Clinical Practice Guidelines

Acute liver failure

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About these slides

- These slides give a comprehensive overview of the EASL clinical practice guidelines on the management of acute (fulminant) liver failure

- The guidelines were published in full in the May 2017 issue of the Journal of Hepatology
  - The full publication can be downloaded from the Clinical Practice Guidelines section of the EASL website
  - Please cite the published article as: European Association for the Study of the Liver. EASL 2017 Clinical Practice Guidelines on the management of acute (fulminant) liver failure. J Hepatol 2017;66:1047–81

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Definition and clinical course of ALF

- In hepatological practice, ALF is a highly specific and rare syndrome, characterized by an acute deterioration of liver function without underlying chronic liver disease

SEVERE ACUTE LIVER INJURY (ALI)

- No underlying chronic liver disease*
- Liver damage (serum aminotransferases 2–3x ULN)
- Impaired liver function (jaundice and coagulopathy†)

Up to 12 weeks post-jaundice, depending on sub-classification

HEPATIC ENCEPHALOPATHY (HE)

Crucial for the diagnosis of ALF
Mental alterations may be initially subtle
Intensive screening at the first sign of HE is mandatory

ALF

*Patients with an acute presentation of chronic autoimmune hepatitis, Wilson disease and Budd–Chiari syndrome are considered as having ALF if they develop hepatic encephalopathy, despite the presence of a pre-existing liver disease in the context of appropriate abnormalities in liver blood tests and coagulation profile; †Usually INR >1.5 or prolongation of PT

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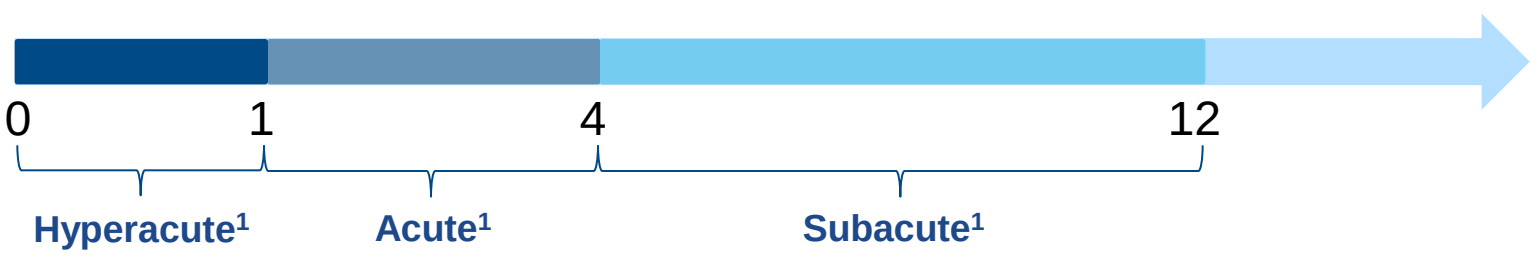
Sub-classifications of ALF

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]
Good	Moderate	Poor	Chance of spontaneous recovery[2]
Paracetamol HAV, HEV	HBV	Non-paracetamol drug-induced	Typical cause[2]

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

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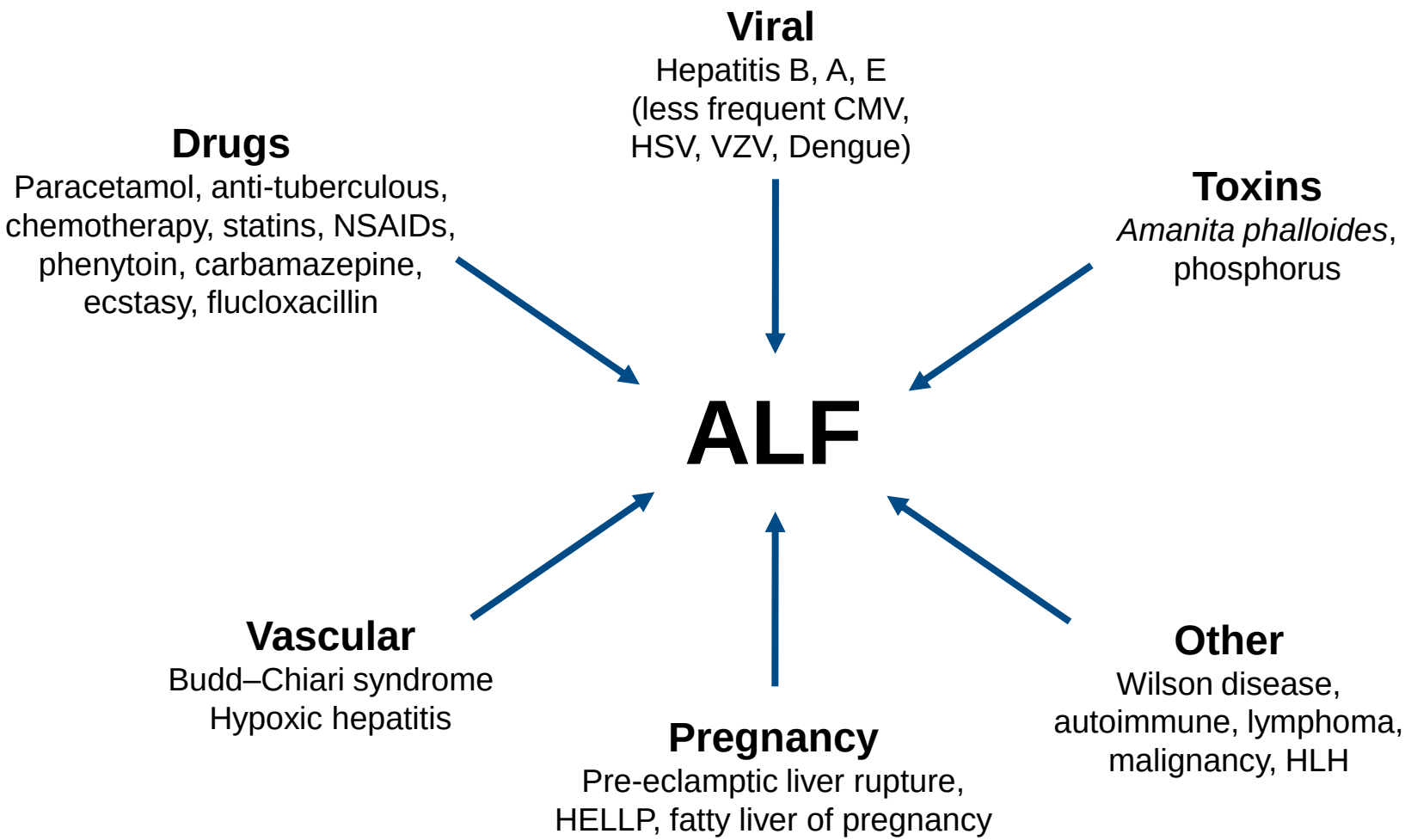
Principal aetiologies of ALF



