# Dutch liver Week 2019
# Acute liver failure

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# Disclosures

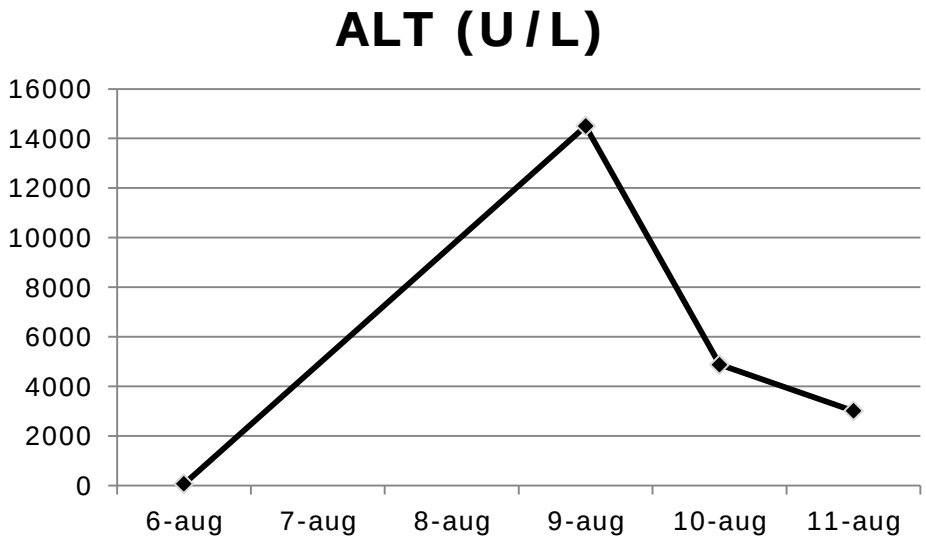
Research grant Gilead and Astellas

# Learning objectives presentation

- Definition acute liver failure (ALF)
- Aetiology
- Assessment and management
- Outcome

# Clinical case ALF

- 52-year old Asian woman
- Admitted: (viral) gastroenteritis and dehydration
- Mild elevated transaminases (ALT 62 U/L and AST 83 U/L)




09-08

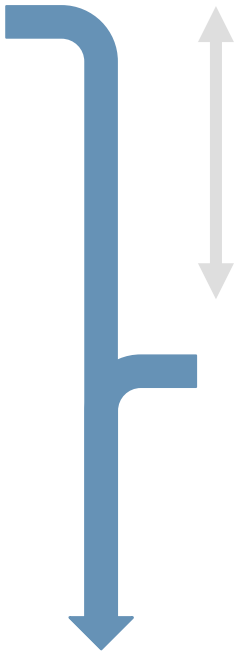
- INR > 10
- Bilirubin 72 µmol/L
- Ammoniak 482 µmol/L
- Glucose 3.1 mmol/L
- pH 7.21

