ACUTE LIVER FAILURE

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DEFINITION

EASL Clinical Practical Guidelines on the management of acute (fulminant) liver failure. J Hepatol. 2017 May;66(5):1047-1081. doi: 10.1016/j.jhep.2016.12.003. PMID: 28417882.

History Behind the Definition

- Initially defined by Trey and Davidson (1970)
  - 'potentially reversible condition, the consequence of severe liver injury, with an onset of hepatic encephalopathy (HE) within 8 weeks of the appearance of first symptoms and in the absence of pre-existing liver disease'

- 1993, redefined to take account the aetiology, frequency of complications and prognosis
  - Considering jaundice as the first symptom-hyperacute liver failure describes patients developing HE within 7 days of noting jaundice
  - ALF-HE develops between 8 and 28 days of noting jaundice
  - Sub ALF-HE within 5 to 12 weeks of jaundice
  - After 28 weeks-chronic liver disease

DEFINITION

- International Association for the Study of the Liver (IASL)
  - 1999-hyperacute ALF less than 10 days, fulminant as 10 to 30 days and subacute as 5 to 24 weeks
- Hyperacute ALF-severe coagulopathy, markedly increased transaminases and initially only moderate, if any, increase in bilirubin; greater chance of spontaneous recovery despite having extrahepatic organ failure
- Subacute ALF-milder increase in serum transaminases, deep jaundice and mild to moderate coagulopathy; Often have splenomegaly, ascites and shrinking liver volume-but once HE develops, there is a low chance of spontaneous survival

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DEFINITION

- Clinical course of Acute Liver Failure (ALF) is initiated by severe Acute Liver Injury (ALI)
  - **2-3 times elevation** of transaminases
  - Associated with impaired liver function-**jaundice, encephalopathy and coagulopathy (INR >1.5)**
  - In a patient **without** chronic liver disease
- Absence of pre-existing disease
  - Specific exceptions-acute de novo presentation of autoimmune hepatitis and Budd-Chiari syndrome; Wilson's disease also considered an exception

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Type of ALF	Time frame	Examples	Risk of cerebral edema	Risk of death
Hyperacute	<7 d	Acetaminophen hepatitis A & E ischemic injury	High	Low
Acute	7–21 d	Hepatitis B	Intermediate	Intermediate
Subacute	>21 d and <26 wk	Nonacetaminophen DILI	Low	High

ALF, acute liver failure; DILI, drug-induced liver injury.

ALF PRESENTATIONS

Table 2. The clinical course of different ALF aetiologies.

Precipitant	Examples	Presentation
Viral	Hepatitis A, E, B (less frequent CMV, HSV, VZV, Dengue)	Acute/fulminant
Drugs/toxins	Paracetamol (acetaminophen), phosphorous, *Amanita phalloides*	Acute/fulminant and subacute/subfulminant
	Anti-tuberculous, chemotherapy, statins, NSAI, phenytoin, carbamazepine, ecstasy, flucloxacillin	Acute/fulminant
Vascular	Budd Chiari	Acute/fulminant and subacute/subfulminant
	Hypoxic hepatitis	Acute/fulminant
Pregnancy	Pre-eclamptic liver rupture, HELLP, fatty liver of pregnancy	Acute/fulminant
Other	Wilson disease, autoimmune, lymphoma, malignancy, HLH	Acute/fulminant and subacute/subfulminant

CMV, cytomegalovirus; HSV, Herpes simplex; NSAI, non-steroidal anti-inflammatory; HELLP, haemolysis, elevated liver enzymes, low platelets; HLH, haemophagocytic lymphohistiocytosis.

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EPIDEMIOLOGY

EPIDEMIOLOGY

Table 3. Epidemiological studies of ALF in different countries.

Country	UK*	US	Canada	Scandinavia	France	Spain	Chile†	Australasia	Sudan	India	Germany
Reference	Bernal *et al.* [16]	Ostapowicz *et al.* [17]	Tessier *et al.* [18]	Brandsaeter *et al.* [19]	Ichai *et al.* [20]	Escorsell *et al.* [21]	Uribe *et al.* [22]	Gow *et al.* [23]	Mudawi *et al.* [24]	Khuroo *et al.* [25]	Hadem *et al.* [26]
No. of cases	310	308	81	315	363	267	27	80	37	180	109
Years	1994–2004	1998–2001	1991–1999	1990–2001	1986–2006	1992–2000	1995–2003	1988–2001	2003–2004	1989–1996	2008–2009
Paracetamol (%)	43	39	15	17	7	2	0	36	0	0	9
Non-paracetamol drug reactions (%)	8	13	12	10	21	14	7	6	8	0.6	32
Hepatotropic viruses (%)	7	12	30	12	33	37	37	14	27	68 (44 Hep E)	21
Indeterminate (%)	30	17	27	43	18	32	44	34	38	31	24
Other causes (%)	13	19	16	17	21	15	11	10	27	0	14

* Patients listed for orthotopic liver transplantation only.
† Paediatric patients only.