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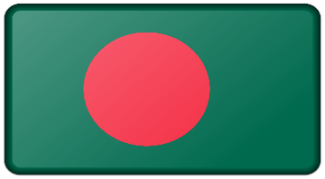
Aetiology of ALF varies with geography

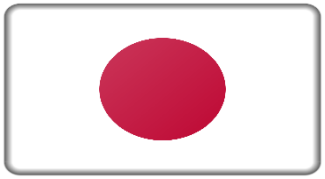
Top three causes of ALF in selected countries



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%

*'Other causes' refers to identified causes that are not: HAV, HBV, HEV, paracetamol or other drugs

Bernal W, Wendon J. New Eng J Med 2013;369:2525–34

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Assessment and management at presentation

- **Immediate measures**
  - Exclude cirrhosis, alcohol-induced liver injury or malignant infiltration
  - Initiate early discussions with tertiary liver/transplant centre
    - Even if not immediately relevant
  - Screen intensively for hepatic encephalopathy
  - Determine aetiology
    - To guide treatment and determine prognosis
  - Assess suitability for liver transplant
    - Contraindications should not preclude transfer to tertiary liver/transplant centre
  - Transfer to a specialized unit early
    - If the patient has an INR >1.5 and onset of hepatic encephalopathy or other poor prognostic features

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Assessment and management at presentation

- **Immediate measures**
  - Exclude cirrhosis, alcohol-induced liver injury or malignant infiltration
  - Initiate early discussions with tertiary liver/transplant centre
    - Even if not immediately relevant

Recommendations	Grade of evidence	Grade of recommendation
The clinical picture and the radiology of subacute liver failure can mimic cirrhosis	II-3	1
The indications for liver biopsy in ALF are limited.* Incidence of **underlying chronic liver disease, malignancies or alcohol-induced liver disease should be excluded**	II-3	1
Early referral of patients to a specialist centre will allow appropriate delineation of those likely to benefit from transplantation and offers an environment where focused expertise provides the greatest chance of spontaneous survival without LTx	III	1

*Should be performed preferably by a transjugular route, in an experienced centre, with access to a histopathologist with liver experience

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Assessment and management at presentation

- **Immediate measures**
  - Determine aetiology to guide treatment, especially LTx

Primary or secondary causes of ALF and need for transplantation

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

Possible indication for emergency LTx **No indication for emergency LTx**

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Differential diagnosis based on clinical features

Aetiology	Clinical features
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	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 ALP ratio; Kayser–Fleischer ring; low serum uric acid level; markedly increased urinary copper
Mushroom poisoning	Severe gastrointestinal 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
Malignant infiltration	History of cancer, massive hepatomegaly; elevated ALP or other tumour markers
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

Possible indication for emergency LTx **No indication for emergency LTx**

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Aetiologies with no indication for LTx

- **Malignant infiltration of the liver** and **acute ischaemic injury** are not indications for LTx

Recommendations	Grade of evidence	Grade of recommendation
In patients with a history of cancer or significant hepatomegaly, **malignant infiltration should be excluded** by imaging or liver biopsy	II-3	1
Acute ischaemic injury will resolve after improvement of haemodynamic status, and **is not an indication for emergency LTx**. It can occur in the absence of a proven period of hypotension	II-3	1

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Aetiologies with possible indication for LTx

- **Drug-induced liver injury** is the most frequent cause of severe ALI and ALF
  - Especially paracetamol overdose

Recommendations	Grade of evidence	Grade of recommendation
At admission, a **toxicology screen and determination of paracetamol level are necessary in every patient,** although levels will frequently be negative. If the patient already has coagulopathy and increased serum aminotransferases, **N-acetyl cysteine therapy should be given**	II-2	1
Prognosis is worse in patients with staggered ingestion of paracetamol. These cases are more likely to develop multiple organ failure when compared to those with a single ingestion point	II-3	1
ALF caused by non-paracetamol drug-induced hepatotoxicity is a diagnosis of exclusion	III	2