# 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)



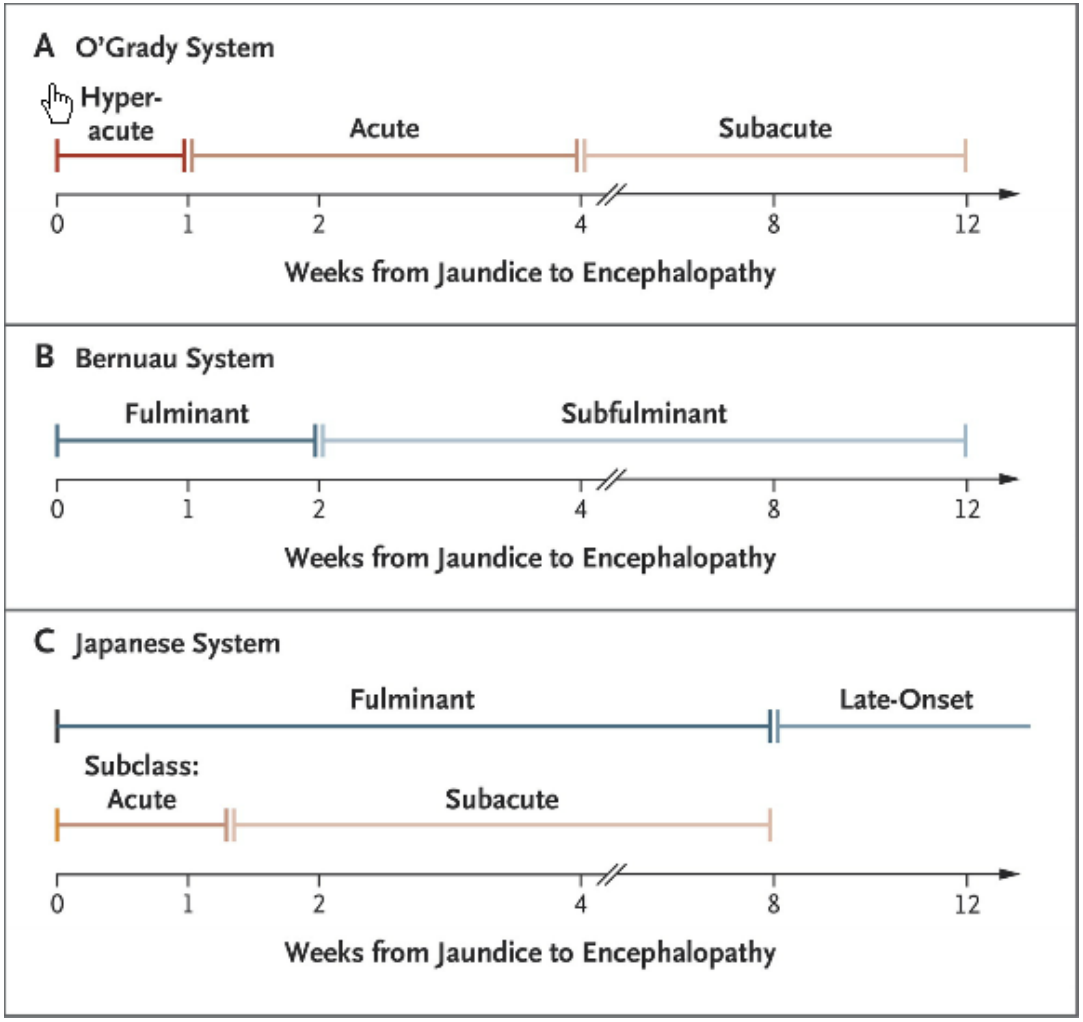
Up to 12 weeks post-jaundice, depending on sub-classification

