Acute liver failure

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Conflicts of interest

- Research grants:
  - Roche, Astellas, Ferring, Novartis, Janssen-Cilag, Abbvie, Gilead
- Consultancy Agreements:
  - CAF, Intercept, Gore, BMS, Abbvie, Novartis, MSD, Janssen-Cilag, Promethera Biosciences, Ono Pharma, Durect, Gilead

Clinical Practice Guidelines

EASL JOURNAL OF HEPATOLOGY

EASL Clinical Practical Guidelines on the management of acute (fulminant) liver failure☆

European Association for the Study of the Liver*

Summary

The term acute liver failure (ALF) is frequently applied as a generic expression to describe patients presenting with or developing an acute episode of liver dysfunction. In the context of hepatological practice, however, ALF refers to a highly specific and rare syndrome, characterised by an acute abnormality of liver blood tests in an individual without underlying chronic liver disease. The disease process is associated with development of a coagulopathy of liver aetiology, and clinically apparent altered level of consciousness due to hepatic encephalopathy. Several important measures are immediately necessary when the patient presents for medical attention. These, as well as additional clinical procedures will be the subject of these clinical practice guidelines.

Introduction

The term acute liver failure (ALF) is frequently applied as a generic expression to describe patients presenting with or developing an acute episode of liver dysfunction. It is characterised by a deterioration in liver function tests, and potentially associated with dysfunction in other organs. ALF is frequently, but often incorrectly used to describe both acute deterioration in liver function in patients with chronic liver disease (a condition that should be termed acute-on-chronic liver failure [AoCLF]), or liver involvement in systemic disease processes. Liver injury secondary to alcohol, which presents as alcoholic hepatitis, and other forms of AoCLF, can be difficult to distinguish from ALF on occasion. However, there are clear differences, and different forms of management are required.

Following extensive liver resection, patients with or without underlying chronic liver disease, may develop a clinical syndrome of jaundice, coagulopathy and hepatic encephalopathy (HE). The presentation is very similar to that of a post-transplant "small for size syndrome" scenario. These syndromes are not considered within the scope of ALF, but do feature in some ALF databases, such as the European Liver Transplant Registry (ELTR). Extensive liver trauma is also included in ALF databases, but is not a cause of ALF unless there is loss of both venous and arterial inflows.

In the context of hepatological practice, ALF refers to a highly specific and rare syndrome, characterised by an acute abnormality of liver blood tests in an individual without underlying chronic liver disease. The disease process is associated with development of a coagulopathy of liver aetiology, as opposed to the coagulation disturbance seen in sepsis, and clinically apparent altered level of consciousness due to HE. The condition of patients who develop coagulopathy, but do not have any alteration to their level of consciousness is defined as acute liver injury (ALI). Thus, the term ALF is appropriately used to describe patients who develop both coagulopathy and altered mentation and will be the subject of these clinical practice guidelines.

The features of coagulopathy, increased serum transaminases, abnormal bilirubin and altered levels of consciousness may be seen in patients with a variety of systemic disease processes. Therefore, if there is no primary liver insult, these patients should be considered to have a secondary liver injury and not ALF; management should focus on the treatment of any underlying disease processes.

The evidence and recommendations in these guidelines have been graded according to the Grading of Recommendations Assessment Development and Evaluation (GRADE) system [1]. The strength of recommendations reflects the quality of the underlying evidence. The GRADE system offers two grades of recommendation: strong (1) or weak (2) (Table 1). The CPGs thus consider the quality of evidence: the higher the quality of evidence, the more likely a strong recommendation is warranted; the greater the uncertainty, the more likely a weaker recommendation is warranted.

Definitions and main clinical features of ALF

The clinical course of ALF is initiated with a severe ALI. This is characterised by a two- to threetimes elevation of transaminases (as a marker of liver damage) associated with impaired liver function, i.e., jaundice and coagulopathy, in a patient without a

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† Juan Cordoba passed away during the preparation of this chapter.

Casus (1)

- Man, 56 jaar
- 2012 leversteatose (4-5 alcoholische consumpties/dag)

Na verblijf in Spanje partner met geelzucht (acute HAV) einde maart

10/04/2017 bil 18 mg/dl

INR 5.1

ALT 2400 u/l

HE graad 2 (interval met geelzucht ≤ 7d)

Echo bovenbuik : nl

Toxico screening paracetamol : 9.2 mg/l

Op lijst dringende LTx

Casus (2)

- Onder behandeling met N acetylcysteine
  - Geen HE
  - INR 2,0
  - Bil 20 mg/dl

  Van wachtlijst LTx
- Progressief
  - HE graad 1
  - INR 2.7
  - Bil 40 mg/dl
  - Bloedplaatjes 48
  - Echo bb : cirrose met ascites en splenomegalie
- LTx 17/05/2017 wegens subacuut leverfalen.