Europe

- Burden is unclear with poor data collection
- However 8% of all transplants-performed due to ALF as the primary indication
- Of the 8%
  - 19% was viral infection, 18% drug induced liver injury, 4% toxic and 3 % postoperative/traumatic
  - 56% unknown or other cause

- Thought viral indication has reduced, Asia and Africa still has it as the commonest cause
- DILI is the most common cause now. Paracetamol predominantly

Africa

- Unfortunately not much data available
- Viral induced is seen to be the most common cause

Germani G, Theocharidou E, Adam R, Karam V, Wendon J, O'Grady J, et al. Liver transplantation for acute liver failure in Europe: outcomes over 20 years from the ELTR database. J Hepatol 2012;57:288–296.

Bernal W, Auzinger G, Dhawan A, Wendon J. Acute liver failure. Lancet 2010;376:190–201.

EPIDEMIOLOGY

Table B1: Clinical and demographic characteristics for adult liver transplant recipients

	2016	2017	2018	2019	202
Number of transplants	*36*	*46*	*44*	*47*	*34*
Age (%)					
18–34 years	22	22	16	28	21
35–49 years	28	19	21	19	35
50–64 years	36	48	52	42	32
65 years or older	14	11	11	11	12
Sex (%)					
Female	36	37	43	55	41
Self-reported race (%)					
Black	25	29	14	23	18
White	69	61	73	55	67
Indian	6	4	9	20	6
Mixed	0	4	4	2	9
Unknown	0	2	0	0	0
Primary Disease (%)					
Acute liver failure	8	9	16	13	9
ASH/NASH	28	26	25	21	15
Cholestatic	25	31	25	36	50
Hepatitis B	3	4	5	0	3
Hepatitis C	3	4	0	5	3
Metabolic	5	13	4	4	0
Malignancy	25	2	9	6	11
Other	3	11	16	15	9
Transplant history (%)					
First	94	93	98	93	97
Re-transplant	6	7	2	9	3
Blood type (%)					
A	56	39	32	26	23
B	8	15	25	15	21
AB	6	4	7	4	9
O	30	41	36	55	47
Health Care Sector (%)					
Funded	84	89	89	94	91
State	14	11	11	6	9
Wait time (%)					
< 31 days	33	35	45	45	35
31–60 days	11	13	21	21	12
61–90 days	11	15	11	6	3
3–<6 months	25	22	9	13	29
6–<12 months	14	9	7	4	18
1–<2 years	6	6	7	11	3

ASSESSMENT

1. Rule out Cirrhosis and/or Alcohol Induced Liver Injury

- Clinical picture and radiology of subacute ALF can mimic cirrhosis
  - Loss of hepatic mass and regenerative nodules induce irregular contours of liver; along with ascites and mild splenomegaly-can lead one to think cirrhosis
  - Medical history is obviously crucial in these cases
- Indications for liver biopsy are limited
  - If done-then trans-jugular with experienced radiologist and liver histopathologist
- Early referral to liver centres would be the best to do

Disease group	Hepatic/primary ALF (Emergency transplantation may be a treatment option)	Extrahepatic/secondary liver failure and AoCLF (Emergency transplantation is not a treatment option)
Acute liver failure	Drug related Acute viral hepatitis Toxin-induced ALF Budd-Chiari syndrome Autoimmune Pregnancy related	Ischaemic hepatitis (HH) Systemic diseases: • Haemophagocytic syndromes • Metabolic disease • Infiltrative disease • Lymphoma • Infections (e.g., malaria)
Chronic liver disease 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

2. SEARCH FOR AN AETIOLOGY

Aetiology	Clinical features
Malignant infiltration	History of cancer, massive hepatomegaly; elevated alkaline phosphatase or other tumour markers.
Acute ischemic injury	Marked elevation of aminotransferases, increased lactic dehydrogenase and creatinine, which normalise soon after stabilisation of haemodynamic instability. Patients with severe congestive heart disease or respiratory disease.
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.
Non-paracetamol drug toxicity	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.
Wilson disease	Young patient with Coombs (DAT) negative haemolytic anaemia with a high bilirubin to alkaline phosphatase ratio; Kayser-Fleischer ring; low serum uric acid level; markedly increased urinary copper.
Mushroom poisoning	Severe gastro-intestinal symptoms after ingestion; development of early AKI.
Autoimmune	Usually subacute presentation – may have positive autoantibodies, elevated globulin and characteristic lymphocyte pattern when compared to viral and seronegative aetiologies.

