Acute Liver Failure

Bilal Bobat
Liver Unit WDGMC

Introduction

Definition

- Acute Liver failure is the presence of liver based coagulopathy and altered mental state

- Differentiated from:
    - Acute Decompensation
    - Acute on Chronic Liver Failure

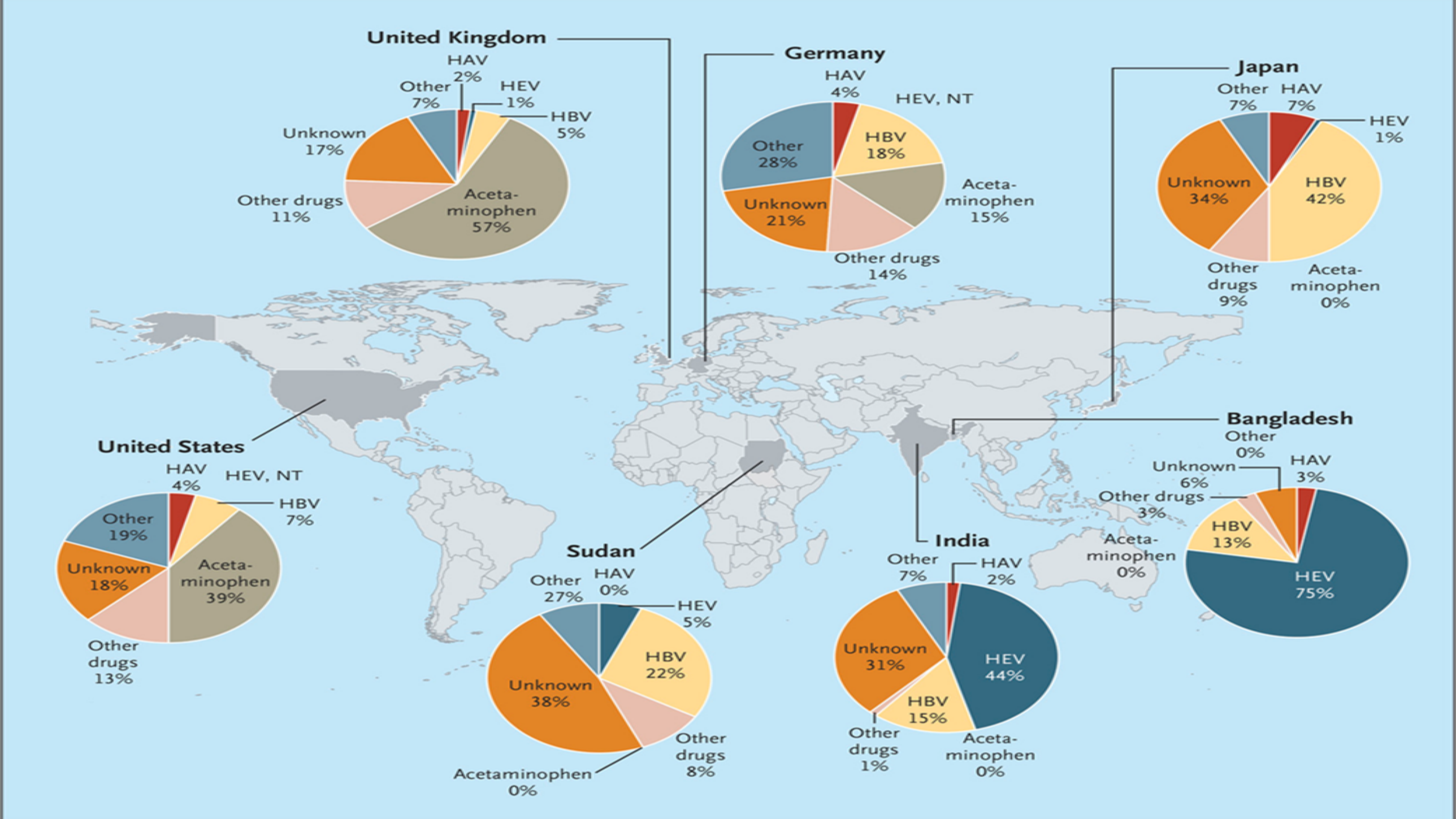
Causes of Acute Liver Failure

Who is eligible for priority transplant consideration?