Definitions

No underlying chronic liver disase (dd ACLF)

- Acute liver injury (ALI) =
  - ALT elevation
  - Bilirubin elevation
  - INR > 1.5
- Acute liver failure :
  = ALI + hepatic encephalopathy *

*Initial mental alterations may be subtle !

Katoonizadeh and Nevens F, Liver Int 2006

No ALF (different clinical picture and prognosis)

- Following extensive liver resection
- Small for size syndrome after livertransplantation
- Multiple organ failure (heat shock)
- Hypoxic hepatitis (right heart dysfunction)
  - The absence of documented episode of hypotension does not exclude this condition !
  - AST > 10,000 IU/l

Also ALF (despite underlying chronic liver disease)

- De novo autoimmune hepatitis :
  start steroids but stop and consider LTx if lack of improvement < 7d
- Budd-Chiari syndrome :
  pain, ascites, hepatomegaly
- Wilson :
  high bilirubin/alkaline phosphatase (hemolysis)

Clinical picture

- Interval bilirubin – encephalopathy

	Lab test	Aetiology	Prognosis
Hyperacute (< 7d) and Acute (1-4 wks)	ALT +++/INR +++	HAV HBV	Cerebral oedema
Subacute * (5-12 wks)	Bilirubin ++	DILI/unknown	Worse

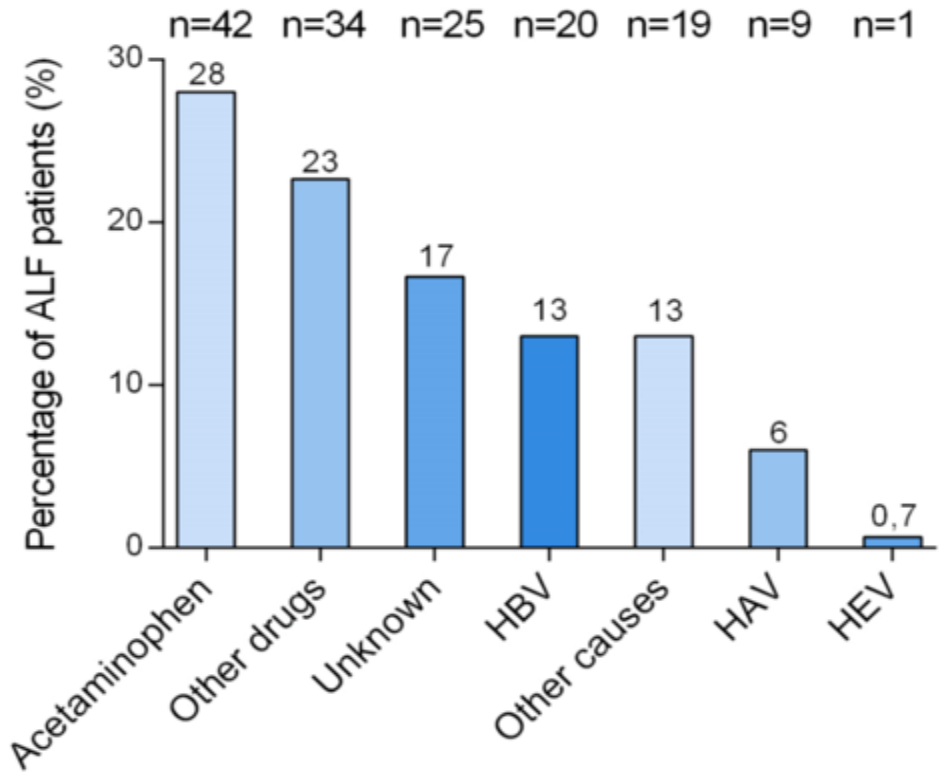
* - Shrinking liver volume mimicks cirrhosis !

(Splenomegaly, Ascites)

- Acute encephalopathy indicates surinfection with very short window for LTx

Aetiology

- Overall - 50% unknown
  - 20 % viral
  - 20 % DILI (especial paracetamol)
    toxico screening ad admission
- UZ Leuven



Van Hauwaert A and Nevens F, 2015

Need of transjugular biopsy ?