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Aetiologies with possible indication for LTx

- **Viral and autoimmune ALF**
  - HBV (most common), HAV, HEV, and VZV, HSV-1 and -2 (rare) can cause ALF
  - Existence of other autoimmune conditions should raise suspicion of autoimmune hepatitis

Recommendations	Grade of evidence	Grade of recommendation
Always screen **for viral aetiologies** and co-factor effects	II-2	1
Suspect **autoimmune aetiology** in patients presenting other autoimmune disorders. Liver biopsy may be needed if elevated globulin fraction and autoantibodies are absent. Early treatment with steroids may be effective but **list for emergency LTx if no improvement within 7 days**	II-2	1

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Aetiologies with possible indication for LTx

- **Uncommon aetiologies**
  - In most cases a potential positive effect of specific intervention will be too late to be beneficial
    - Consideration for emergency LTx should not be delayed

Recommendations	Grade of evidence	Grade of recommendation
Assessment of the clinical context is crucial to identify less common causes of ALF	III	1
Acute **Budd–Chiari syndrome** should be suspected in ALF presenting with gross ascites. Diagnosis is based on imaging techniques	II-3	1
Wilson disease should be suspected with Coombs-negative haemolytic anaemia and high bilirubin to ALP ratio	II-3	1
In cases of **HELLP and AFLP in pregnancy**, the treatment of choice is prompt delivery of the baby, especially in case of elevated lactate levels and hepatic encephalopathy. Screening for putative fatty acid defects should be offered	II-3	1
Screen for systemic diseases presenting as ALF	III	1

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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

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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
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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;
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Assessment and management at presentation

- **Immediate measures**
  - Assess suitability for liver transplant and initiate early discussions with transplant unit
    - Even if not immediately relevant

Suggested criteria for referral of cases of ALF to specialist units

Paracetamol and hyperacute aetiologies	Non-paracetamol
Arterial pH <7.30 or HCO_3 <18	pH <7.30 or HCO_3 <18
INR >3.0 day 2 or >4.0 thereafter	INR >1.8
Oliguria and/or elevated creatinine	Oliguria/renal failure or Na <130 mmol/l
Altered level of consciousness	Encephalopathy, hypoglycaemia or metabolic acidosis
Hypoglycaemia	Bilirubin >300 µmol/l (17.6 mg/dl)
Elevated lactate unresponsive to fluid resuscitation	Shrinking liver size

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Assessment and management at presentation

- **Immediate measures**
  - Transfer to a specialized unit early
    - Evolution of ALF is highly unpredictable
    - Experience of specialized units is required to improve patient outcomes

Recommendations	Grade of evidence	Grade of recommendation
Diagnosis of ALF should be always considered with respect to the **full clinical picture**; appropriate investigations and discussion with a tertiary centre should be undertaken. This is especially important in cases of subacute clinical course	III	1
Frequent senior clinical review (twice daily minimum) and assessment of physiological parameters, blood results and metabolic status should be carried out	III	1
Hourly urine output should be assessed as a marker of renal function, alongside creatinine	III	1
Clinical deterioration with extrahepatic organ involvement should result in transfer to critical care and tertiary centre	III	1

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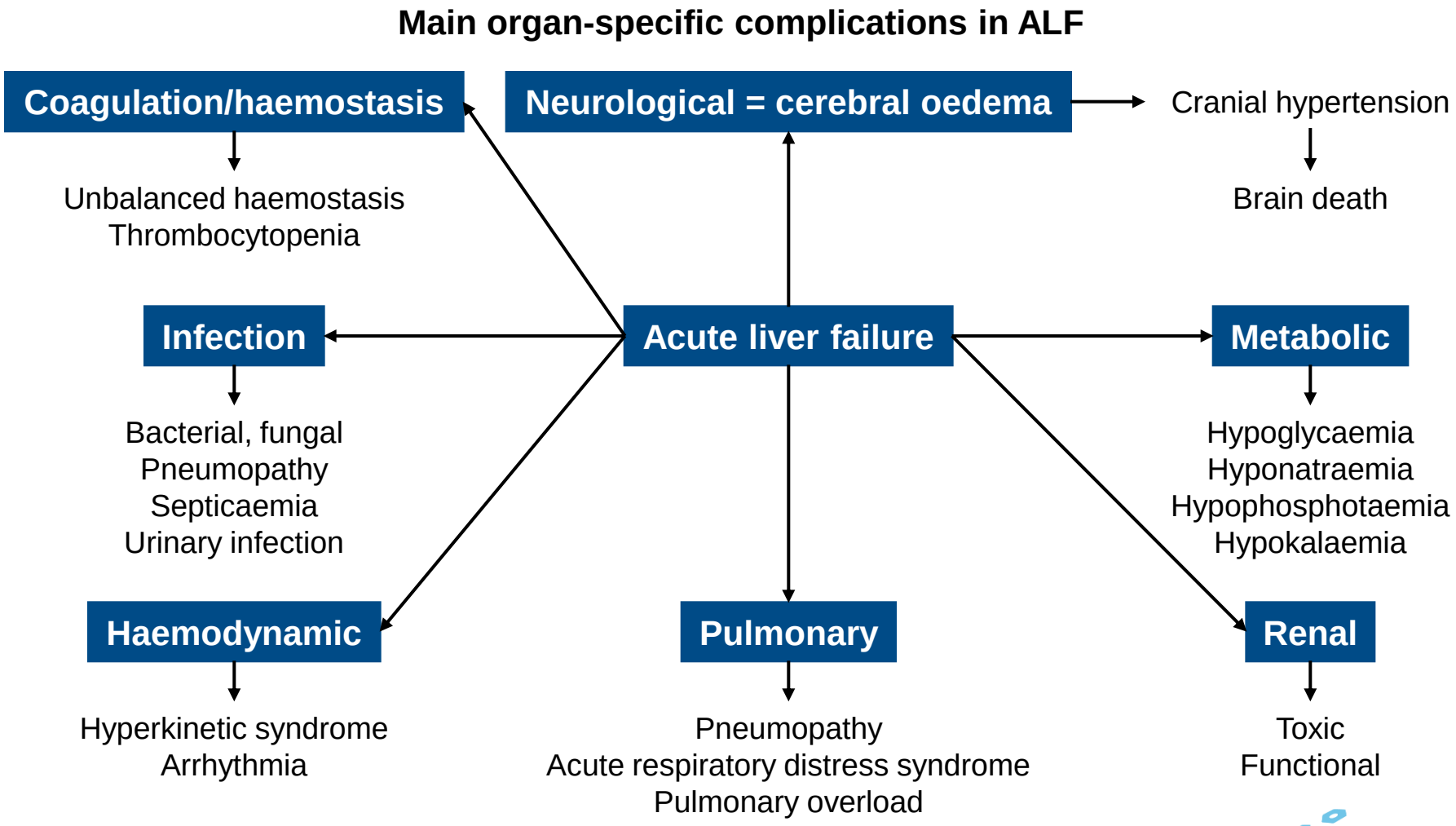
Organ-specific management