**HEPATIC ENCEPHALOPATHY (HE)**

**ALF**

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

# Classification of ALF

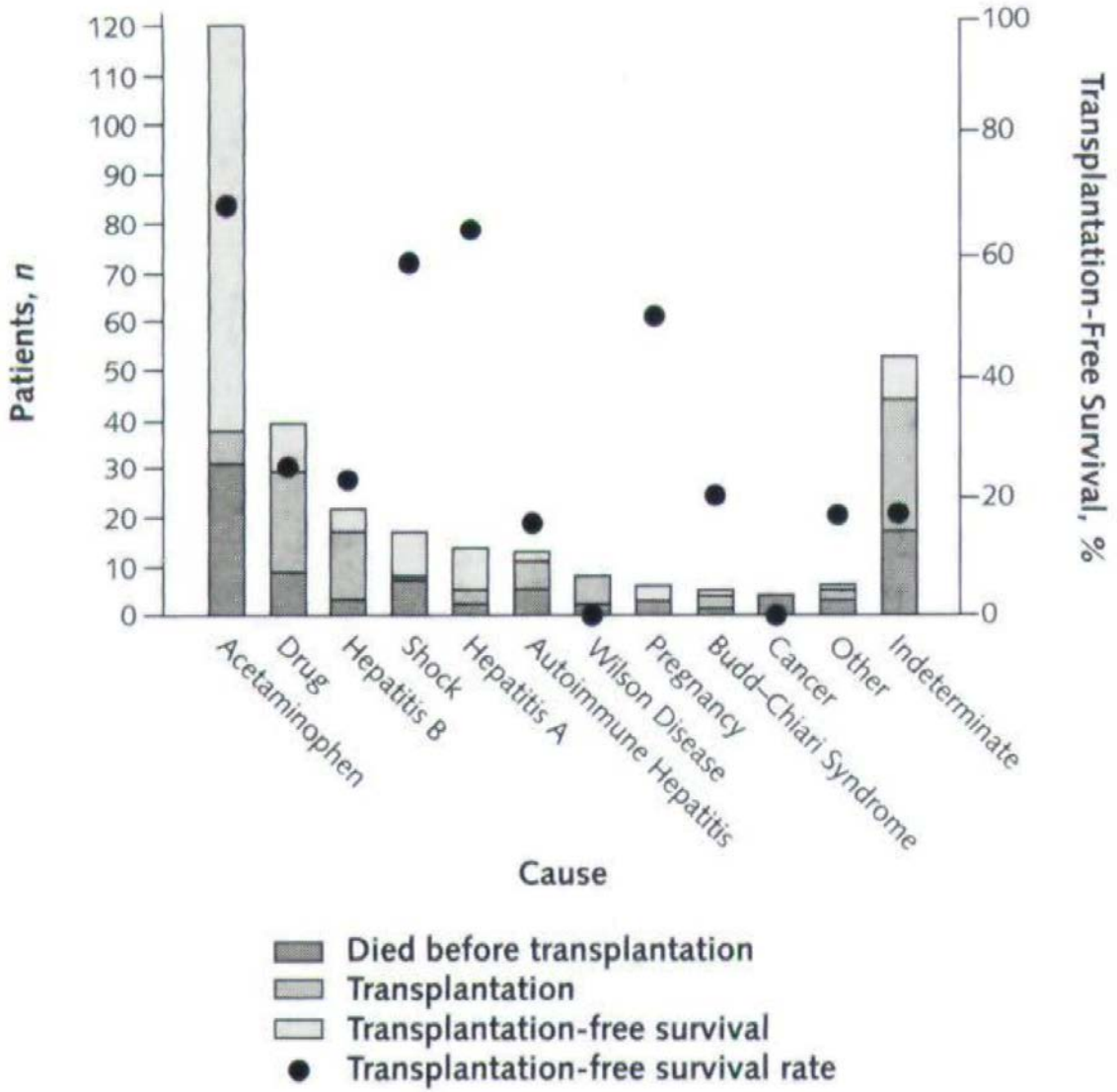


# Sub-classifications of ALF

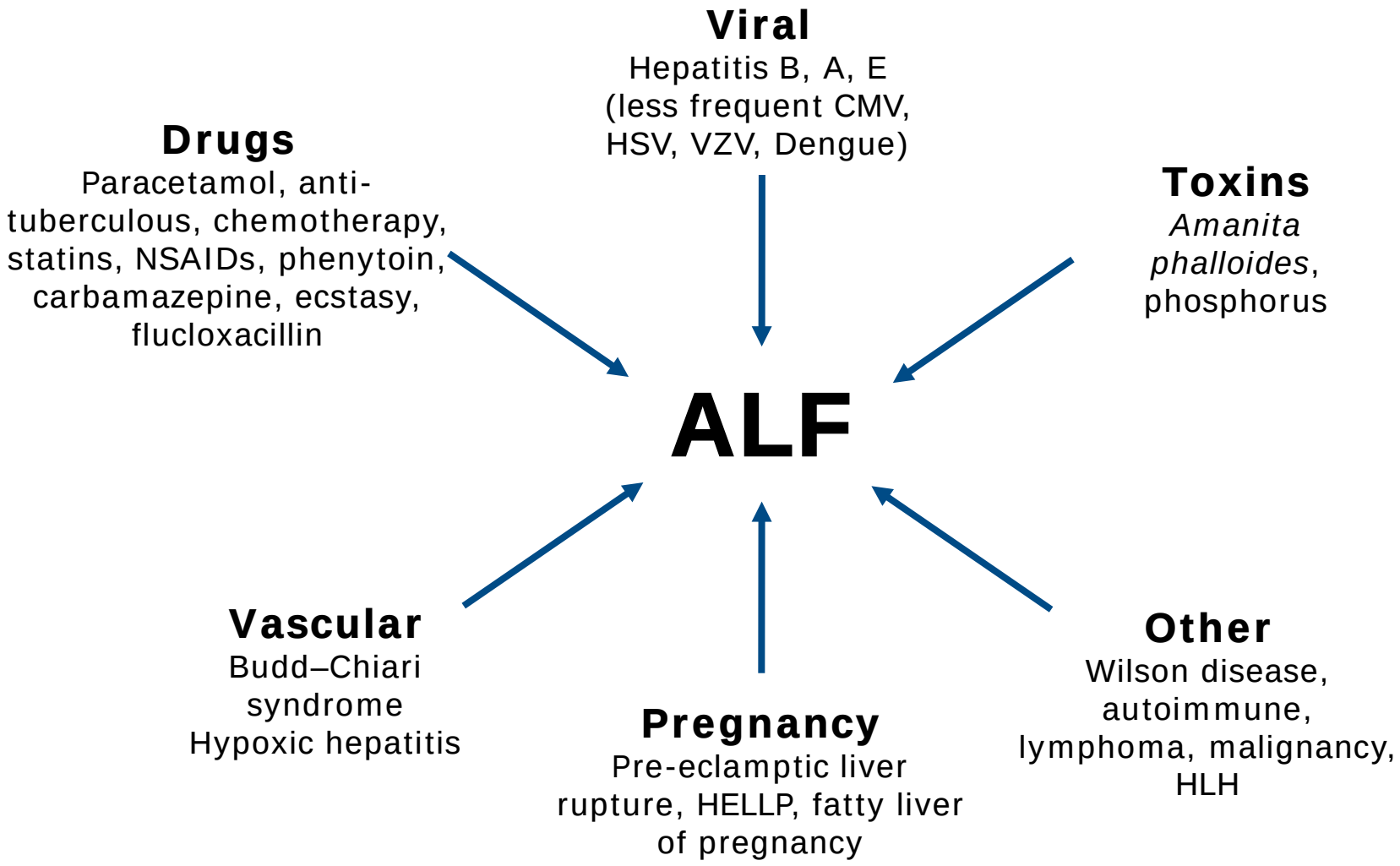
## Weeks from development of jaundice to development of HE[1]


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

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


Patients, n
120
110
100
90
80
70
60
50
40
30
20
10
0
100
80
60
40
20
0
Transplantation-Free Survival, %
Acetaminophen
Drug
Hepatitis B
Shock
Hepatitis A
Autoimmune Hepatitis
Wilson Disease
Pregnancy
Budd–Chiari Syndrome
Cancer
Other
Indeterminate
Cause
Died before transplantation
Transplantation
Transplantation-free survival
Transplantation-free survival rate

# Principal aetiologies of ALF




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

# Aetiology ALF Erasmus MC, n=115

| Oorzaak | Aantallen (%) |
|---|---|
| Hepatitis-B-virus | 24 (21) |
| Hepatitis-A-virus | 2 (2) |
| Overige virussen | 4 (4) |
| Paracetamol | 14 (12) |
| Medicamenten | 17 (15) |
| Overig bekend | 21 (18) |
| Onbekend | 33 (29) |

