Clinical Practice Guidelines

Acute liver failure

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About these slides

- 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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Background

Definition of ALF

Sub-classifications

Disease burden

Principal aetiologies

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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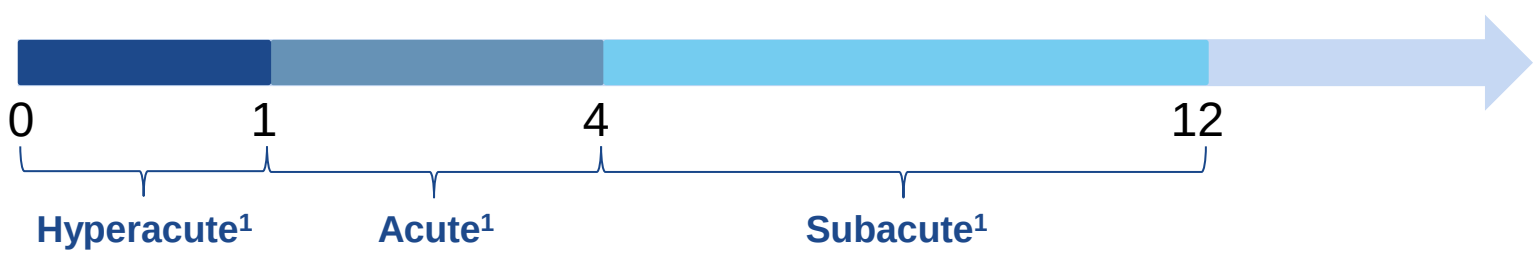
Sub-classifications of ALF

Weeks from the 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;
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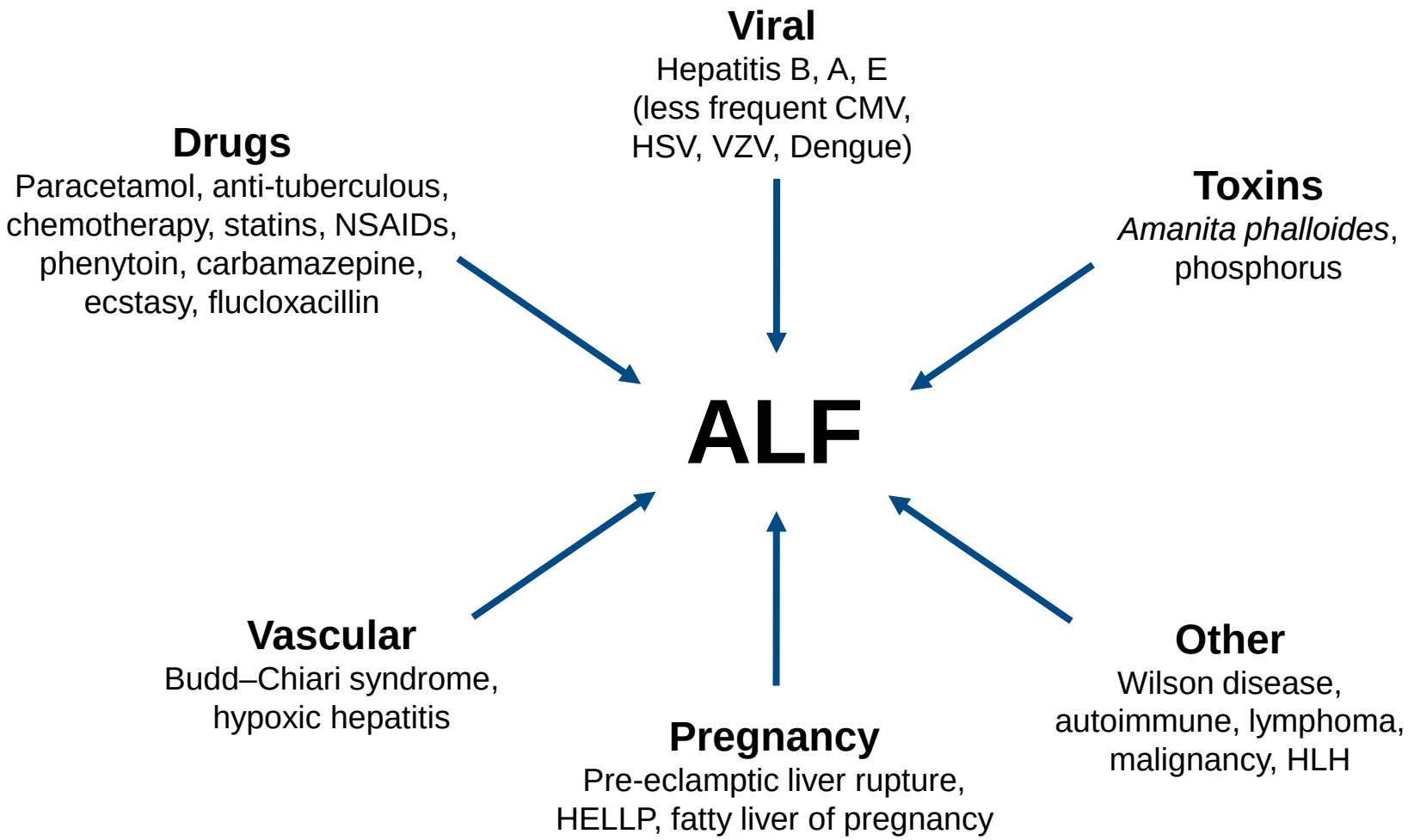
Burden of ALF in Europe