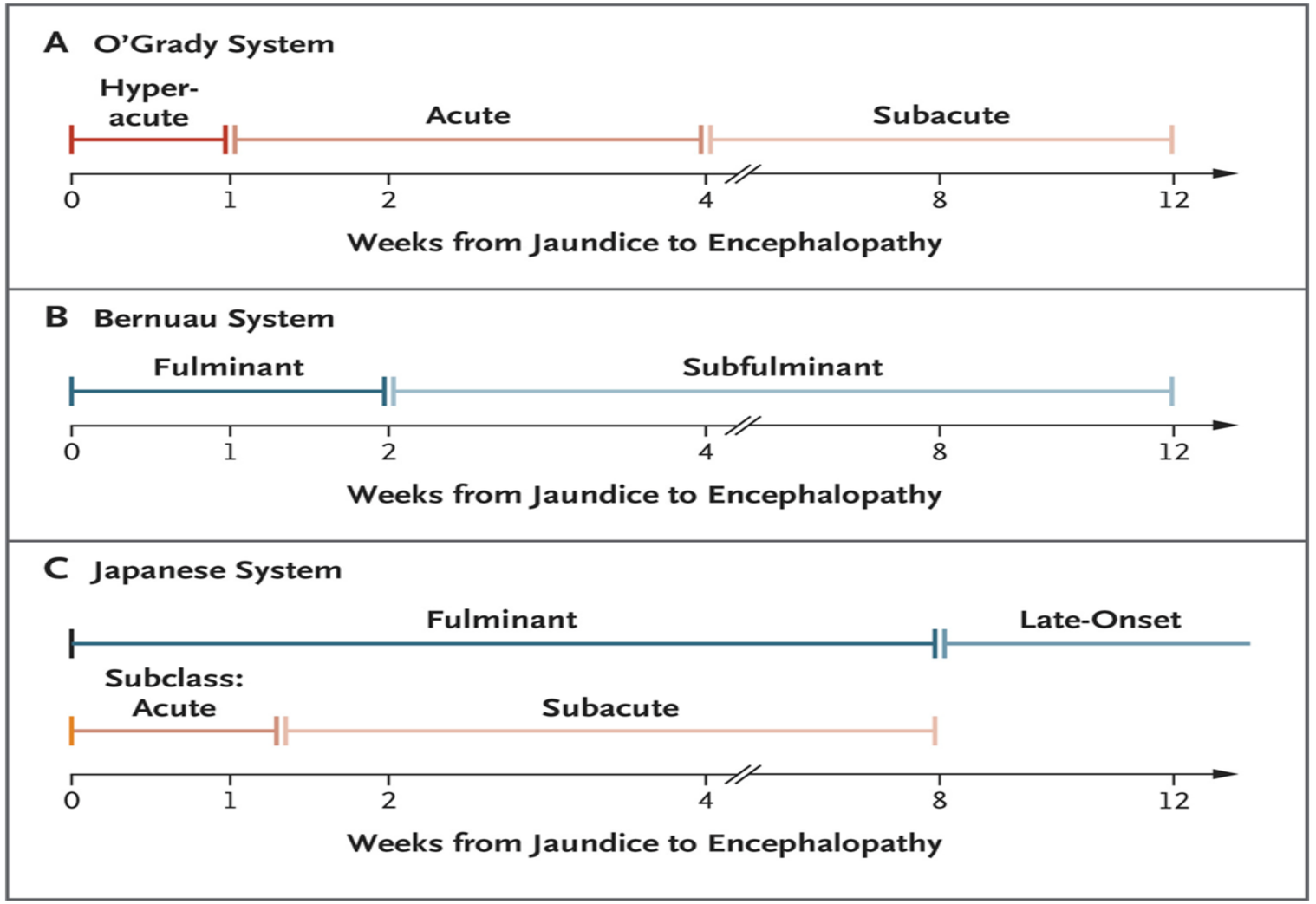
Disease group	Hepatic/primary ALF	Extrahepatic/secondary liver failure and ACLF
Acute liver failure	Drug related Acute viral hepatitis Toxin-induced ALF Budd–Chiari syndrome Autoimmune Pregnancy related	**Hypoxic hepatitis (aka ischaemic)** Systemic diseases: • Haemophagocytic syndromes • Metabolic disease • **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