# 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

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 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?**

**Algemeen laboratoriumonderzoek**

- **Bloedgroep/resus/irregulaire AL/coombstest, Hb, Ht, leukocytendifferentiatie, trombocyten, natrium, kalium, ureum, creatinine, calcium, fosfaat, bilirubine, alkalisch fosfatase, gammaGT, ASAT, ALAT, LDH, amylase, CPK, cholesterol, glucose**
- Voorts:
  Stollingsonderzoek (APTT, PTT, fibrinogeen, aanvullend FDP, AT III en factor V), eiwitspectrum, albumine, TSH, lactaat, arterieel ammoniak, arteriële bloedgasanalyse

**Specieel laboratoriumonderzoek (gericht op oorzaak)**
(**vet gedrukt**: in eerste ronde (binnen enkele uren bekend): dun gedrukt: in tweede ronde).

- Viraal HAV: **anti-HAV IgM**
  HBV: **HBs-antigeen**, anti-HBs, **anti-HBcore**, HBe-antigeen, anti-Hbe, HBV DNA
  HCV: **anti-HCV**, HCV RNA
  HDV: anti-HDV, HDV RNA
  HEV: anti-HEV, HEV RNA
  Overig: **IgG/IgM**, CMV, HSV, EBV IgM, **anti-HIV**
- Voorts ANA, ASMA, AMA, ceruloplasmine, **toxicologiescreening** (serum + urine)

**Microbiologisch onderzoek**

- Kweken van bloed, urine, sputum, neus, ascites (indien aanwezig)

**Beeldvormend onderzoek**

- Echodoppler/CT-bovenbuik
- Gastroscopie, alleen op indicatie
- ECG
- X-thorax
- Consult neuroloog (klinische beoordeling, uitsluiten andere oorzaken van coma, derhalve is doorgaans EEG en CT-cerebrum noodzakelijk)
- Consult oogarts (bij patiënten < 40 jaar, spleetlamponderzoek vanwege KF-ring)

# Potentially Treatable Causes of ALF

- Acetaminophen
- HBV
- HSV
- Autoimmune Hepatitis
- Budd-Chiari Syndrome
- Amanita Phalloides
- Pregnancy-related ALF
- M. Wilson