- Rare syndrome whose true prevalence across Europe is unknown
- Incidence of virally induced ALF has declined substantially in Europe
  - remains the most common cause worldwide
- Most frequent etiology of ALF in Europe is now drug-induced liver injury (DILI)

Principal aetiologies of ALF



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Aetiology of ALF varies with geography

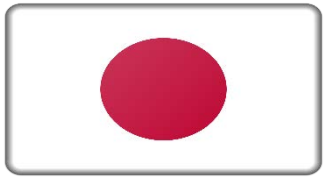
Top three causes of ALF in selected countries

Bangladesh
HEV 75%
HBV 13%
Unknown 6%

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%

*'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

Guidelines

Key recommendations

Topics

1. Assessment and management at presentation
2. Organ-specific management
   - Cardiovascular
   - Respiratory
   - Gastrointestinal
   - Metabolic
   - Acute kidney injury and renal replacement therapy
   - Coagulation
   - Sepsis, inflammation, and anti-inflammatory
   - The brain in ALF
3. Artificial and bioartificial liver devices
4. Liver transplantation

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Assessment and management at presentation

- **Úvodný manažment**
  - Exclude cirrhosis, alcohol-induced liver injury, or malignant infiltration
  - Initiate early discussions with tertiary liver/transplant center
  - Screen intensively for hepatic encephalopathy
  - Determine etiology
    - To guide treatment and determine prognosis
  - Assess suitability for liver transplant
  - 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

Determine etiology to guide treatment, especially LT

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 LT **No indication for emergency LT**

