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ALF a primer

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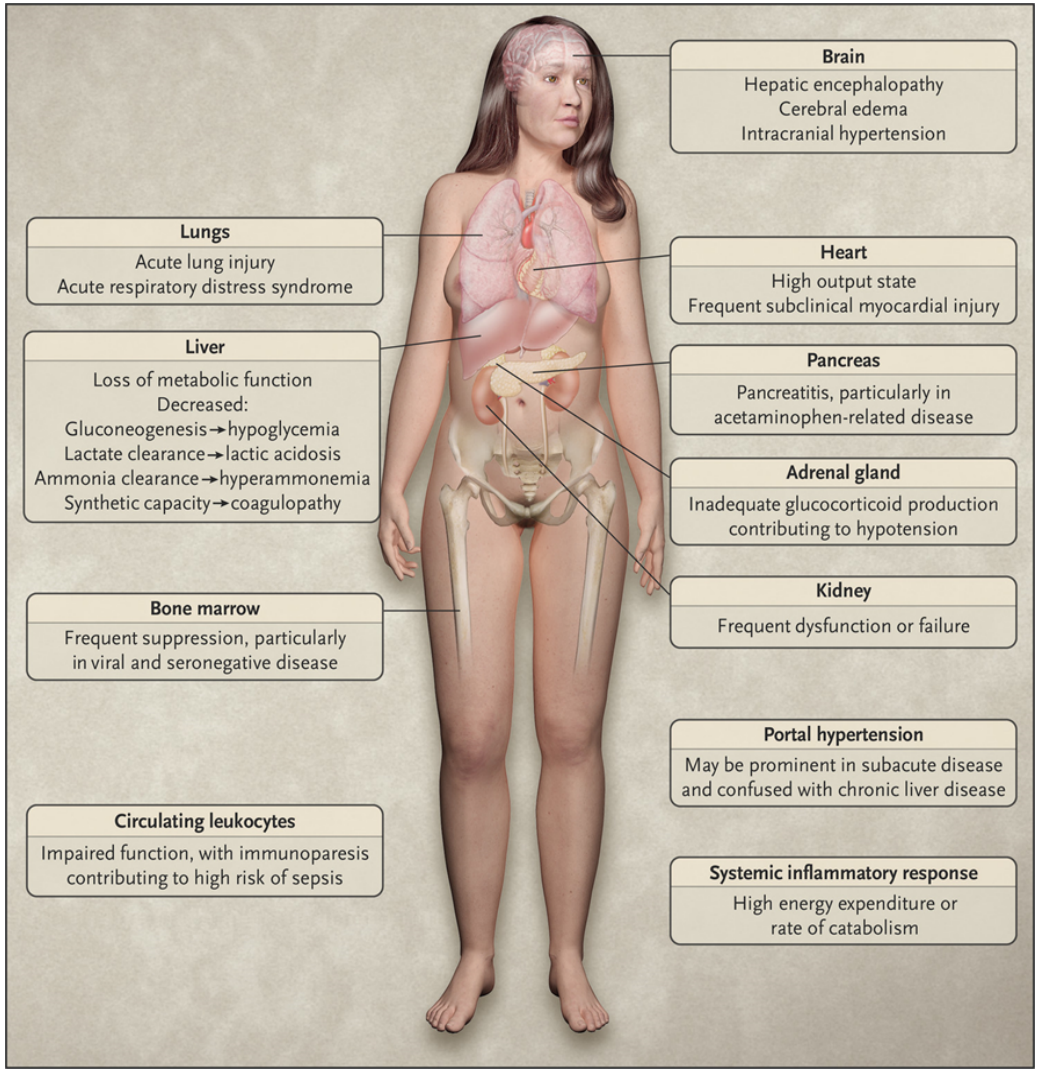
Objectives