Eligible

Not Eligible


United Kingdom
HAV 2%
HEV 1%
HBV 5%
Other 7%
Unknown 17%
Other drugs 11%
Aceta-minophen 57%
Germany
HAV 4%
HEV, NT
HBV 18%
Other 28%
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%

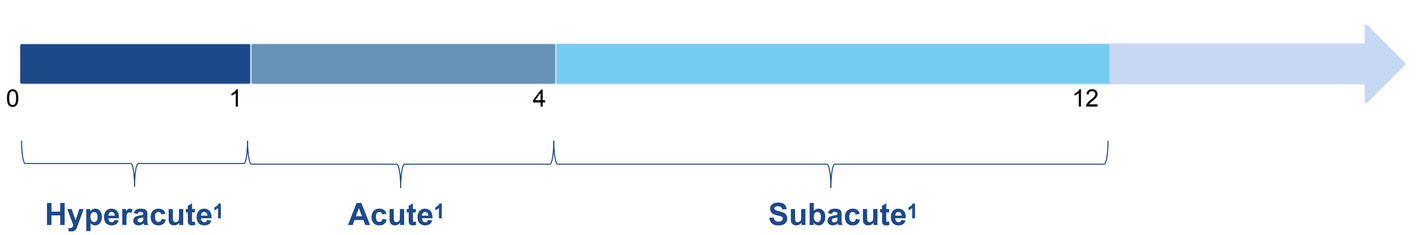
Classification Systems for Acute Liver Failure



Bernal W, N Engl J Med 2013; 369:2525-2534

Classification - Why is this Important?

Weeks from development of jaundice to development of HE[1]



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

+++ High severity; ++ Medium severity; + Low severity; +/- Present or absent

1. O'Grady JG, et al. Lancet 1993;342:273–5; 2. Bernal W, et al. Lancet 2010;376:190–201;

Aetiology as a prognosticator

	Paracetamol (n=1195)	Ischaemia (n=181)	Drug-induced liver injury (n=283)	Autoimmunity (n=173)	Hepatitis B virus (n=188)	Hepatitis A virus (n=39)	Pregnancy (n=27)	All other causes (n=528)
Age (median, years)	37	53	47	46	45	50	31	40
Women (%)	75%	58%	67%	81%	45%	44%	100%	64%
Jaundice coma (median, days)	1	2	12	16	8	4	7	7
Hepatic encephalopathy grade 3 or higher (%)	54%	56%	36%	27%	51%	54%	54%	44%
Alanine aminotransferase (median, IU/L)	3780	2311	654	404	1410	2229	43	758
Bilirubin (median, mg/dL)	4·3	3·8	19·6	22·8	19·2	12·0	9·0	16·2
Transplanted* (%)	9%	2%	39%	57%	40%	33%	4%	36%
Transplant-free survival* (%)	65%	57%	★24%	★14%	★19%	51%	78%	★22%
Overall survival* (%)	72%	58%	58%	63%	53%	77%	82%	55%

Data were collected between Jan 1, 1998, and March 31, 2019. Total number of patients=2614. *Represents outcomes 21 days after admission to the Acute Liver Failure Study Group Registry.

Table 1: **Comparison of demographics, admission laboratory results, and outcome between different causes of acute liver failure in the Acute Liver Failure Study Group Registry**

Principles of Management

- Specific and Non Specific
- Referral to a Transplant centre
- Early Continuous Renal Replacement Therapy
- Neurological Support
- N-Acetylcystiene
- Hold the Lactulose