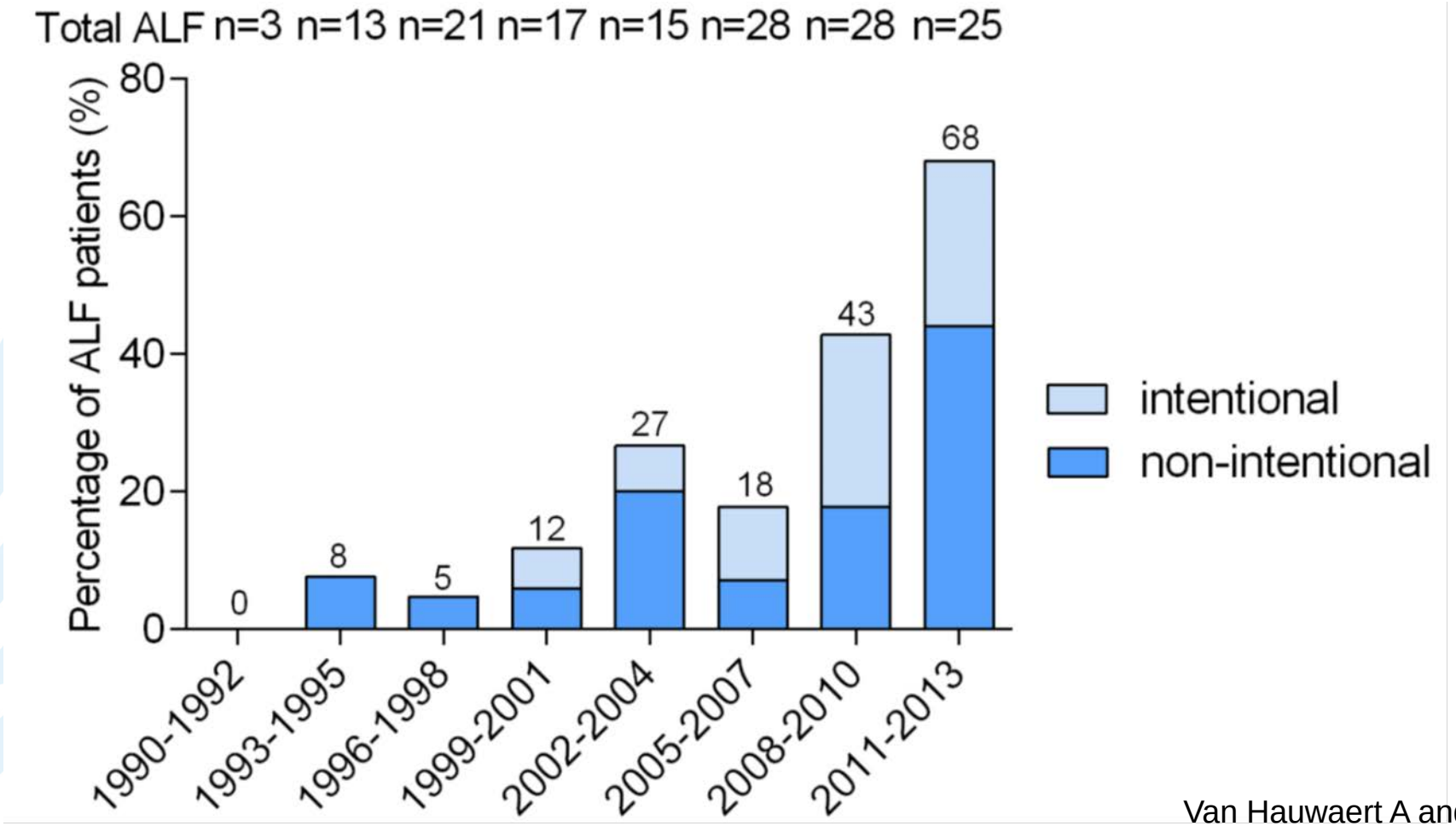
- NO : not helpfull for prognosis (sample error)
- But :
  - To exclude
    - Alcohol induced ALI
    - Malignany (metastatic breast cancer, lymphoma)

      massive hepatomegaly, alkaline phosphatase

Paracetamol

- Suicidal or accidental
- Increased sensitivity (decreased glutathione)
  - Fasting
  - Alcohol
  - Phenytoin
- Usually undetectable at time of presentation
- Clinical picture :
  - ALT > 10.000 IU/l
  - Metabolic acidosis – lactaat elevated
  - Acute kidney injury