3. Rule out aetiologies with No Indication for Liver Transplantation

- Malignant infiltration of the liver
  - Which can occur in the setting of metastatic breast cancer and lymphoma
  - Make diagnosis early as these patients are not for liver transplant
  - Rule out with imaging and/or liver biopsy

- Acute ischaemic injury
  - Common in elderly patients and cardiac patients
  - Primary problem causing the ischaemia needs to be addressed
  - Pattern: >10000 IU/L AST and at least twice the value of ALT. Frequently bilirubin levels are normal initially. HE and hyperammonaemia are not frequent

- Other systemic disease
  - HLH (However case reports show possible benefit if sought early)
  - Infections such as malaria, dengue and rickettsiosis
  - Systemic mitochondrial failure following toxin ingestion (yellow phosphorus)-unclear

- Rich NE, Sanders C, Hughes RS, Fontana RJ, Stravitz RT, Fix O, et al. Malignant infiltration of the liver presenting as acute liver failure. Clin Gastroenterol Hepatol 2015;13:1025–1028. [33] Rowbotham D, Wendon J, Williams R. Acute liver failure secondary to hepatic infiltration: a single centre experience of 18 cases. Gut 1998;42:576–580.
- Price B, Lines J, Lewis D, Holland N. Haemophagocytic lymphohistiocytosis: A fulminant syndrome associated with multiorgan failure and high mortality that frequently masquerades as sepsis and shock. S Afr Med J 2014;104:401–406. [41] Anand AC, Garg HK. Approach to clinical syndrome of jaundice and encephalopathy in tropics. J Clin Exp Hepatol 2015;5:S116–S130.

3. RULE OUT AETIOLOGIES WITH NO INDICATION FOR LIVER TRANSPLANTATION

Table 6: Contraindications to liver transplantation.

Absolute contraindications
Severe cardiopulmonary disease
Extrahepatic malignancy (oncologic criteria for cure not met)
Active alcohol/substance abuse
Acute alcoholic hepatitis
Active infection/uncontrolled sepsis
Lack of psychosocial support/inability to comply with medical treatment
Brain death
Relative contraindications
Advanced age
Acquired immune deficiency syndrome
Cholangiocarcinoma
Diffuse portal vein thrombosis

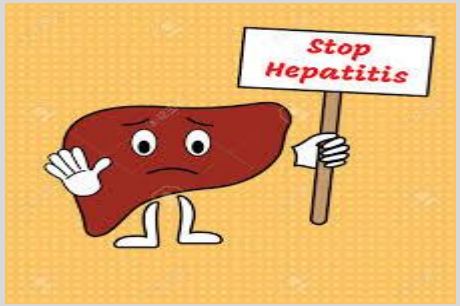
4. Aetiologies form as Possible Indication for Liver Transplantation

Drug Induced Hepatotoxicity

- Paracetamol overdose
  - Characterised by extreme elevations of aminotransferases and normal bilirubin levels, metabolic acidosis, elevated serum lactate, hypoglycaemia and AKI
  - Very early presentation of POD-marked metabolic acidosis and elevated lactate BUT only mild elevation of transaminase levels and minimal coagulopathy
    - Considered a direct drug effect relating to functional mitochondrial standstill and resolving with falling paracetamol levels

- Non Paracetamol
  - Diagnosis of exclusion
  - Rule out common drugs-anti TB drugs, antibiotics (nitrofurantoin and ketoconazole), anti-epileptics, NSAIDS
  - Herbal, illicit drugs

4. Aetiologies form as Possible Indication for Liver Transplantation



Viral Hepatitis

- HBV
  - most common viral cause however decreasing with vaccination
  - Reactivation of chronic carriers seen during/after treatment induced immunosuppression OR patients on rituximab in context of chemotherapy
- HAV
  - Less than 1%, ALF common in elderly
- HEV
  - Recent travel to endemic areas
  - Hyperacute presentation with low mortality. Worse outcomes with elderly, undiagnosed underlying chronic liver disease and pregnancy women
- Other Viral
  - HSV 1 and 2, VZV are rare causes of ALF
  - Undergo testing if aetiology is not clear (could just be a co-factor)

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4. Aetiologies form as Possible Indication for Liver Transplantation

Autoimmune Hepatitis

- Presence of other autoimmune disorders should alert you to AIH
- Elevated globulin fraction and positive autoantibodies (can be absent initially)
- Treatment with steroids may be effective early on but predisposes one to developing sepsis