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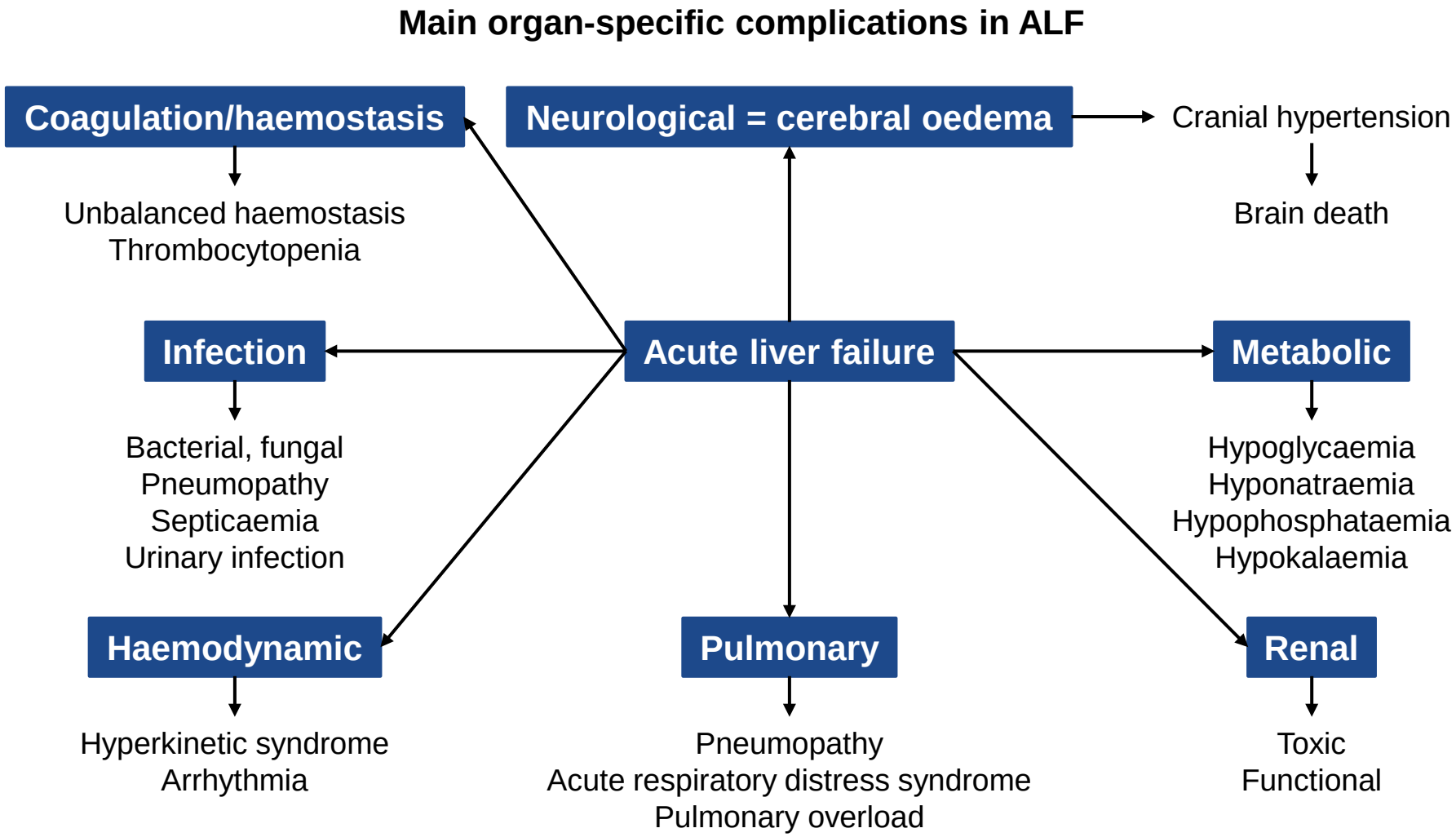
Organ-specific management