# Clinical case ALF

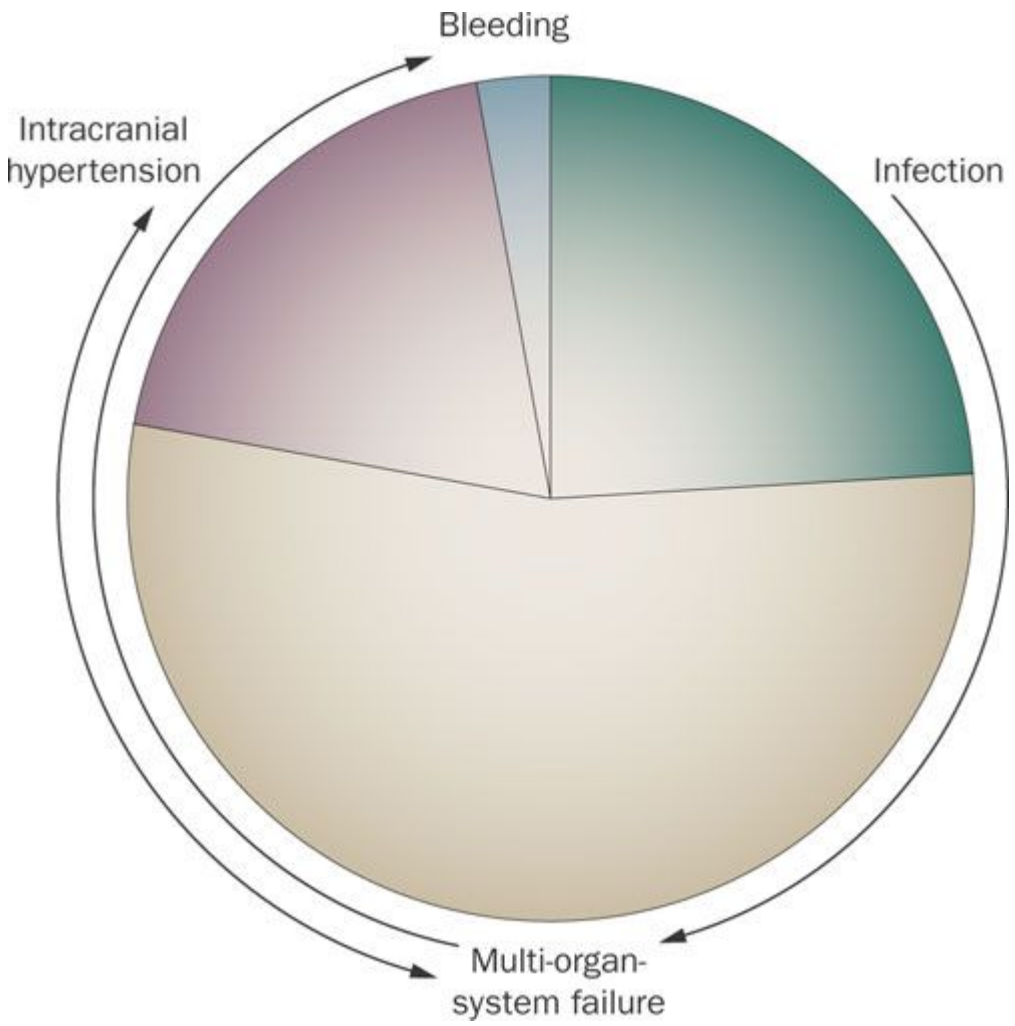
- Anamnesis: mushroom ingestion (Amanita phalloides)

At arrival UMCG:

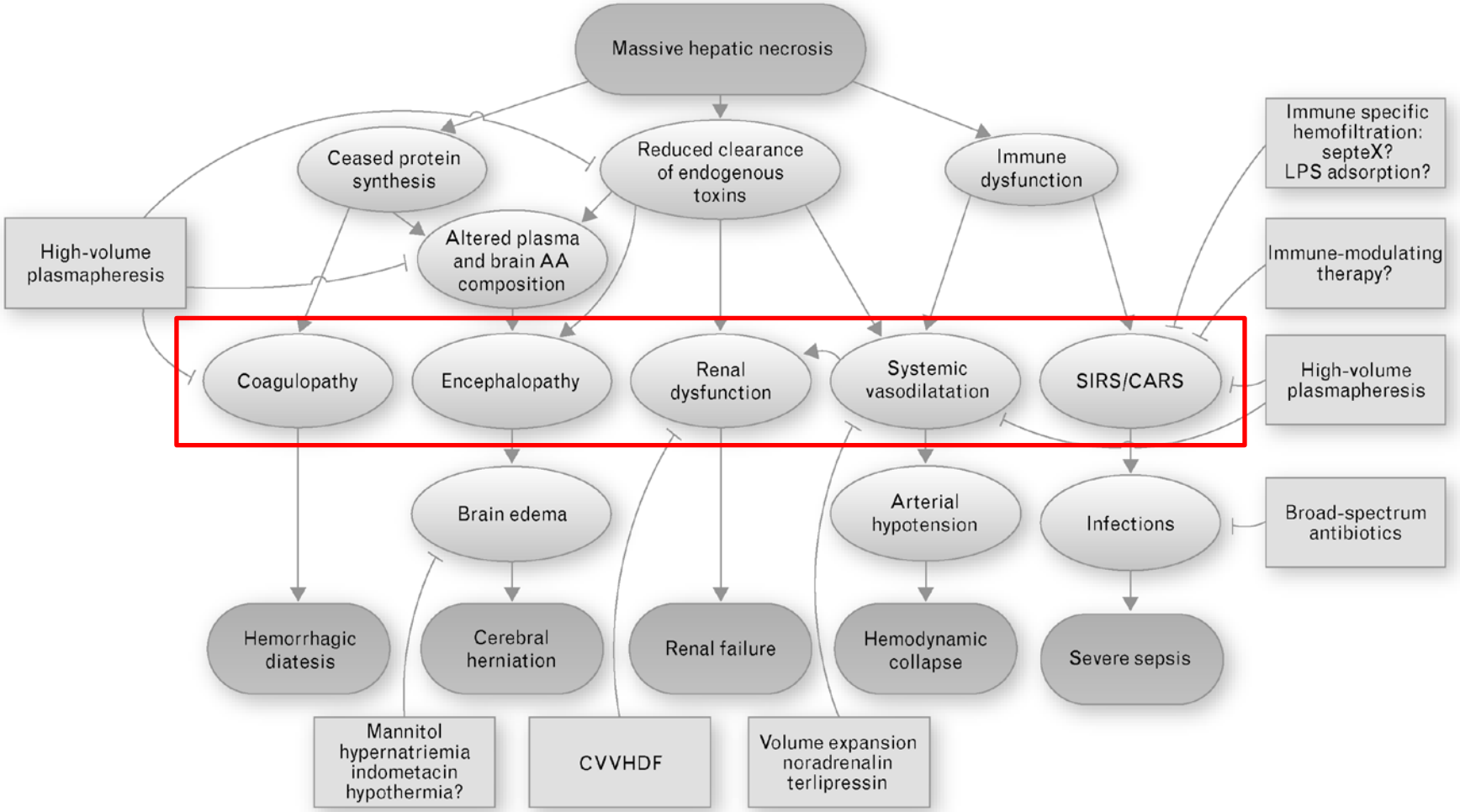
- Acute liver failure
- Hemodynamic instable
- Grade 4 coma
- Multi-organ failure