Paracetamol (UZ Leuven)



Van Hauwaert A and Nevens F, 2015

DILI

- Types
  - Hepatocellular : acute
  - Cholestatic : subacute
- Several weeks after ingestion !
- Drugs :
  - Isoniazid
  - Nitrofurantoin, ketoconazole
  - Phenytain, valproate
  - Non-steroidal anti inflammatory drugs
  - Propylthiouracil
    disulfiram
  - Herbal medicine – nutritional supplements

Aetiology (others)

- HBV
  - reactivation (rituximab)
- HAV
  - older patients
  - homosexuals
- HEV
  - Probably underestimated

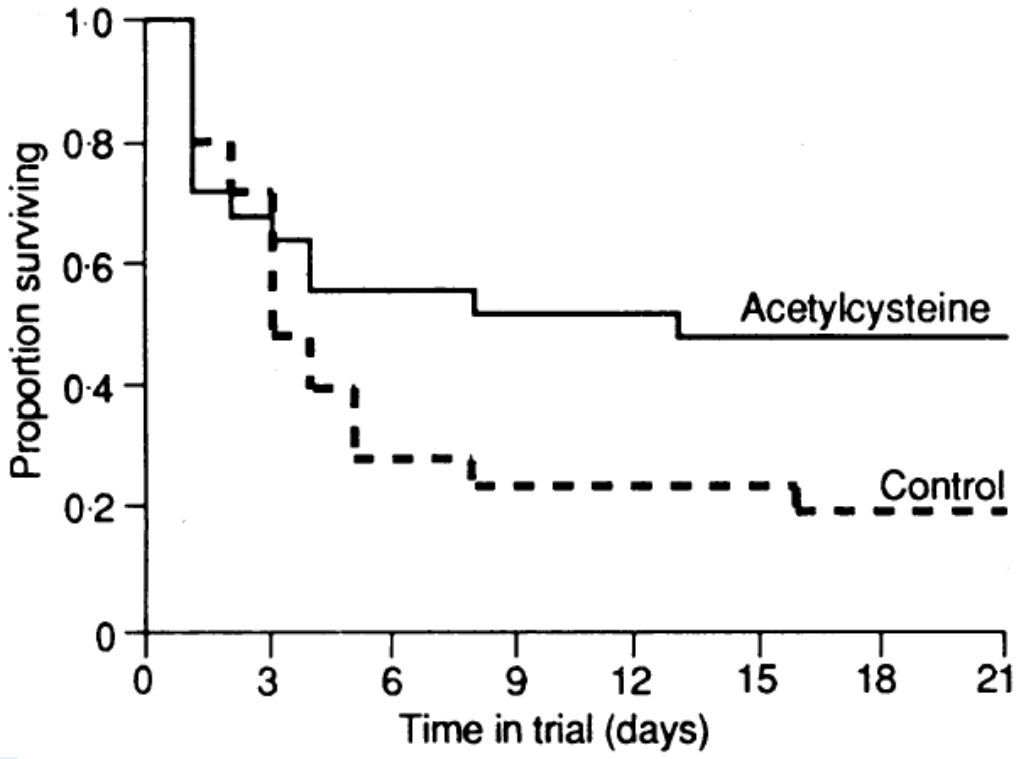
Prognosis and Treatment

- Clinial review twice daily
- Urine output
- Correction of hypoglycemia
  hyponatremia
- No routine use of frozen plasma or other coagulation factors
- No prophylactic antibiotics
  but low threshold to start
  antifugal therapy in case or prolonged critical care

- Grade 3 or 4 hepatic encephalopathy : intubation
- In case of intracranial hypertension :
  - Mannitol
  - Short-term hyperventilation