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Organ-specific management: cardiovascular

- Most patients presenting with ALF or severe ALI develop systemic vasodilation with reduced effective central blood volume

Recommendations	Grade of evidence	Grade of recommendation
Most patients are volume depleted at presentation and require crystalloid volume resuscitation	II-1	1
Persistent hypotension requires critical care management, with application of vasopressive agents guided by appropriate monitoring techniques	II-3	1
Noradrenaline is the vasopressor of choice	III	1
Volume overload is as detrimental as underfilling	II-2	1
Hypoxic hepatitis will require consideration of inotropic agents	II-3	1
A blood pressure target has not been defined in the literature	III	2
Hydrocortisone therapy does not reduce mortality but does decrease vasopressor requirements	II-1	1

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Organ-specific management: respiratory

- Invasive airway management is required in the face of progression to high-grade HE to ensure airway protection

Recommendations	Grade of evidence	Grade of recommendation
Standard sedation and lung protective ventilator techniques should be utilized in patients with ALF	II-3	1
Avoid excessive hyper or hypocarbia	III	1
Regular chest physiotherapy should be carried out and ventilator-associated pneumonia avoided	III	1

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Organ-specific management: gastrointestinal

- Guidance regarding nutritional needs in patients with ALF is largely empirical
  - Oral nutrition should be encouraged in patients with ALI
  - Progressive HE or anorexia is likely to result in decreased calorie intake

Recommendations	Grade of evidence	Grade of recommendation
Patients with ALF have increased resting energy expenditure. Therefore, enteral or parenteral nutrition is warranted	II-3	1
Avoid nasogastric feeding in those with progressive encephalopathy	III	1
Monitor ammonia when instituting enteral nutrition	III	1
PPI administration should be balanced against the risk of ventilator- associated pneumonia and *Clostridium difficile* infection	II-3	1
Consider stopping PPI when enteral feeding has been established	III	1

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Organ-specific management: metabolic

- ALF is frequently associated with electrolyte and metabolic imbalance
  - Hypoglycaemia and hyponatraemia
  - Acidosis
  - Alterations in serum phosphate, magnesium, ionised calcium and potassium

Recommendations	Grade of evidence	Grade of recommendation
Stringent attention to detail and normalization of biochemical abnormalities is warranted in patients with ALF	III	1
Hypoglycaemia is common in patients with ALF, is associated with increased mortality and needs to be corrected avoiding hyperglycaemia	II-3	1
Hyponatraemia is detrimental to outcome and should be corrected to maintain concentrations 140–150 mmol/L	II-2	1
Lactate elevation is related to increased production and decreased clearance, and remains a poor prognostic marker. RRT is indicated to correct acidosis and metabolic disturbances	II-3	1

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AKI and renal replacement therapy

- 40–80% of ALF patients referred to liver units have AKI
  - Associated with increased mortality and longer hospital stays
  - Increased age, paracetamol-induced ALI, SIRS, hypotension, and infection increase risk

Recommendations	Grade of evidence	Grade of recommendation
Early institution of extracorporeal support (RRT) should be considered for persistent hyperammonaemia, control of hyponatraemia and other metabolic abnormalities, fluid balance and potentially temperature control	III	1
Anticoagulation of RRT circuits remain a matter of debate, and close monitoring of metabolic status should be undertaken if citrate is utilized	II-2	1
Continuous RRT should always be undertaken in critically ill patients with ALF, as opposed to intermittent haemodialysis	III	1