- Bernal W, Ma Y, Smith HM, Portmann B, Wendon J, Vergani D. The significance of autoantibodies and immunoglobulins in acute liver failure: a cohort study. J Hepatol 2007;47:664–670. [90]
- Bernal W, Meda F, Ma Y, Bogdanos DP, Vergani D. Disease-specific autoantibodies in patients with acute liver failure: the King's College London Experience. Hepatology 2008;47:1096–1097. [91] Heneghan MA,
- Yeoman AD, Verma S, Smith AD, Longhi MS. Autoimmune hepatitis. Lancet 2013;382:1433–1444. [92]
- Karkhanis J, Verna EC, Chang MS, Stravitz RT, Schilsky M, Lee WM, et al. Steroid use in acute liver failure. Hepatology 2014;59:612–621.

For assessing the severity of the disease:
PT, INR or factor V and full coagulation screen including fibrinogen
Liver blood tests including LDH and conjugated and unconjugated bilirubin and creatinine kinase
Assessment of renal function: • urine output: hourly. • low urea is a marker of severe liver dysfunction. • creatinine may be difficult to assay in the context of elevated bilirubin.
Arterial blood gas and lactate
Arterial ammonia
For aetiology:
Toxicology screen in urine and paracetamol serum level
Serological screen for virus infections • HBsAg, anti-HBc IgM (HBV DNA), delta 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: ANA, ASMA, anti-soluble liver antigen, globulin profile, ANCA, HLA typing
For testing for complications:
Lipase or amylase

INVESTIGATIONS

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Diagnostic tests:

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

Routine monitoring:

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

Standard care:

- Glucose infusions (10–20%): glycemic target ± 140 mg/dl, Na 135–145 mmol/L
- Stress ulcer prophylaxis
- Restrict clotting factors unless active bleeding
- N-acetylcysteine in early stage, even in non-paracetamol cases

Preventative measures:

- Avoid sedatives
- Avoid hepatotoxic and nephrotoxic drugs

In case of hepatic encephalopathy:

- Transfer to an appropriate level of care (ideally critical care) at the first symptoms of mental alterations
- Quiet surrounding, head of bed >30°, head in neutral position and intubate, ventilate and sedate if progresses to >3 coma.
- Low threshold for empirical start of antibiotics if hemodynamic 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)

MONITORING AND STANDARD CARE

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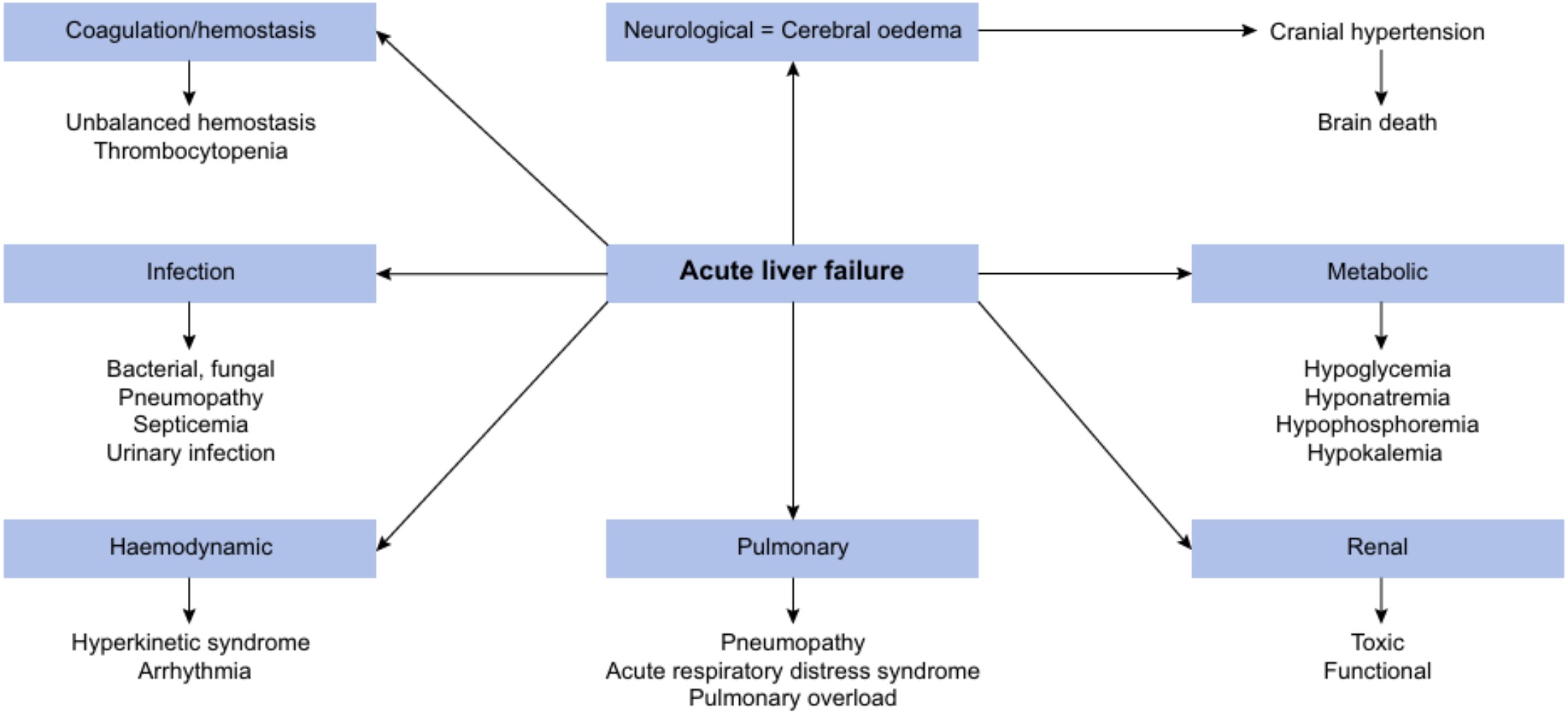
MANAGEMENT