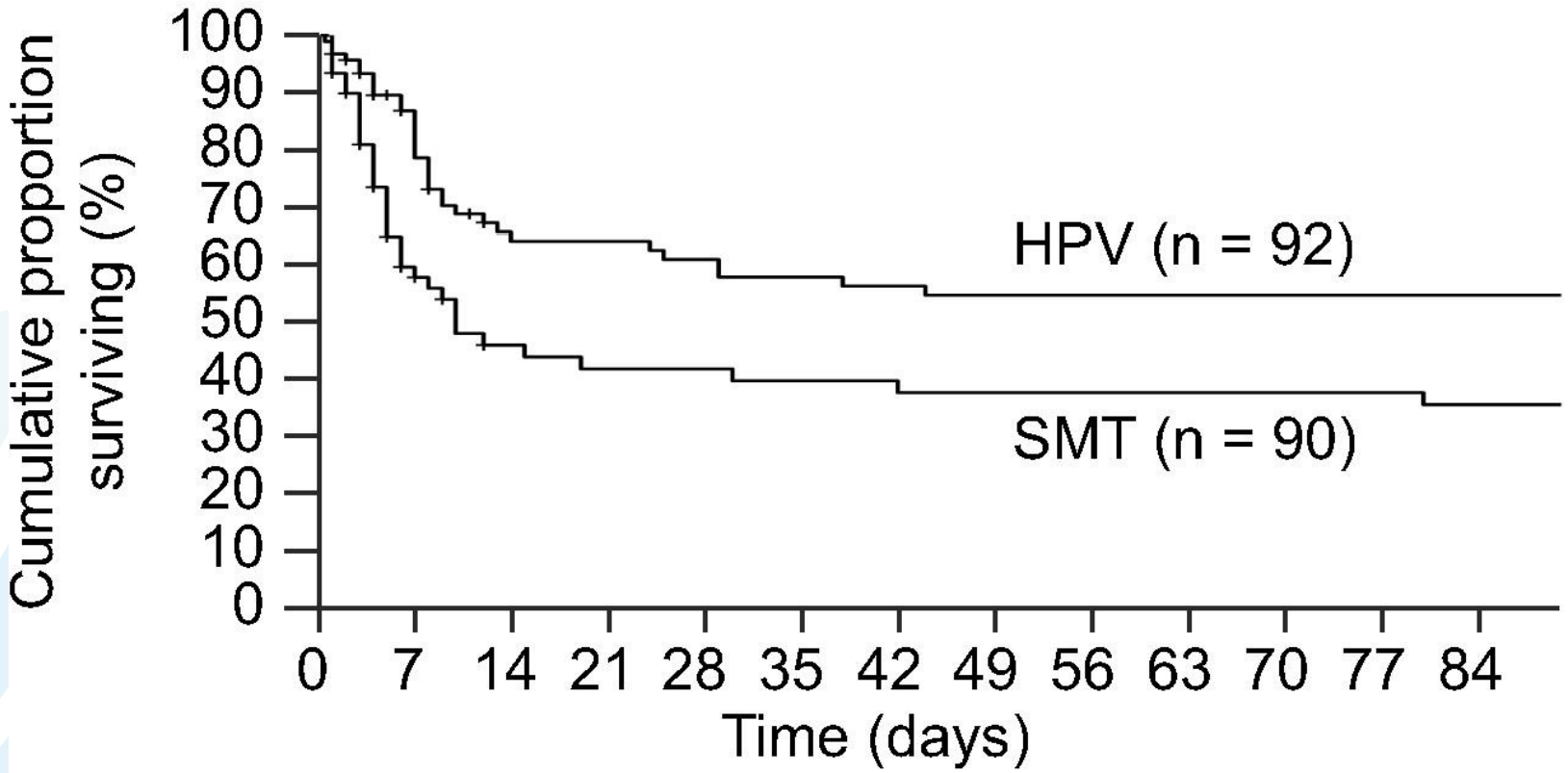
Treatment

- Acetylcysteine



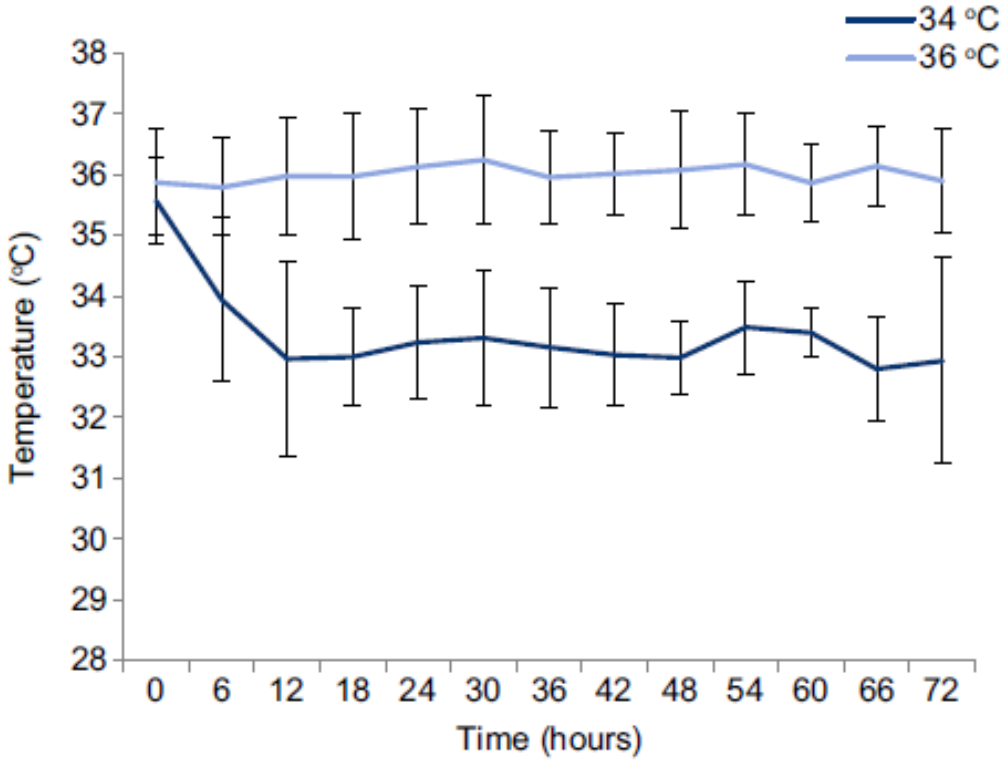
Keays P, BMJ 1991

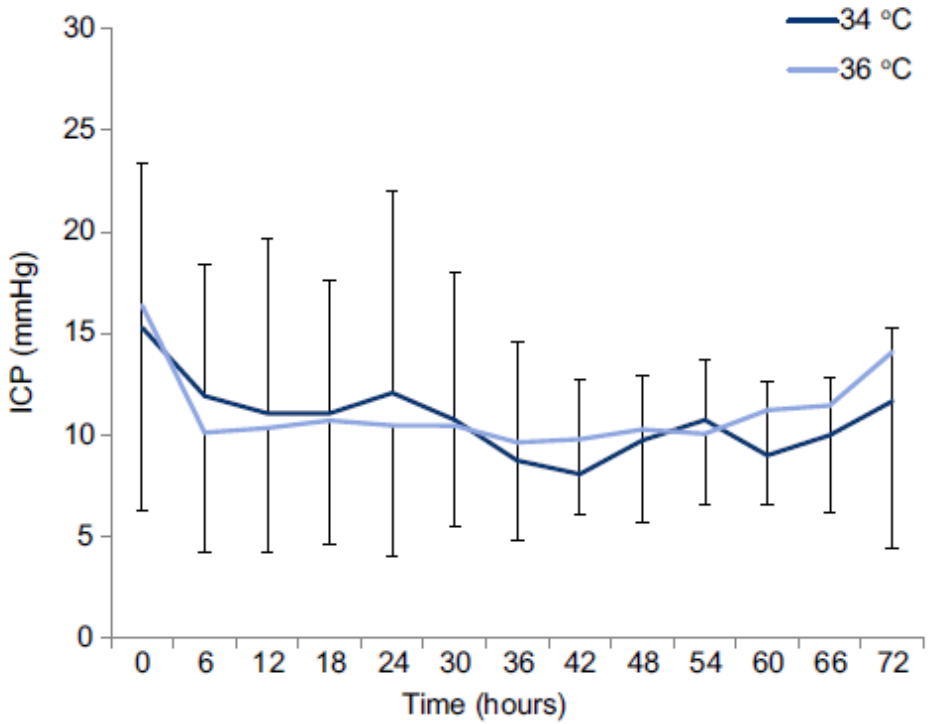
Plasma exchange



Stolze Larsen F, J Hepatol 2016

Hypothermia





Bernal W, J Hepatol 2016

Emergency liver transplantation

- Criteria

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

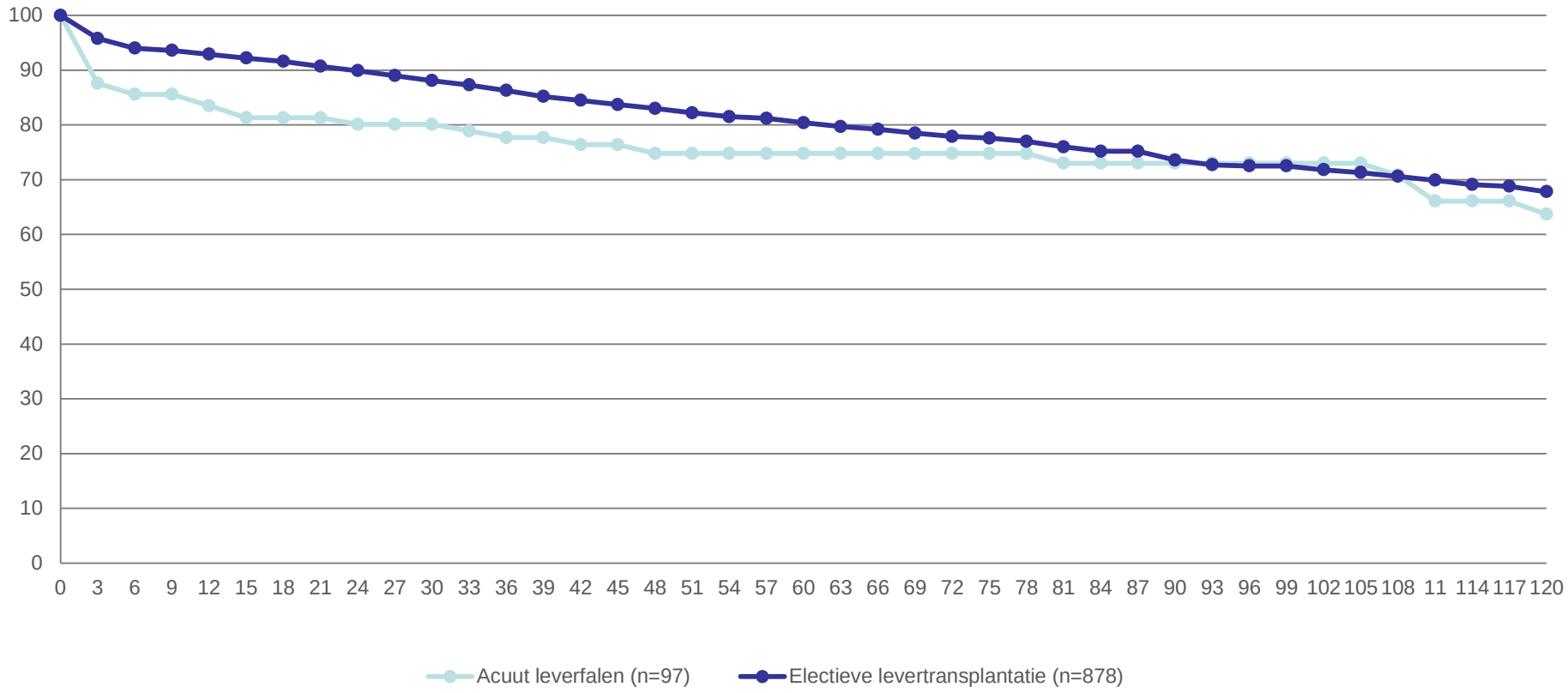
  or
- Factor V <30% if age >30 year

EASL Guidelines, J Hepatol 2017

Emergency liver transplantation

- Results

Tienjaars patiëntenoverleving (1997-2016) voor transplantatie omwille van acuut leverfalen versus electieve levertransplantatie (zonder gecombineerde of retransplantaties) Bron: UZ Leuven



Multiple choice (1)

- Wat bepaalt de prognose van een “acute liver injury” ?
  - INR
  - Bilirubine
  - ALT
  - Hepatische encephalopathie

Multiple choice (2)

- Wat heeft de slechtste prognose in geval van ALF?
  - HBV
  - Subacuut leverfalen
  - Paracetamol
  - Hyperacuut ALF type HAV

Conclusions (1)

- The development of encephalopathy is the requirement for ALF but initial mental alterations may be subtle
- Subacute liver failure mostly due to drug induced ALF is the most frequent type, has the worse prognosis and mimicks cirrhosis
- Paracetamol induced ALF is characterized by metabolic acidosis and acute kidney injury

Conclusions (2)

- Acetylcysteine is the only proven non surgical therapy for ALF

- The only liver saving therapy for ALF is emergency liver transplantation