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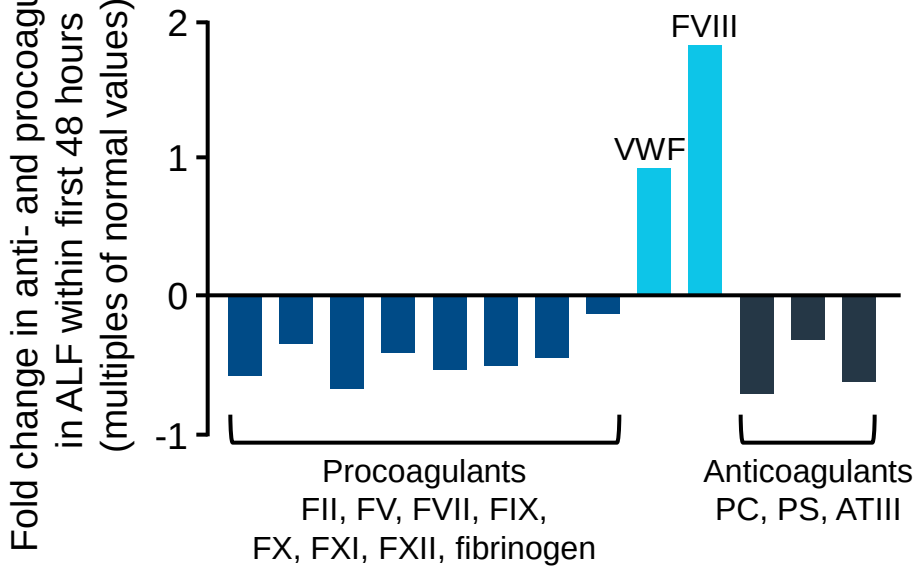
Coagulation: monitoring and management

- Rapid changes in PT or INR are characteristic of ALF
  - Significant prognostic value
- Common in ALF
  - Thrombocytopenia
  - Reduced circulating pro- and anti-coagulant proteins
  - Increased PAI-1
- Abnormal coagulation does not translate to increased risk of bleeding
  - Most patients' coagulation is normal despite abnormal INR and PT

Balanced relationship between reduced procoagulants and anticoagulants at admission to ICU with ALF[1]



1. Agarwal B, et al. J Hepatol 2012;57:780–6;
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Coagulation: monitoring and management

- Prophylactic correction of coagulation or platelet levels is not necessary
  - May instead adversely affect prognosis
  - May increase the risk of thrombosis or transfusion-related acute lung injury

Recommendations	Grade of evidence	Grade of recommendation
The routine use of fresh frozen plasma and other coagulation factors is not supported, and should be limited to specific situations, such as insertion of ICP monitors or active bleeding	II-3	1
Haemoglobin target for transfusion is 7 g/dl	II-2	1
Venous thrombosis prophylaxis should be considered in the daily review	III	1

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Sepsis, inflammation and anti-inflammatory management

- Patients with ALF are at increased risk of developing infections, sepsis and septic shock
  - Severe, untreated infection may preclude LTx and complicate the post-operative course
- ALF is associated with dynamic immune dysfunction
  - Imbalance can contribute to organ failure and death

Recommendations	Grade of evidence	Grade of recommendation
Antibiotics, non-absorbable antibiotics, and antifungals have not been shown to improve survival in ALF	II-2	1
Regular surveillance cultures should be performed in all patients	III	1
Early anti-infection treatments should be introduced upon appearance of progression of hepatic encephalopathy, clinical signs of infections, or elements of SIRS	II-3	1
Antifungal therapy in those with prolonged critical care support for multiple organ failure should be considered*	II-3	1

*Guided by the use of biomarkers

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The brain in ALF: hepatic encephalopathy

- HE tends to fluctuate
  - May progress from a trivial lack of awareness to deep coma
- Multiple additional manifestations
  - Headache, vomiting, asterixis, agitation, hyperreflexia and clonus
- Clinical diagnosis is one of exclusion
- Course dictated by outcome and phenotype of liver failure
  - Usually parallels evolution of liver function parameters
- Neurological outcomes may be worse in some circumstances
  - Coexistence of infection
  - Presence of inflammation without sepsis
  - Other organ failure

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The brain in ALF: management of HE

- 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 barotraumas
    - 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§

*Grade 3 coma in this context is not defined by asterixis (hepatic flap) but by the development of marked agitation and frequent aggression with a decrease in GCS (usually E1–2, V 3–4 and M4); †Grade 4 coma is associated with marked reduction in GCS (E1, V 1–2 and M1–3); ‡This may protect from ICH and reduce the risk of seizures; §E.g. levetiracetam or lacosamide (prophylactic use of antiepileptic drugs is not warranted)