- 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*

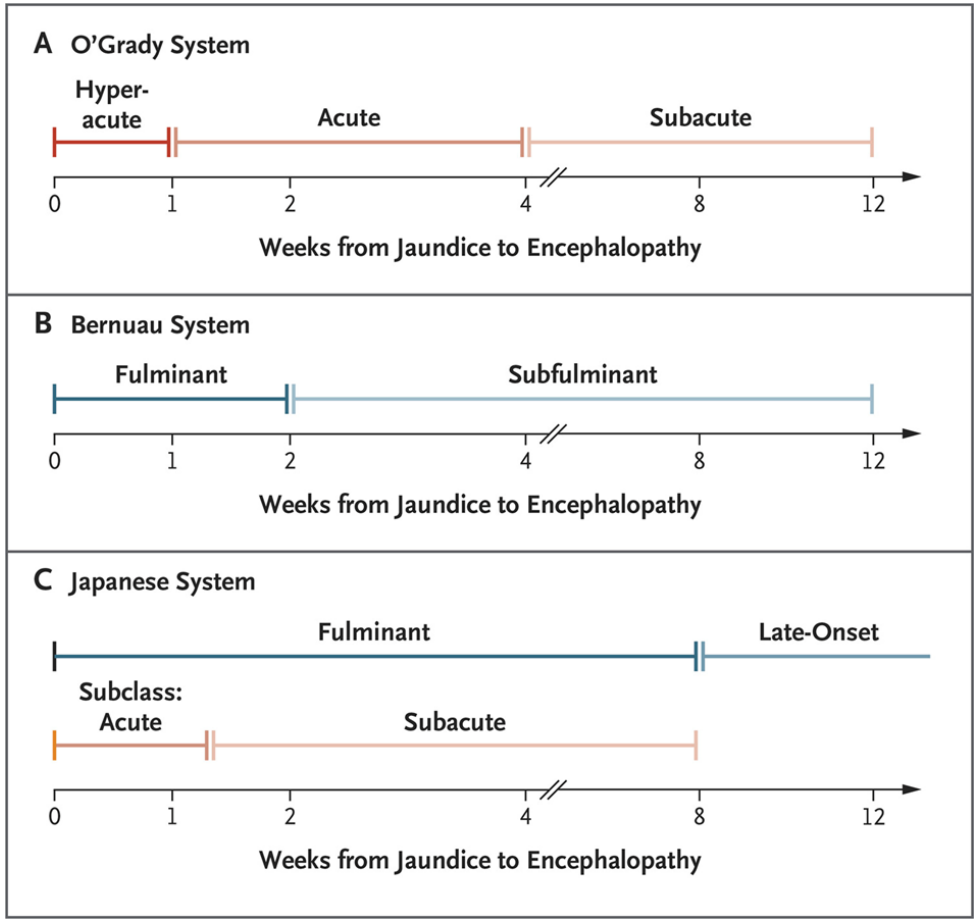
Clinical Features of Acute Liver Failure



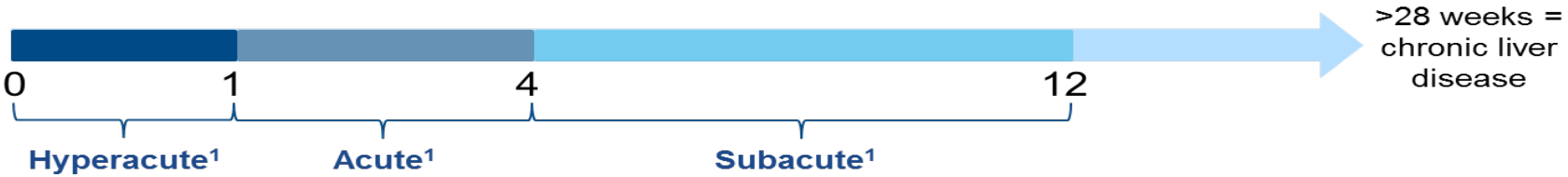
Incidence

- Rare clinical syndrome
- <10 per million developed world
- USA 2000 cases/yr
- EU?

