- 4/5 post transplant mortalities were within 10 days post operatively.
Take home message

• Identification of the aetiology of ALF whenever possible and initiation of specific treatment

• Supportive and symptomatic management of ALF, with timely transfer to the critical care unit

• Early discussion with liver transplant specialists and safe transfer of patients to a liver transplant centre when required.
Acknowledgements

All the members of the Wits Transplant Team