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MANAGEMENT

Cardiovascular Management

- General critical care literature supports crystalloid use over colloid use
  - However should be guided by the biochemical parameters
  - Normal saline, Ringers Lactate
  - However volume overload needs to be avoided with appropriate monitoring

- Persistent hypotension (despite adequate volume loading)
  - Recommended is norepinephrine
  - Consider vasopressin if norepinephrine requirements increase

- Blood pressure targets has not been defined as yet
- Hydrocortisone therapy does not reduce mortality but does assist in decreasing vasopressor requirements

MANAGEMENT

Respiratory Management

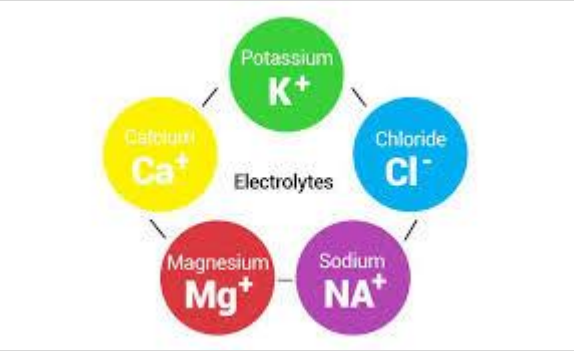
- Invasive airway management is required in the setting of progression to high grade HE
- Avoid non-invasive ventilatory support in patients at risk of HE (avoids high risk of neurological deterioration, aspiration and poor compliance
- Sedation-short acting opiate and propofol (monitor BPs)
- Lung protective ventilatory settings
  - Low volume tidal volumes
  - Appropriate levels of PEEP
  - Avoid hypercarbia/hypocarbia
- Regular chest physiotherapy to avoid ventilator associated pneumonia

MANAGEMENT

Gastrointestinal Management

- Oral nutrition encouraged and low tolerance to enteral feeding
  - Patients with ALF have increased energy expenditure
  - Early enteral feeding will minimise loss of muscle mass and reduce risk of gastrointestinal haemorrhage
- Mitochondrial dysfunction in some patients
  - Lipid loads will not be metabolised and may accumulate compounding liver injury
  - Monitoring lipid profile along with creatine kinase is required. Target trigylcerides to <3 mmol/L
- Release of free fatty acids
  - Released into splanchnic circulation
  - These circulating amino acids may aggravate the hyperammonaemia and precipitates cerebral oedema and intracranial hypertension
  - Avoid this by monitoring plasma ammonia
- Monitor for pancreatitis
- Proton pump inhibitors (PPIs)
  - Normally administered
  - Balanced against risk of ventilator associated pneumonia and Clostridium Difficike infection
  - Consider stopping when enteral feeding is established