Classification Systems for Acute Liver Failure

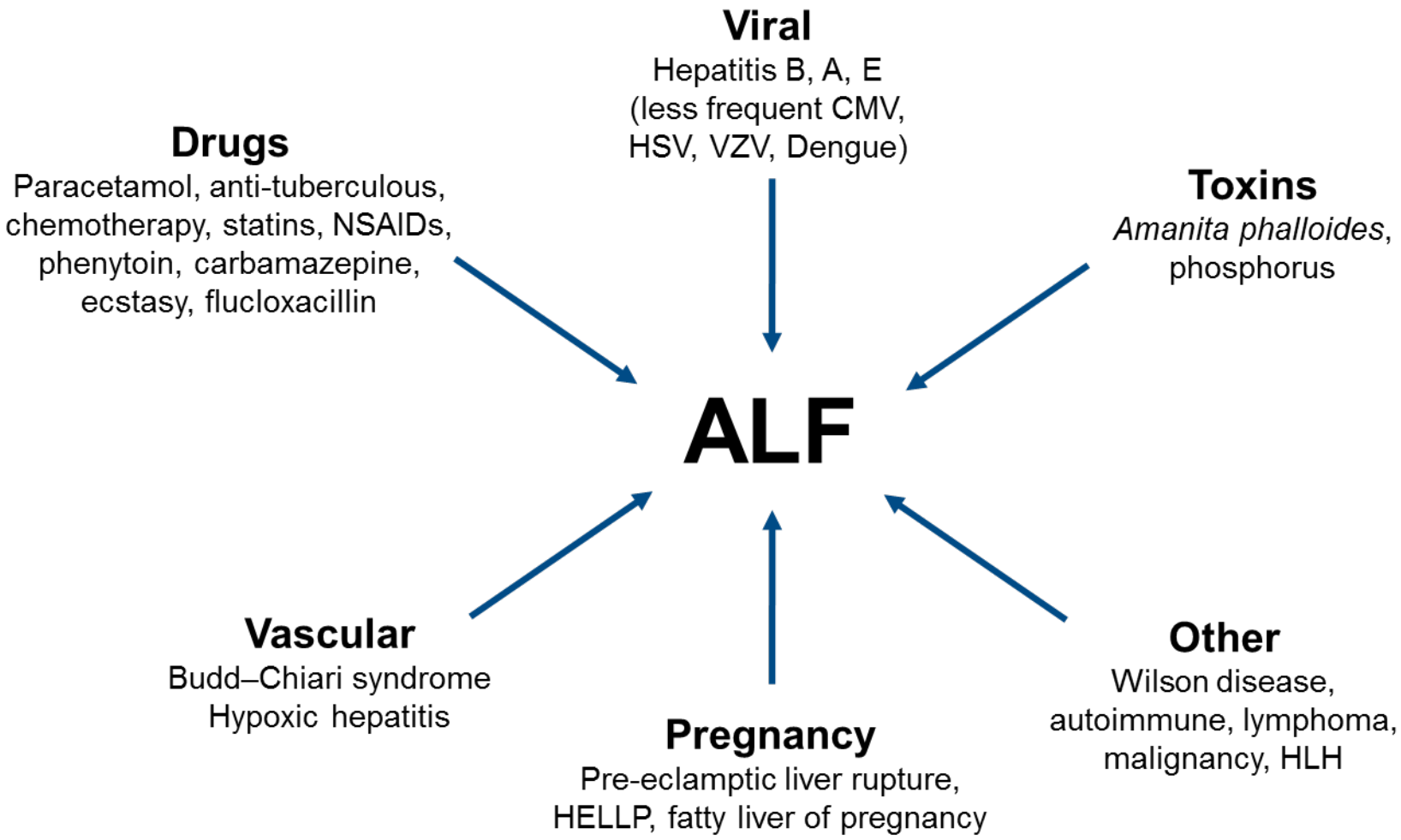


Sub-classifications of ALF



Hyperacute[1]	Acute[1]	Subacute[1]	
+++	++	+	Severity of coagulopathy[2]
+	++	+++	Severity of jaundice[2]
++	++	+/-	Degree of intracranial hypertension[2]
Good	Moderate	Poor	Chance of spontaneous recovery[2]
Paracetamol HAV, HEV	HBV	Non-paracetamol drug-induced	Typical cause[2]

Principal Etiologies of ALF



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, pyrizinamide
- 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