Differential diagnosis based on clinical features

Aetiology	Clinical features	Specific Management
Paracetamol	Very high levels of aminotransferases and low level of bilirubin. Rapidly progressive disease, acidosis and renal impairment. Low phosphate may be seen as a good prognostic marker but replacement is required	N- Acetylcystiene use for Paracetamol and Non Paracetamol induced DILI
Non-paracetamol	Subacute clinical course can mimic cirrhosis, clinically and radiographically	
Acute Budd–Chiari syndrome	Abdominal pain, ascites and hepatomegaly; loss of hepatic venous signal and reverse flow in portal vein on ultrasound	Decompressive TIPS and Anticoagulation
Wilson disease	Young patient with Coombs (DAT)-negative haemolytic anaemia with a high bilirubin to ALP ratio; Kayser–Fleischer ring; low serum uric acid level; markedly increased urinary copper	Plasmapheresis will buy time to liver transplant
Mushroom poisoning	Severe gastrointestinal symptoms after ingestion; development of early AKI	Penicillin G
Autoimmune	Usually subacute presentation – may have positive autoantibodies, elevated globulin and characteristic lymphocyte pattern when compared to viral and seronegative aetiologies	Be cautious with steroids in Fulminant AIH
Acute ischaemic injury	Marked elevation of aminotransferases, increased lactic dehydrogenase and creatinine, which normalize soon after stabilization of haemodynamic instability. Patients with severe congestive heart disease or respiratory disease	Restore Haemodynamic status

GASTROENTEROLOGY 2009;137:856–864
EASL CPG ALF. J Hepatol 2017;66:1047–81

General support outside ICU: anamnesis

Questions for patients and relatives at admission

Search for an aetiology
- Has the patient used any medication, in particular paracetamol, over the last 6 months?
- Has the patient any history of substance abuse?
- Has the patient ever experienced depression or made a suicide attempt?
- Has the patient complained of gastrointestinal affects after eating mushrooms?

Identify conditions that could cause ALF
- Is the patient pregnant?
- Has the patient travelled in HBV or HEV endemic areas?
- Has the patient received immunosuppressive therapy or chemotherapy?
- Does the patient have a history of autoimmune disease?

Decide whether emergency LTx is feasible
- Does the patient have a history of a chronic liver disease?
- Is the patient currently using and dependent on alcohol or other drugs?*
- Do they have a recent history of cancer?†
- Do they have severe congestive heart disease or a respiratory co-morbidity?

What was the interval between onset of jaundice and first signs of HE?

*Based on the individual case; †Specialist input required

EASL CPG ALF. J Hepatol 2017;66:1047–81

General support outside ICU

Diagnosis, monitoring and care at admission

Diagnostic tests

- Cultures (respiratory, blood, urine)
- Chest X-ray/ECG/liver echography: axial imaging of the abdomen and chest may also be required
- ECG

Routine monitoring

- Oxygen saturation, blood pressure, heart rate, respiratory rate, hourly urine output
- Clinical neurological status

Standard care

- Glucose infusions (10–20%)*
- Stress ulcer prophylaxis
- Restrict clotting factors unless active bleeding
- NAC in early stage, even in non-paracetamol cases

Preventative measures

- Avoid sedatives
- Avoid hepatotoxic and nephrotoxic drugs

In case of HE

- Transfer to an appropriate level of care (ideally critical care) at the first symptoms of mental alterations
- Quiet surrounding, head of bed >30°C, head in neutral position and intubate, ventilate, and sedate if progression to >3 coma
- Low threshold for empirical start of antibiotics if haemodynamic deterioration and/or increasing encephalopathy with inflammatory phenotype
- In case of evolving HE, intubation and sedation prior to the transfer
- Ensure volume replete and normalize biochemical variables (Na, Mg, PO_4, K)

*Glycaemic target ± 140 mg/dl, Na 135–145 mmol/l;
EASL CPG ALF. J Hepatol 2017;66:1047–81

General support outside ICU

Laboratory analyses at admission

Assess disease severity

- PT, INR or factor V and full coagulation screen
- Liver blood tests*
- Renal function
  - Urine output: hourly
  - Urea†
  - Creatinine may be difficult to assay in the context of elevated bilirubin
- Arterial blood gas and lactate
- Arterial ammonia

Check aetiology

- Toxicology screen in urine and paracetamol serum level
- Viral serological screen
  - HBsAg, anti-HBc IgM (HBV DNA), HDV if positive for HBV
  - anti HAV IgM
  - anti-HEV IgM
  - anti-HSV IgM, anti-VZV IgM, CMV, HSV, EBV, parvovirus and VZV PCR
- Autoimmune markers‡