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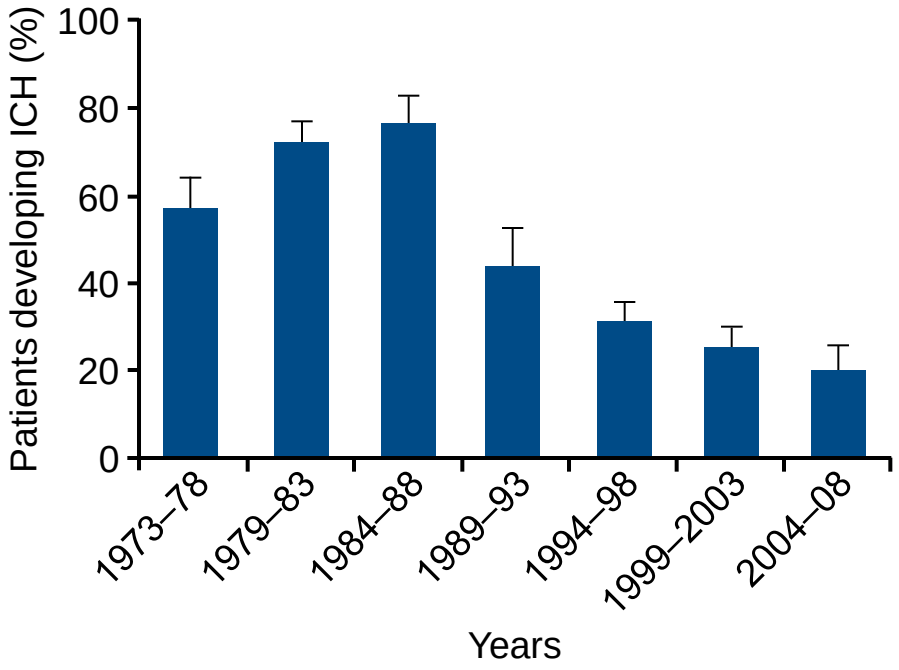
The brain in ALF: intracranial hypertension

- Brain oedema-induced ICH is a classic complication of HE in ALF
- Incidence of ICH has decreased recently[1]
  - Improvements in preventative medical care
  - Use of emergency LTx in high-risk patients[2]
- Still may affect one-third of cases who progress to Grade 3 or 4 HE
- Risk of ICH is highest in patients with:
  - Hyperacute or acute phenotype
  - Younger age
  - Renal impairment
  - Need for inotropic support
  - Persistent elevation of arterial ammonia

Decrease in the incidence of ICH in patients with ALF*[1]



*Proportion of 1,549 patients with ALF developing clinical signs of ICH. Error bars are 95% CI; p<0.00001

1. Bernal W, et al. J Hepatol 2013;59:74–80; 2. Bernal W, et al. J Hepatol 2015;62(1 Suppl):S112–20; EASL CPG ALF. J Hepatol 2017;66:1047–81

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The brain in ALF

- Regular clinical and neurological examination is mandatory
  - Detection of early signs of HE and progression to high-grade HE is critical

Recommendations	Grade of evidence	Grade of recommendation
Patients with low-grade encephalopathy should be frequently evaluated for signs of worsening encephalopathy	III	1
In patients with grade 3 or 4 encephalopathy, intubation should be undertaken to provide a safe environment and prevention of aspiration. Regular evaluation for signs of intracranial hypertension should be performed	III	1
Transcranial Doppler is a useful non-invasive monitoring tool	II-3	1

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The brain in ALF

- Additional monitoring is required in some patients

Recommendations	Grade of evidence	Grade of recommendation
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)	II-3	1
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	II-2	1

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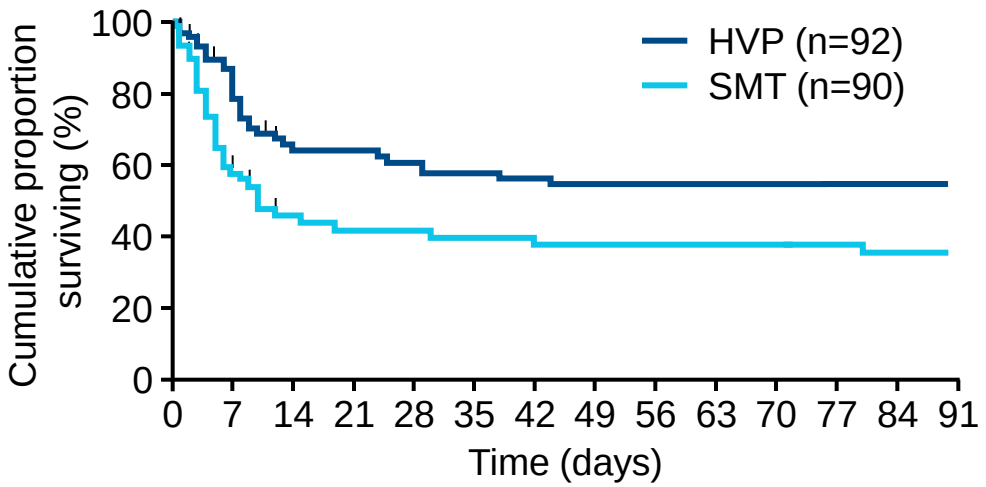
Artificial and bioartificial liver devices

- Liver-assist devices are intended to provide a ‘bridge’ to LTx or recovery of liver function, reducing the need for transplant
  - Experience with “liver support devices” to date has been disappointing
  - High-volume plasma exchange improved outcome in an RCT in ALF*



Recommendations	Grade of evidence	Grade of recommendation
Liver support systems (biological or adsorbent) should only be used in the context of RCTs	II-1	1
Plasma exchange in RCTs has been shown to improve transplant-free survival in patients with ALF and to modulate immune dysfunction	I	1
Plasma exchange may be of greater benefit in patients who are treated early and who will not ultimately undergo liver transplant	I	2

*HVP defined as exchange of 8–12 or 15% of ideal body weight with fresh frozen plasma, for 3 days was superior to SMT regarding transplant-free and overall hospital survival