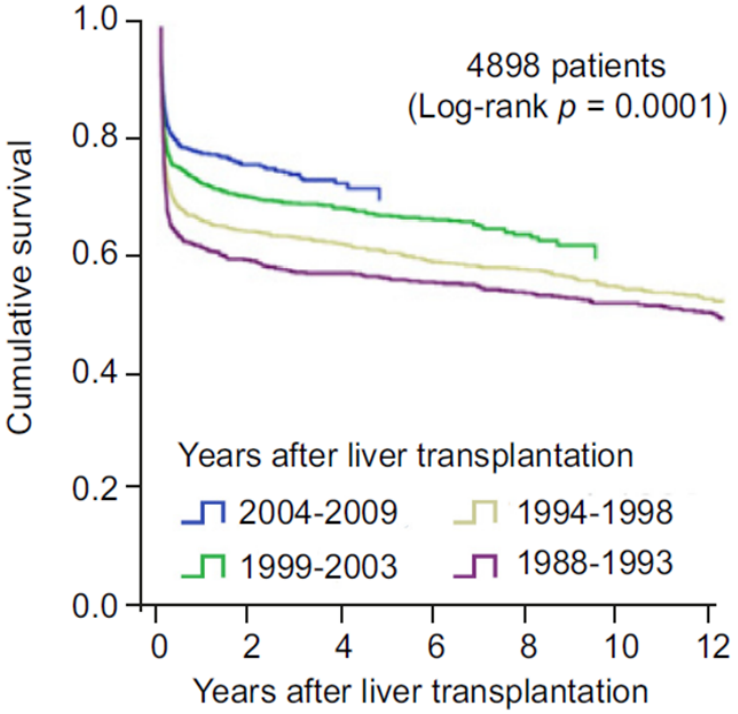
- 40% of cases in developing countries
- Misdiagnoses DILI
- Mortality 25%

Alarm causes?

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

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 2. Criteria for the Selection of Patients with Acute Liver Failure for Transplantation.*

Factor	King's College Criteria	Clichy Criteria	Japanese Criteria
Age†	Yes	Yes	Yes
Cause	Yes	No	No
Encephalopathy†	Yes	Yes	Yes
Bilirubin level	Varies	No	Yes
Coagulopathy†	Yes	Yes	Yes

* The King's College criteria are from O'Grady et al.,[8] the Clichy criteria from Bernuau et al.,[9] and the Japanese criteria from Mochida et al.[10] 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

King's College criteria

ALF due to paracetamol

- Arterial pH <7.3 after resuscitation and
  >24 hours since ingestion
- Lactate >3 mmol/L or
- The 3 following criteria:
  - HE >Grade 3
  - Serum creatinine >300 µmol/L
  - INR >6.5