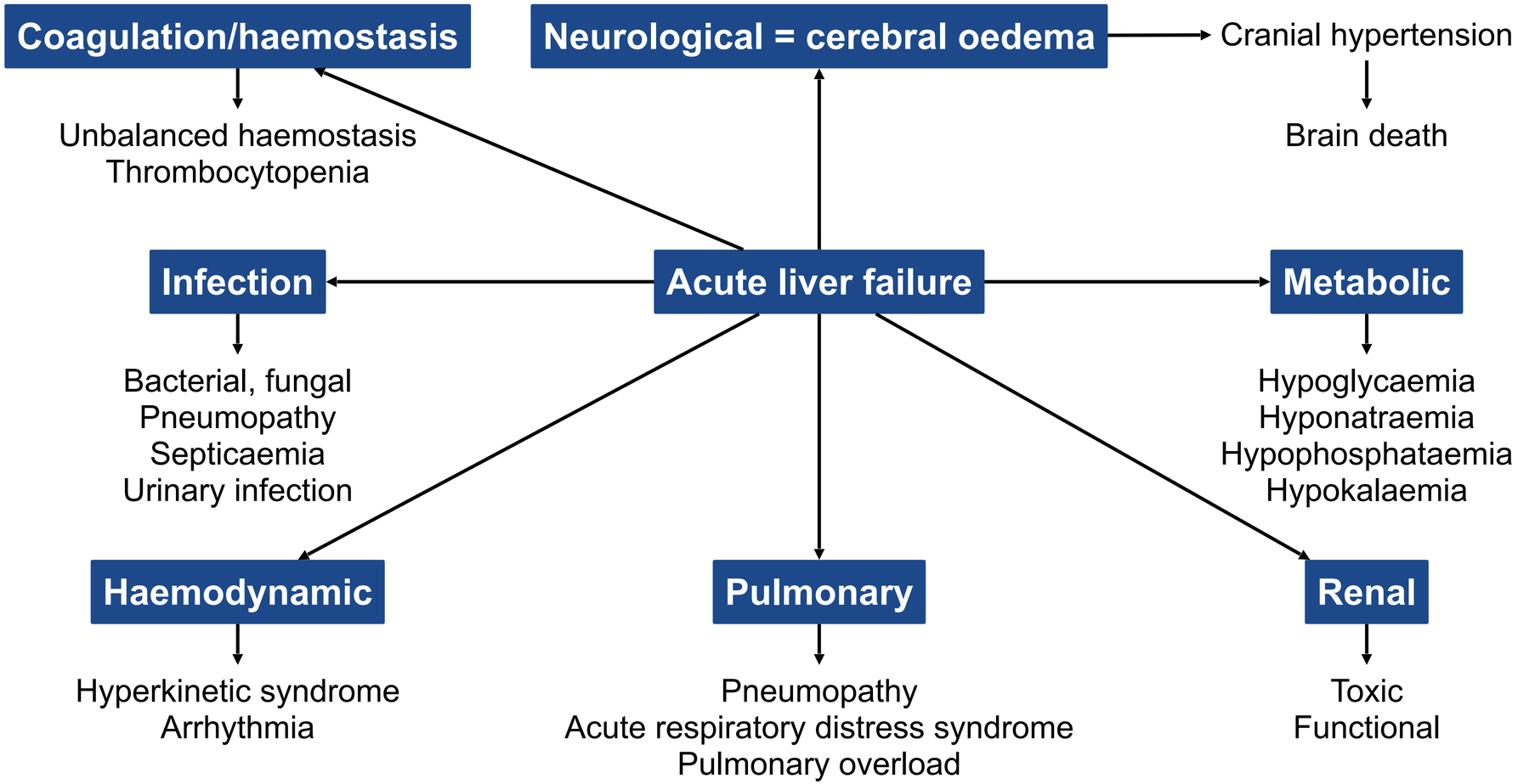
Test for complications

- Lipase or amylase

*Including LDH, conjugated and unconjugated bilirubin and creatinine kinase;
†Low urea is a marker of severe liver dysfunction;
‡ANAs, ASMA, anti-soluble liver antigen, globulin profile, ANCAs, HLA typing
EASL CPG ALF. J Hepatol 2017;66:1047–81