Larsen FS, et al. J Hepatol. 2016;64:69–78; EASL CPG ALF. J Hepatol 2017;66:1047–81

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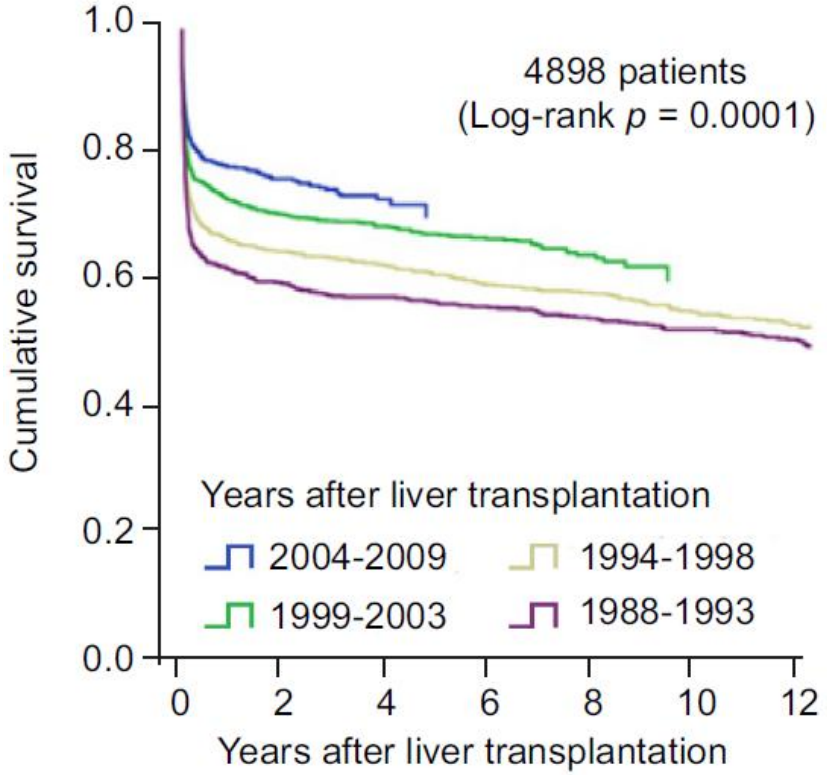
Impact of liver transplantation in ALF

- LTx has been the most significant development in the treatment of ALF in 40 years and has transformed survival
- 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

Patient survival after liver transplantation for ALF, Europe 1988–2009[1]



p<0.001 for survival 2004–2009 vs. previous time periods

1.Germani G, et al. J Hepatol 2012;57:288–96;
EASL CPG ALF. J Hepatol 2017;66:1047–81.

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ALF poor prognosis criteria in use for selection of candidates for liver transplantation

- A variety of prognostic evaluation systems are used to select candidates for transplantation
- Common prognostic criteria:
  - Patient age
  - Presence of HE
  - Liver injury severity (magnitude of coagulopathy or jaundice)
- In general, falling aminotransferases, increasing bilirubin and INR, and shrinking liver are poor prognostic signs
  - Should result in considering transfer of patient to a transplant centre

Factor	Clichy	King's College	Japanese
Age	+	+	+
Aetiology	-	+	-
Encephalopathy	+	+	+
Bilirubin*	-	±	+
Coagulopathy	+	+	+

*Bilirubin not included in paracetamol criteria

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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

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

- Many new marker studies report better diagnostic performance than existing criteria
  - Often small in size, have limited methodological quality and are seldom internally or externally validated
- Few (if any) have been adopted internationally and cannot be recommended for routine use

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

*Gc-globulin is a multifunctional protein involved in the scavenging of actin released from necrotic cells[1]

1. Schiodt FV et al. Liver Transpl 2005;11:1223–7;
EASL CPG ALF. J Hepatol 2017;66:1047–81

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Liver transplantation

- Evaluation of patient prognosis is key at the earliest opportunity

Recommendations	Grade of evidence	Grade of recommendation
Prognostic assessment should take place not only in the transplant centre but also at the site of first presentation, as decisions in relation to patient transfer to a specialist centre must be made at the earliest opportunity	III	1
Development of encephalopathy is of key prognostic importance, with onset indicating critically impaired liver function. In subacute presentations, even low-grade encephalopathy may indicate extremely poor prognosis	II-2	1
Prognosis is worse in patients with more severe liver injury, extrahepatic organ failure and subacute presentations	II-3	1
Transplantation should be considered in those patients fulfilling Clichy or King's College Criteria	II-2	1

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Liver transplantation

- Evaluation of patient prognosis is key at the earliest opportunity

Recommendations	Grade of evidence	Grade of recommendation
Assessment of patients with ALF for emergency LTx requires input from a multidisciplinary team with appropriate experience	III	1
Patients with ALF, potential for deterioration and who may be candidates for LTx, should be transferred to specialist units before the onset of HE to facilitate assessment	III	1
Patients with ALF listed for LTx should be afforded the highest priority for donated organs	III	1
Irreversible brain injury is a contraindication to proceeding with LTx	II-3	1
Patients transplanted for acute HBV infection need ongoing therapy for suppression of viral replication	II-3	1

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Paediatric ALF

SEVERE ACUTE LIVER INJURY
No underlying chronic liver disease
Hepatic-based coagulopathy:
PT >15 seconds or INR >1.5 not corrected by vitamin K in the presence of clinical HE,
or a PT >20 seconds or INR >2.0 regardless of the presence or absence of HE