MANAGEMENT



Metabolic Management

- More common in hyperacute ALF, especially associated with acute kidney injury
- Hypoglycemia
  - Multifactorial pathogenesis (increased hepatic extraction of glucose, increased hepatic glycolysis and impaired gluconeogenesis
  - More prevalent in Paracetomol overdose with AKI
  - In hyperacute ALF-monitor at least 2 hourly HGT's
- Hyperglycemia
  - Can exacerbate raised ICP and should be avoided
  - Target in critically ill patients HGT of 8.3 to 10 mmol/L
- Hypernatremia
  - Should be avoided and aim for concentrations of 140-150 mmol/L
- Acidosis
  - Increased circulating lactate and reduced bicarbonate are common in hyperacute and acute ALF
  - Both have been proposed markers in Paracemtomol induced ALF
- Ions
  - Phosphate, magnesium, ionised calcium and potassium are commonly monitored
  - Hypophosphatemia is a favourable prognostic sign and is associated with liver regeneration; however needs careful replacement

- Schmidt LE, Dalhoff K. Serum phosphate is an early predictor of outcome in severe acetaminophen-induced 2002;36:659–665.
- Moore JK, Love E, Craig DG, Hayes PC, Simpson KJ. Acute kidney injury in acute liver failure: a review. Expert Rev Gastroenterol Hepatol 2013;7:701–712.
- Schetz M, Vanhorebeek I, Wouters PJ, Wilmer A, Van den Berghe G. Tight blood glucose control is renoprotective in critically ill patients. J Am Soc Nephrol 2008;19:571–578.
-] Schneeweiss B, Pammer J, Ratheiser K, Schneider B, Madl C, Kramer L, et al. Energy metabolism in acute hepatic failure. Gastroenterology 1993;105:1515–1521.

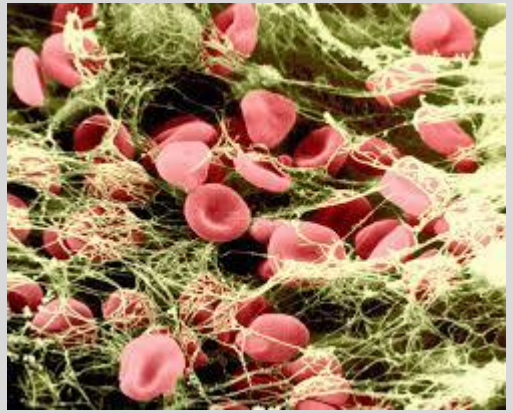
MANAGEMENT

Acute kidney injury and renal replacement therapy

- Strategies to prevent AKI
  - Correct hypotension, treat infections promptly, avoid nephrotoxic treatment balance use of contrast

- Renal replacement therapy in ALF context
  - Manage acidosis, hyperammonaemia and sodium imbalance, facilitate temperature and metabolic control
  - Slack et al-early consideration of RRT should be undertaken in those with ALF with markedly elevated ammonia and encephalopathy. (clear correlation between creatinine clearance and ammonia clearance)

MANAGEMENT



Coagulation

- Routine use of fresh frozen plasma and other coagulation factors is not supported
- Only limited to specific situations like insertion of ICP monitors or active bleeding

- Haemoglobin target for transfusion is 7g/dL

- Venous thrombosis prophylaxis should be considered in the daily review

MANAGEMENT

Sepsis, inflammation and anti-inflammatory management

- Prophylactic antibiotics, non-absorbable antibiotics and antifungal have not shown to improve survival in ALF
- Regular periodic surveillance cultures should be performed in all patients in ALF
- Commence early management upon appearance of worsening hepatic encephalopathy, clinical signs of infection or elements of SIRS
- Antifungal therapy to be considered in those with prolonged critical care support and guided by biomarkers

Table 7. Management according to grade of hepatic encephalopathy (West-Haven Criteria) (36)

Grade of HE	Symptom description	Management in ALF
Grade 1	Trivial lack of awareness Shortened attention span Impairment of addition or subtraction Altered sleep rhythm	• Contact transplant enter and initiative transfe • Obtain baseline CT head
Grade 2	Lethargy or apathy Disorientation for time Obvious personality change Inappropriate behavior Dyspraxia Asterixis	• Transfer to the intensive care unit • Neuro checks q1 hr
Grade 3	Somnolence to semistupor Responsive to stimuli Confusion Gross disorientation Bizarre behavior	• Intubation if appropriate • Repeat CT head • Avoid opioids and benzodiazepines for sedati • Consider propofol due to short half life
Grade 4	Coma	• Repeat CT head • Consider intracranial pressure monitor if transp • Initiate treatment for cerebral edema