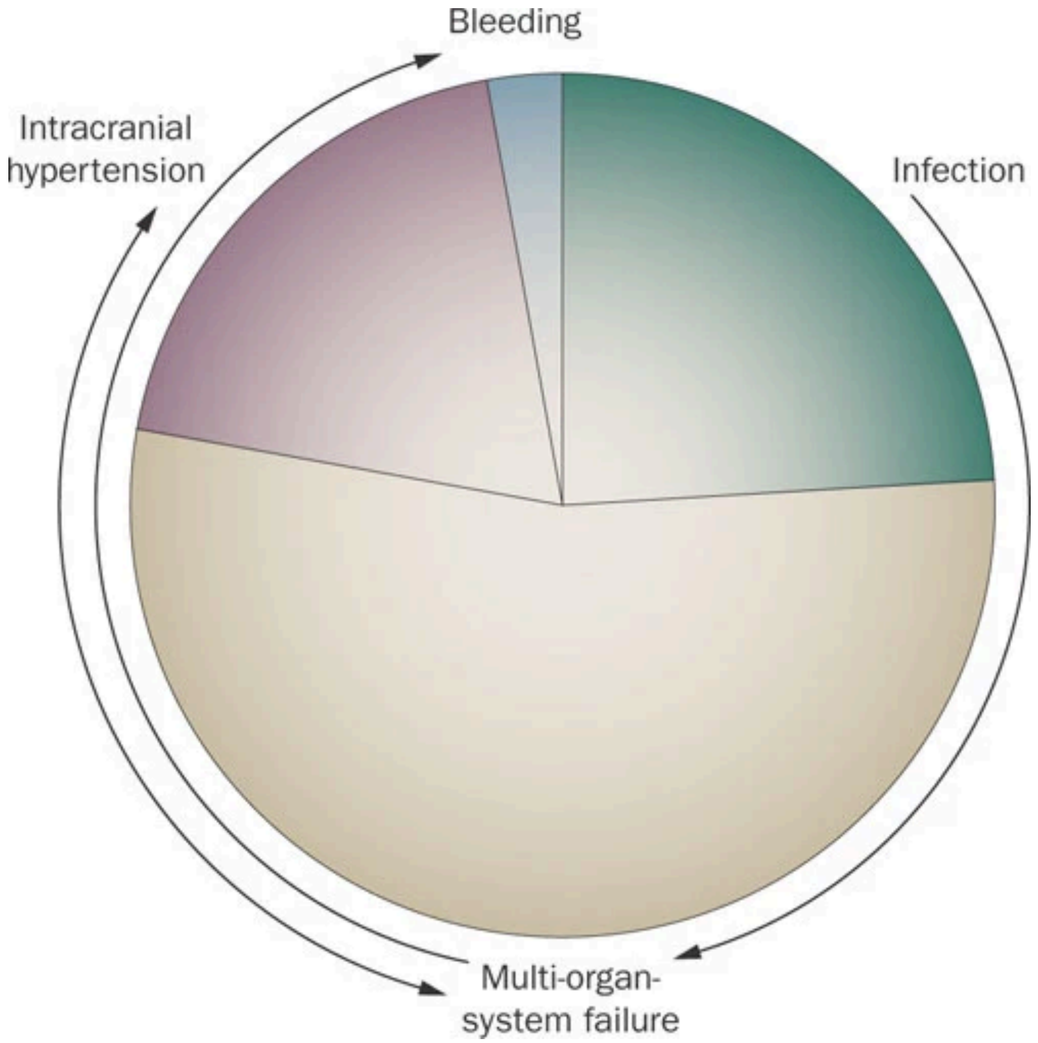
Organ-specific management

Main organ-specific complications in ALF



EASL CPG ALF. J Hepatol 2017;66:1047–81

Proximate causes of death in patients with ALF and how these causes are inter-related.