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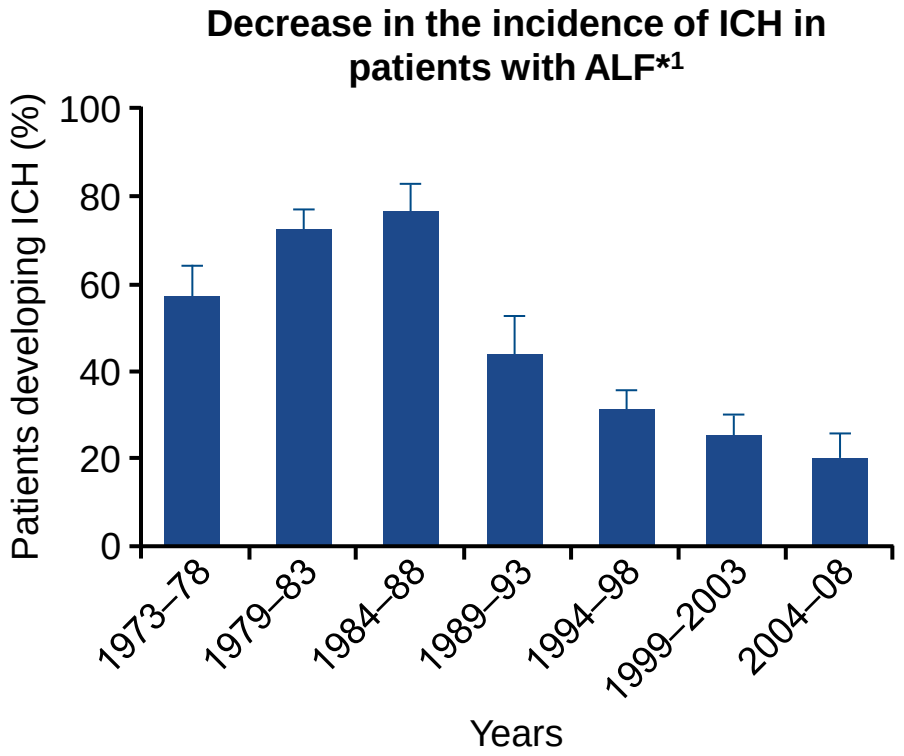
The brain in ALF: hepatic encephalopathy

- 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

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



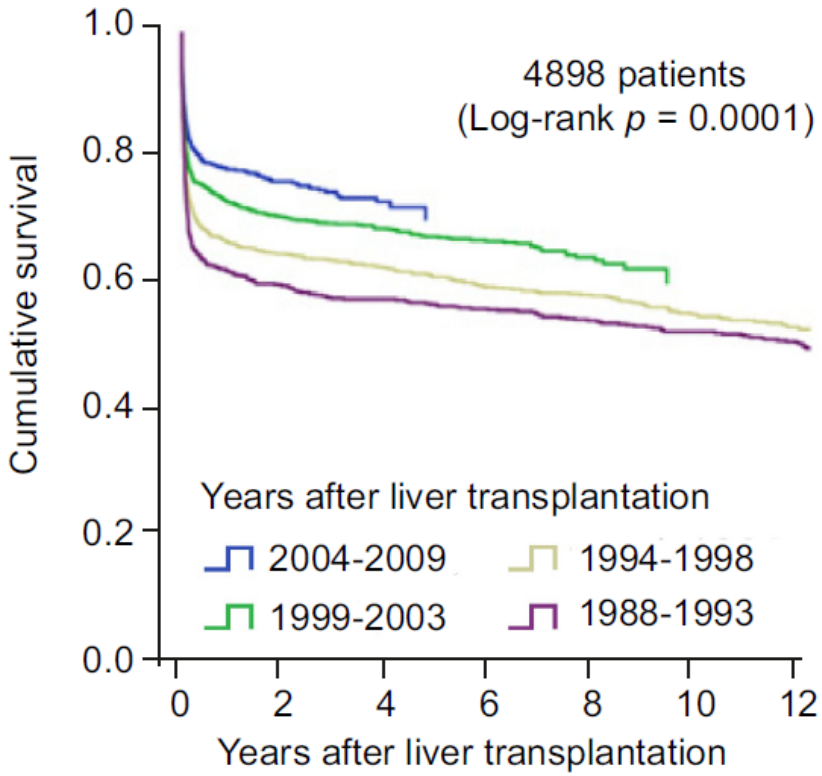
*Proportion of 1,549 patients with ALF developing clinical signs of ICH. Error bars are 95% CI; p<0.00001

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

Impact of liver transplantation in ALF

- LT has been the most significant development in the treatment of ALF in 40 years and has transformed survival
- 1-year survival following emergency LT for ALF is now around 80%
- Selection for LT depends on:
  - Predikcia prežitia bez transplantácie
  - Prežívanie po LT
  - Zváženie, či pacient nie je príliš chorý na transplantáciu

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

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, klesajúce aminotransferases, vzostup bilirubin and INR, zlé prognostické kritériá – pacienta treba urgentne konzultovať s TC

Factor	Clichy	King's College	Japanese
Age	+	+	+
Etiology	-	+	-
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