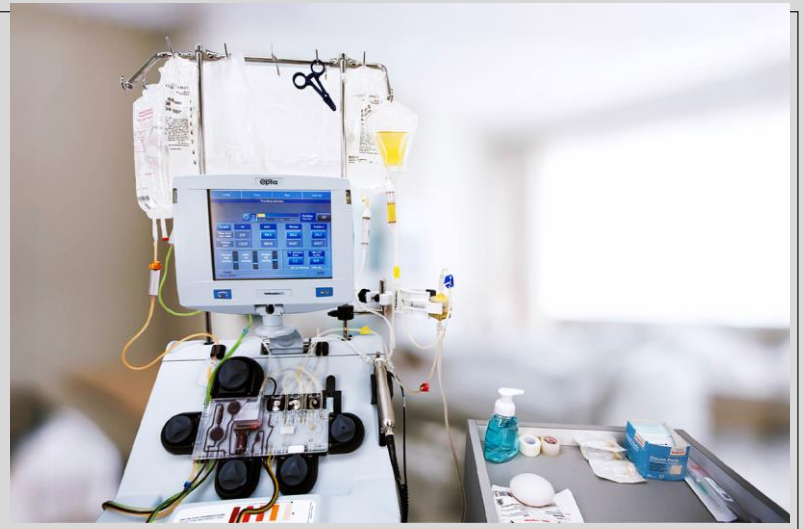
ALF, acute liver failure; CT, computed tomography. HE, hepatic encephalopathy.

MANAGEMENT

The Brain in ALF

- Low grade encephalopathy should be frequently evaluated for worsening HE
- Grade 3 or 4, intubation in safe environment preventing aspiration. Regular evaluation for signs of intracranial hypertension needed
- Trans-cranial Doppler is useful
- Invasive ICP monitoring on selected group who have progressed to Grade ¾
  - Young patients with hyperacute or acute presentation
  - Ammonia level over 150-200 mmol/L (with no resolution with RRT or fluids)
  - Renal impairment
  - Vasopressor support
- ICP
  - Short term mannitol/hypertonic saline should be administered for surges of ICP

MANAGEMENT



Artificial and Bioartificial Liver Devices

- Works as an effective bridge to transplantation/recovery
- MARS (Molecular Absorbent and Recirculating System)
  - Designed to extract protein-bound toxins into the albumin dialysate
- Prometheus System
  - Separates plasma and treats it over adsorbent columns; not much evidence to be beneficial
- Extracorporeal Liver Assist Device (ELAD)-not shown to be beneficial
- Plasma Exchange (reduces levels of circulating inflammatory cytokines0
  - Within first 3 days of admission to critical care-physiological and biochemical effects and decreases ICP; backed by RCT's

Chris-Olaiya A, Kapoor A, Ricci KS, Lindenmeyer CC. Therapeutic plasma exchange in liver failure. World J Hepatol. 2021 Aug 27;13(8):904-915. doi: 10.4254/wjh.v13.i8.904. PMID: 34552697; PMCID: PMC8422921.

LIVER TRANSPLANTATION

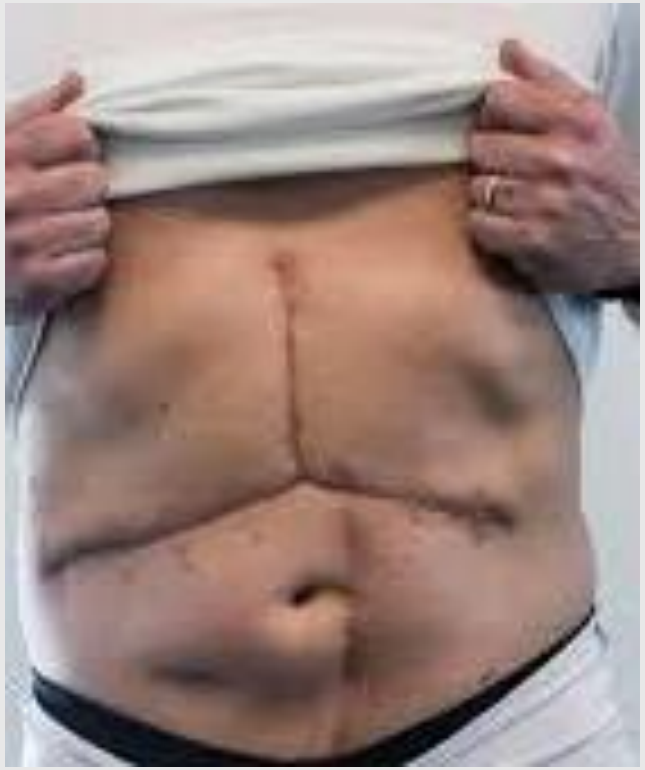
LIVER TRANSPLANTATION

- Use of transplant has transformed survival of ALF
- One year survival at 80%

Assessment and Prognosis

- Encephalopathy
  - In ALF, shows critically impaired liver function
  - In subacute-even low HE may indicate extremely poor prognosis

- Extrahepatic Organ Failure
  - Especially renal is a marker of illness severity and increased mortality



Neuberger J, Gimson A, Davies M, Akyol M, O'Grady J, Burroughs A, et al. Selection of patients for liver transplantation and allocation of donated livers in the UK. Gut 2008;57:252–257.