*Nature Reviews Gastroenterology & Hepatology volume **6**, (2009)*

Management of Hepatic Encephalopathy

- Regular clinical and neurological examination to monitor progression in a quiet environment
- On progression to Grade 3 HE:*
  - Intubate and provide mechanical ventilation to protect the airway, prevent aspiration and provide safer respiratory care
- On progression to Grade 4 HE:†
  - Minimize risk of pulmonary barotrauma
  - Target $PaCO_2$ between 4.5–5.5 kPa (34–42 mmHg) and use propofol as a sedative agent‡
  - Add a short-acting opiate for adequate analgesia
- In case of concern of seizure activity:
- Monitor EEG
- Administer antiepileptic drugs with low risk of hepatotoxicity§

The brain in ALF

Recommendations

Invasive intracranial pressure monitoring should be considered in patients who have progressed to grade 3 or 4 coma, are intubated and ventilated, and deemed at high risk of ICH, based on the presence of >1 of the following variables:

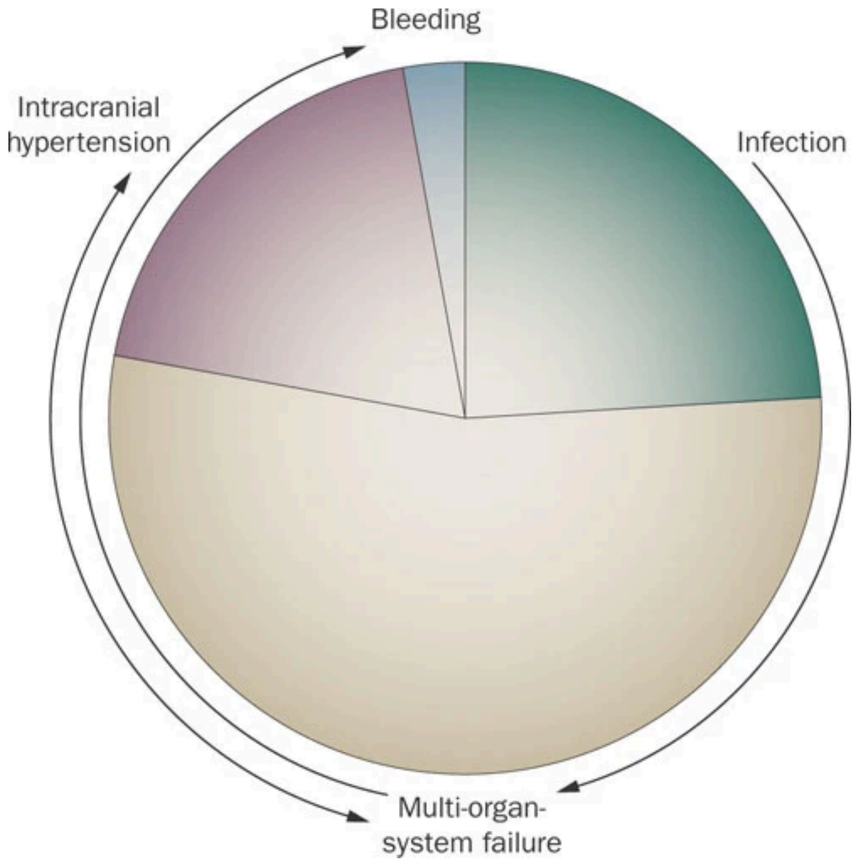
- Young patients with hyperacute or acute presentations
- Ammonia level over 150–200 μmol/L that does not drop with initial treatment interventions (RRT and fluids)
- Renal impairment
- Vasopressor support (>0.1 μg/kg/min)

Mannitol or hypertonic saline should be administered for surges of ICP with consideration for short-term hyperventilation (monitor reverse jugular venous saturation to prevent excessive hyperventilation and risk of cerebral hypoxia). Mild hypothermia and indomethacin may be considered in uncontrolled ICH, the latter only in the context of hyperaemic cerebral blood flow

EASL CPG ALF. J Hepatol 2017;66:1047–81

Sepsis

- Kupffer cell dysfunction and bacterial translocation
- Urinary and Respiratory sources
- Broad spectrum antibiotics and an anti fungal
- Regular surveillance of cultures



Non Specific Management

- Cardiovascular:
  - Assess Volume Status
  - Pressors: Maintain a MAP of >65mmHg
- Renal:
  - CRRT
  - Indications: AKI

    Ammonia control

When to List?