ALF not due to paracetamol

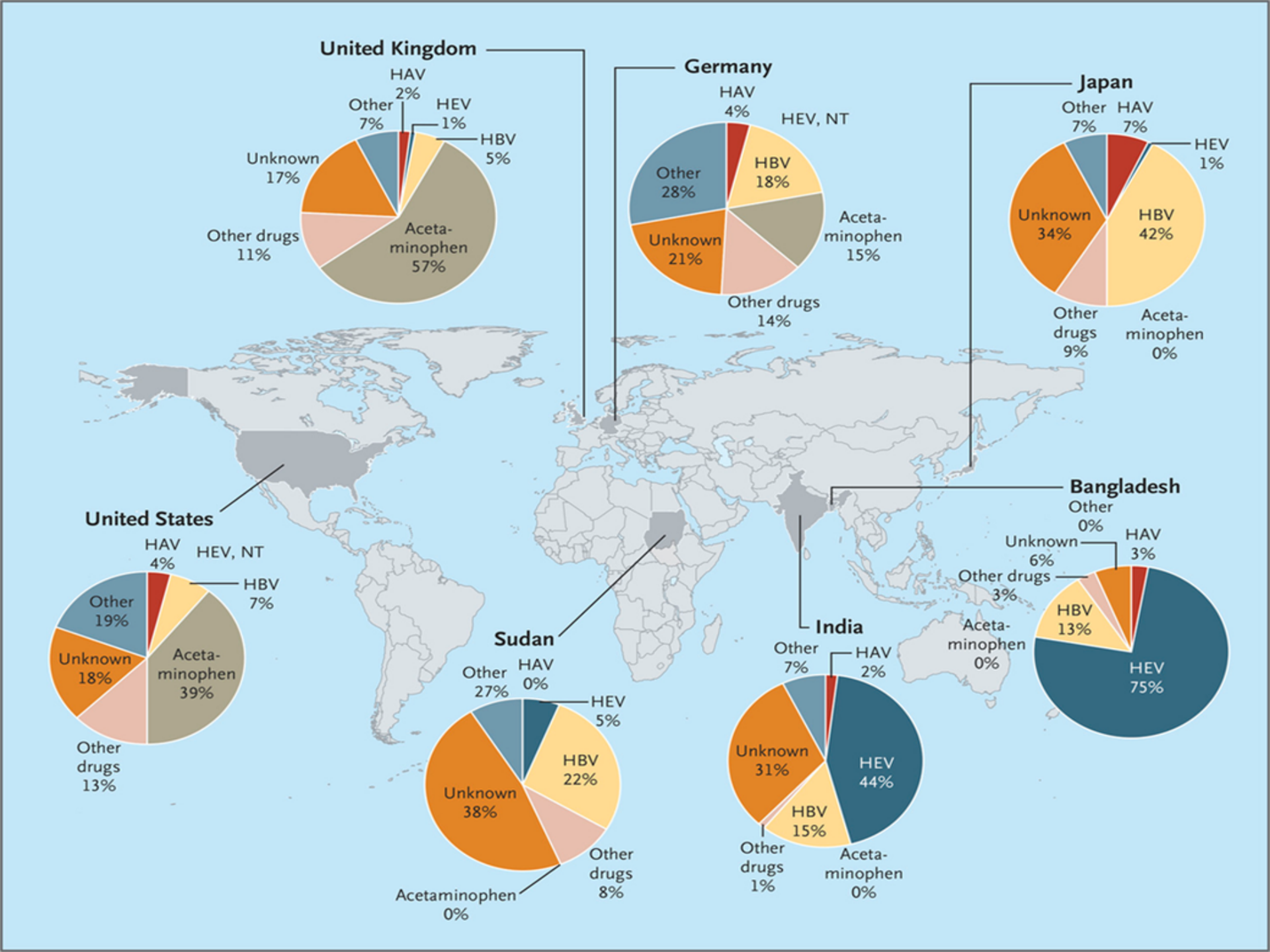
- INR >6.5 or
- 3 out of 5 following criteria:
  - Aetiology: indeterminate aetiology, hepatitis, drug-induced hepatitis
  - Age <10 years or >40 years
  - Interval jaundice encephalopathy >7 days
  - Bilirubin >300 µmol/L
  - INR >3.5

Beaujon-Paul Brousse criteria (Clichy)

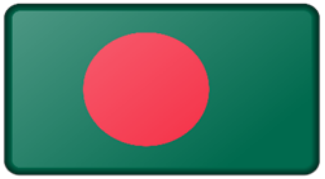
- Confusion or coma (HE stage 3 or 4)
- Factor V <20% of normal if age <30 years
  or
- Factor V <30% if age >30 years

Comparison of traditional criteria for emergency liver transplantation compared with new alternatives

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


United Kingdom
HAV 2%
Other 7%
HEV 1%
HBV 5%
Unknown 17%
Other drugs 11%
Aceta-minophen 57%
Germany
HAV 4%
HEV, NT
Other 28%
HBV 18%
Aceta-minophen 15%
Unknown 21%
Other drugs 14%
Japan
Other 7%
HAV 7%
HEV 1%
Unknown 34%
HBV 42%
Other drugs 9%
Aceta-minophen 0%
United States
HAV 4%
HEV, NT
HBV 7%
Other 19%
Unknown 18%
Aceta-minophen 39%
Other drugs 13%
Sudan
Other 27%
HAV 0%
HEV 5%
HBV 22%
Unknown 38%
Other drugs 8%
Acetaminophen 0%
India
Other 7%
HAV 2%
Unknown 31%
HEV 44%
HBV 15%
Other drugs 1%
Aceta-minophen 0%
Bangladesh
Other 0%
Unknown 6%
HAV 3%
Other drugs 3%
HBV 13%
Aceta-minophen 0%
HEV 75%

Worldwide Causes of Acute Liver Failure



Bangladesh
HEV 75%
HBV 13%
Unknown 6%

Germany
Other causes* 28%
Unknown 21%
HBV 18%

India
HEV 44%
Unknown 31%
HBV 15%

Japan
HBV 42%
Unknown 34%
Other drugs 9%

Sudan
Unknown 38%
Other causes* 27%
HBV 22%

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

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