Table 11. (A) Acute Liver Failure Poor Prognosis Criteria in use for selection of candidates for Liver Transplantation. (B) Criteria for emergency liver transplantation.

A

Factor	Clichy [323]	Kings College [321]	Japanese [6]
Age†	+	+	+
Aetiology	–	+	–
Encephalopathy†	+	+	+
Bilrubin*	–	±	+
Coagulopathy†	+	+	+

B

King's College criteria

ALF due to paracetamol

- Arterial pH <7.3 after resuscitation and >24 h since ingestion
- Lactate >3 mmol/L or
- The 3 following criteria:
  - Hepatic encephalopathy >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 (hepatic encephalopathy stage 3 or 4)
- Factor V <20% of normal if age <30 year
  or
- Factor V <30% if age >30 year

† Factors common to all prognostic models.
* Bilirubin not included in paracetamol criteria.

ABCD

Liver Transplantation

- Two most commonly used criteria are Kings College and Clichy Criteria

Who to Transplant in the Acute Setting

- Psychosocial assessment
  - Often difficult with timeframe
  - Decision based on criteria above
  - However other factors: expected compliance, familial status or environment, situation leading to ALF (e.g. substance users)
  - Thorough history and background check needs to be conducted with the MDT

- Is the patient too sick?
  - Only definitive criteria contraindicating transplant is irretrievable brain injury
  - Defined as a persistent presence of bilateral non-reactive pupils with
    - No spontaneous ventilation
    - Loss of middle cerebral artery flow or loss of grey white matter differentiation
    - Evidence of uncal herniation
  - Bacteremia is not a contraindication if antibiotics on board
  - Vasoplegic shock with rapid increase in vasopressors, haemorrhagic pancreatitis and extensive bowel ischaemia-relative contraindication

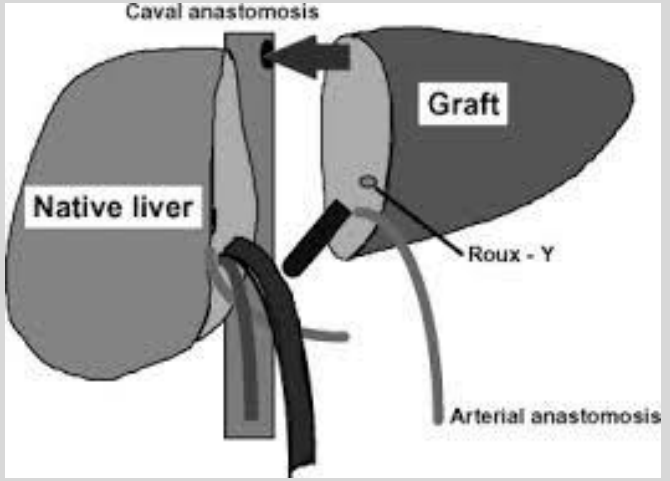
Who to Transplant in the Acute Setting

Type of Graft

- Possibility of best graft may be reduced due to urgency
- Orthotopic Liver transplant done using a cadaveric donor usually due to their high priority on the waiting list
- However may use marginal donors (ages or steatotic grafts) due to urgency; ABO incompatible is even advocated
- In many countries, ALF patients transplant within 72 hours
- With the above reasons, risk of rejection, infection, retransplant and mortality are increased

- Auxiliary Orthotopic Liver Graft (APOLT)-leave part of native liver and transplant the cadaveric donor in an orthotopic position
  - The graft acts as a bridge in helping the patient survive the ALF
  - This is to allow for potential regeneration of the native liver
  - Then to decrease immunosuppression and allow for graft atrophy
  - However risky and lower survival than orthotopic transplant

- Living Donor
  - Rarely used in Europe and USA due to cadaveric availability
  - Developing countries noted to use it more (Asia); not enough data for Africa



Specific Issues and Immediate Complications

- Main cause of morbidity and mortality
  - Sepsis
  - Progressive organ failure in the context of vasoplegic shock
  - Liver graft dysfunction or failure
- Re-transplantation
  - More frequent than elective
  - Usually due to graft dysfunction and hepatic artery thrombosis

CONCLUSION

- The definition of ALF is important as well as identifying the sub-type
- Identify appropriate ALF patients early on and refer quickly
- Make use of simple tools to help decide ALF patients
- A thorough work up and MDT decision
- Supporting an ALF patient in a multi-organ fashion is important to get to transplant!