Multiple Criteria

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

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

A	Age<10 or >40
B	Bilirubin >300mmol/l
C	Coagulation - INR >3.5
D	Duration: Jaundice to HE > 7 days
E	Etiology

Local Data

- 01/04/2012 to 01/05/2018

Wits University Donald Gordon Medical Centre
Patient-centred. Independent. Academic.

MEDICLINIC

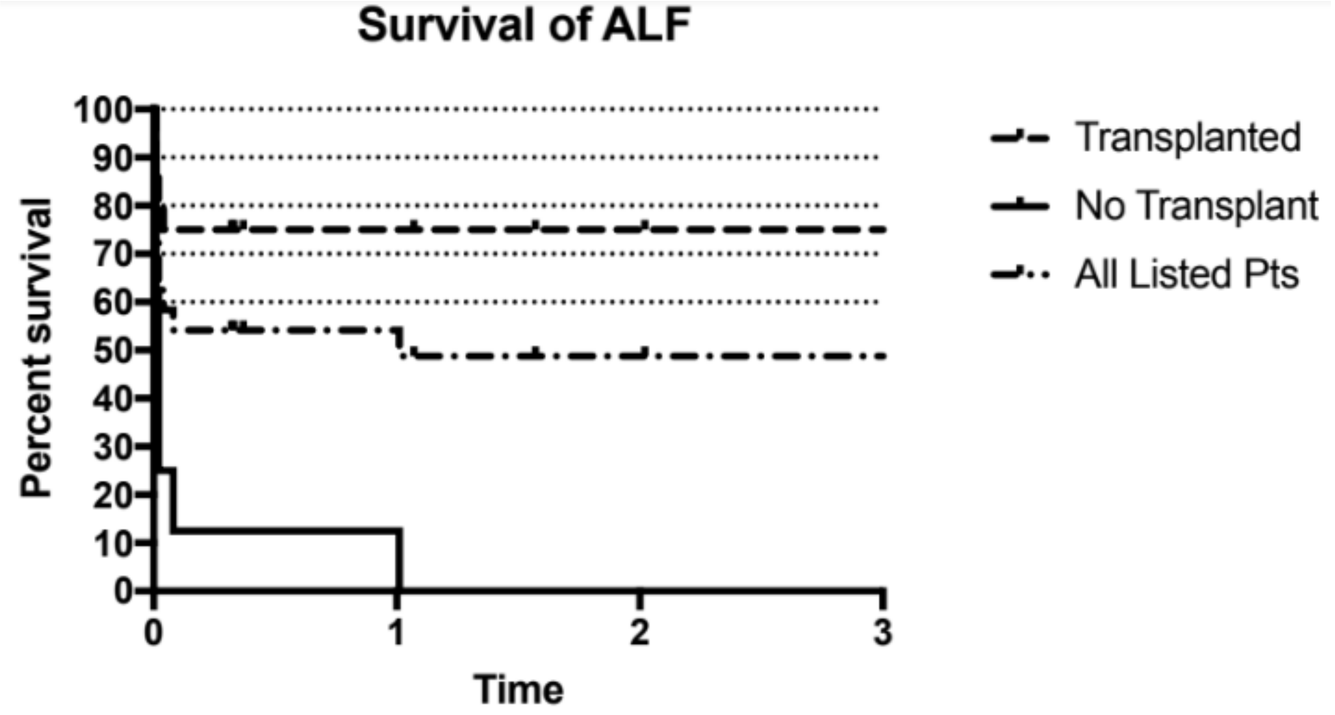
- 25 pts
- Median age 31yrs
- F=20
- 18 African , 5 Caucasian, 2 Asian

- 13 DILI
- 4 viral (hep A and 3 Hep b)
- 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.

Outcomes



Survival curve of patients with ALF seen at Donald Gordon Medical Centre Liver Clinic between 01/04/2012 and 01/05/2018

New Therapies

Bioartificial support systems

- Data has been poor
- Still only used in the setting of randomised trials
- High Volume plasma exchange has shown benefit
- Moderate Hypothermia
- Living Related Adult-Adult Donation

Thank you

Bilal Bobat
Liver Unit WDGMC

Wits University
Donald Gordon
Medical Centre
Patient-centred. Independent. Academic.

MEDICLINIC

WITS
TRANSPLANT
Progressive medicine, exceptional care.