HEPATIC ENCEPHALOPATHY
Non-essential component of ALF in children

ALF

Recommendations	Grade of evidence	Grade of recommendation
The definition of ALF in paediatrics is not dependent upon the presence of encephalopathy	II-3	1
Some aetiologies are specific to paediatric patients – notably metabolic disorders	II-3	1
Transplantation criteria are different to those in adults	II-3	1

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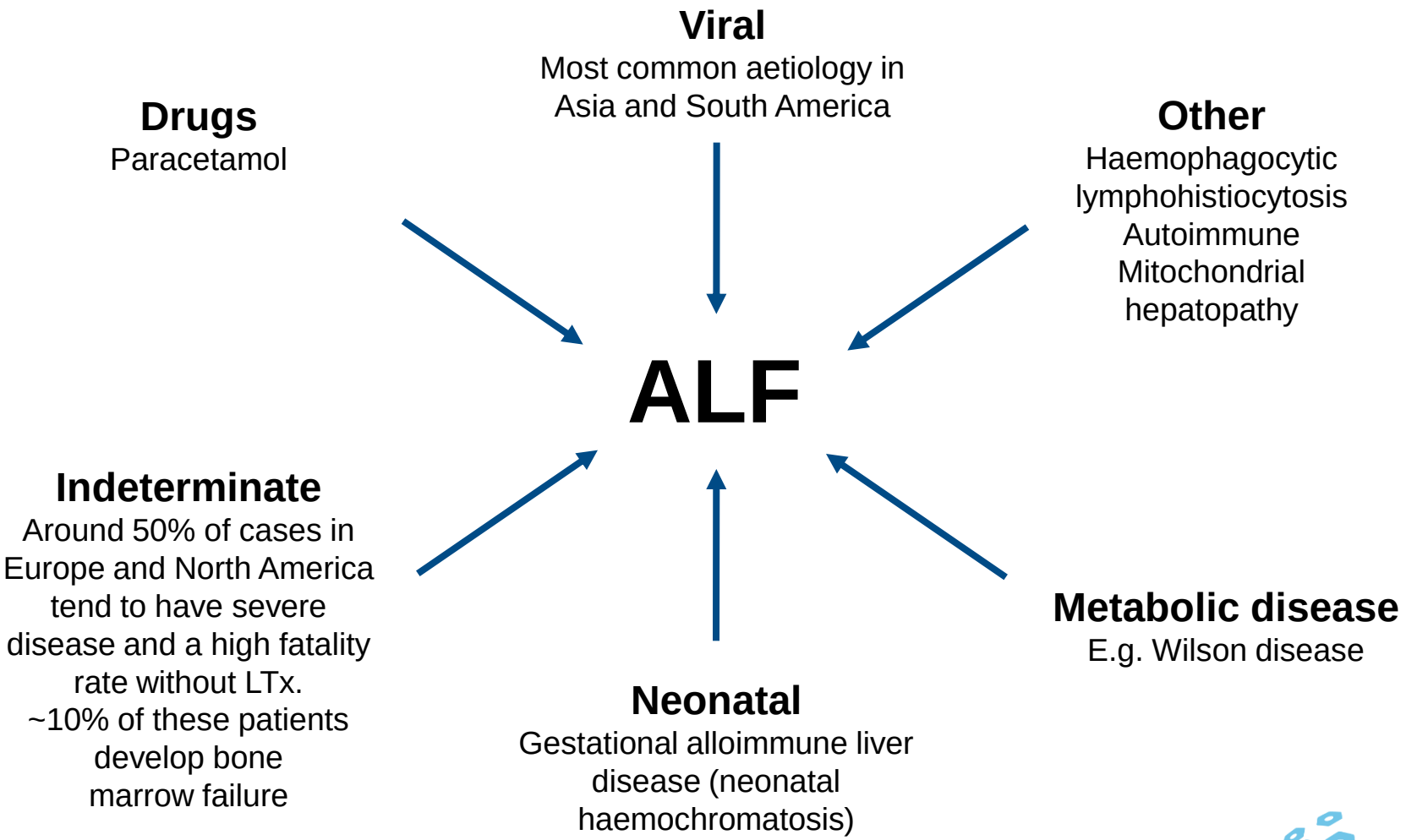
Most common aetiologies of ALF in children



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Most common aetiologies of ALF in children

331 patients with acute liver failure, data from the USA and Canada (PALFSG data set)

- Other
- Metabolic
- Wilson disease
- Autoimmune hepatitis
- Shock
- Viral (not B)
- Hepatitis A
- Drug-related
- Paracetamol
- Unknown

Dhawan A. Liver Transpl. 2008;14 Suppl 2:S80-4.

Liver transplantation in children with ALF

- LTx is the only proven treatment that has improved outcomes in children with ALF who fulfil poor prognostic criteria

Liver transplantation criteria in paediatric ALF
Indications (accepted, not validated) • INR >4 and total bilirubin >300 µmol/L (17.6 mg/dl) irrespective of HE
Contraindications • Fixed and dilated pupils • Uncontrolled sepsis • Severe respiratory failure (ARDS)
Relative contraindications • Accelerating inotropic requirements • Infection unresponsive to treatment • History of progressive or severe neurological problems in which the ultimate neurological outcome may not be acceptable • Systemic disorders such as HLH, where LTx is not curative

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