- Treatment sillibilin and NAC

# Causes of death in ALF



# ALF = multi-organ failure



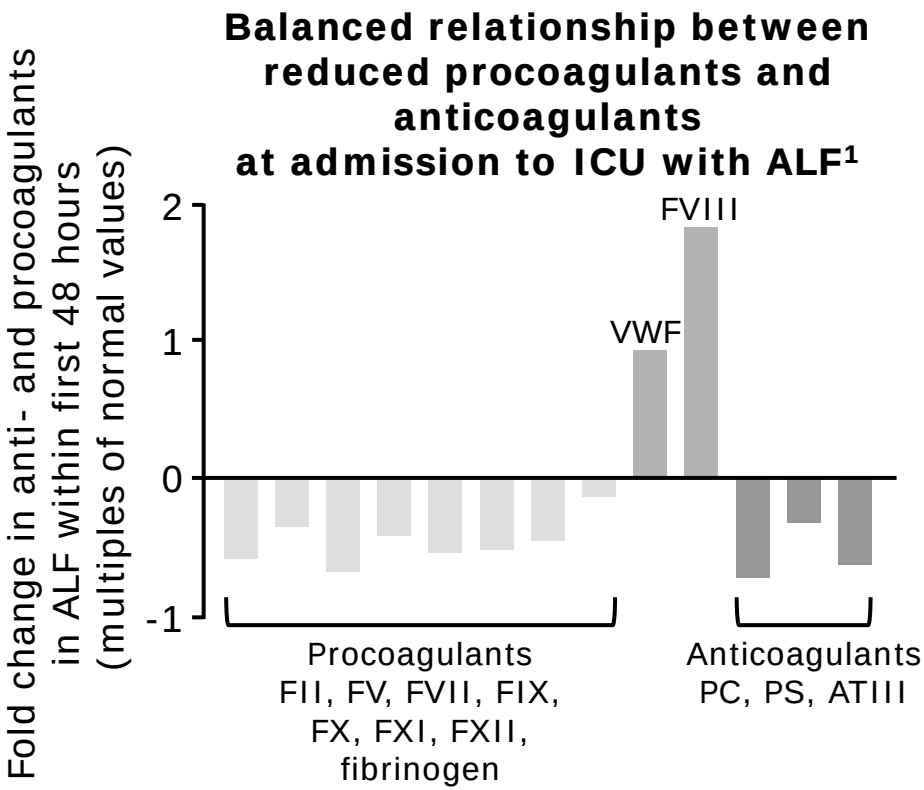

Larsen FS. Current Opinion in Critical Care 2011, 17:160–164

# Coagulation: monitoring and management

Rapid changes in PT or INR are characteristic of ALF
- Significant prognostic value

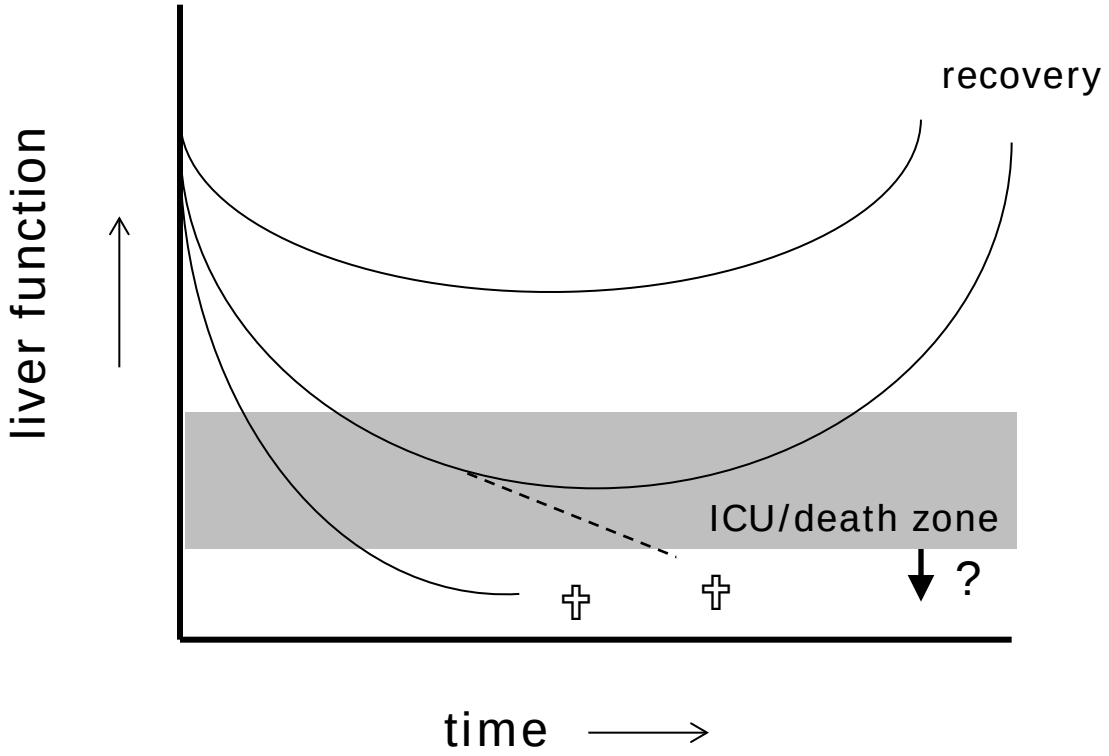
Common in ALF
- Thrombocytopenia
- Reduced circulating pro- and anti-coagulant proteins
- Increased PAI-1

Abnormal coagulation does not translate to increased risk of bleeding
- Most patients' coagulation is normal despite abnormal INR and PT




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

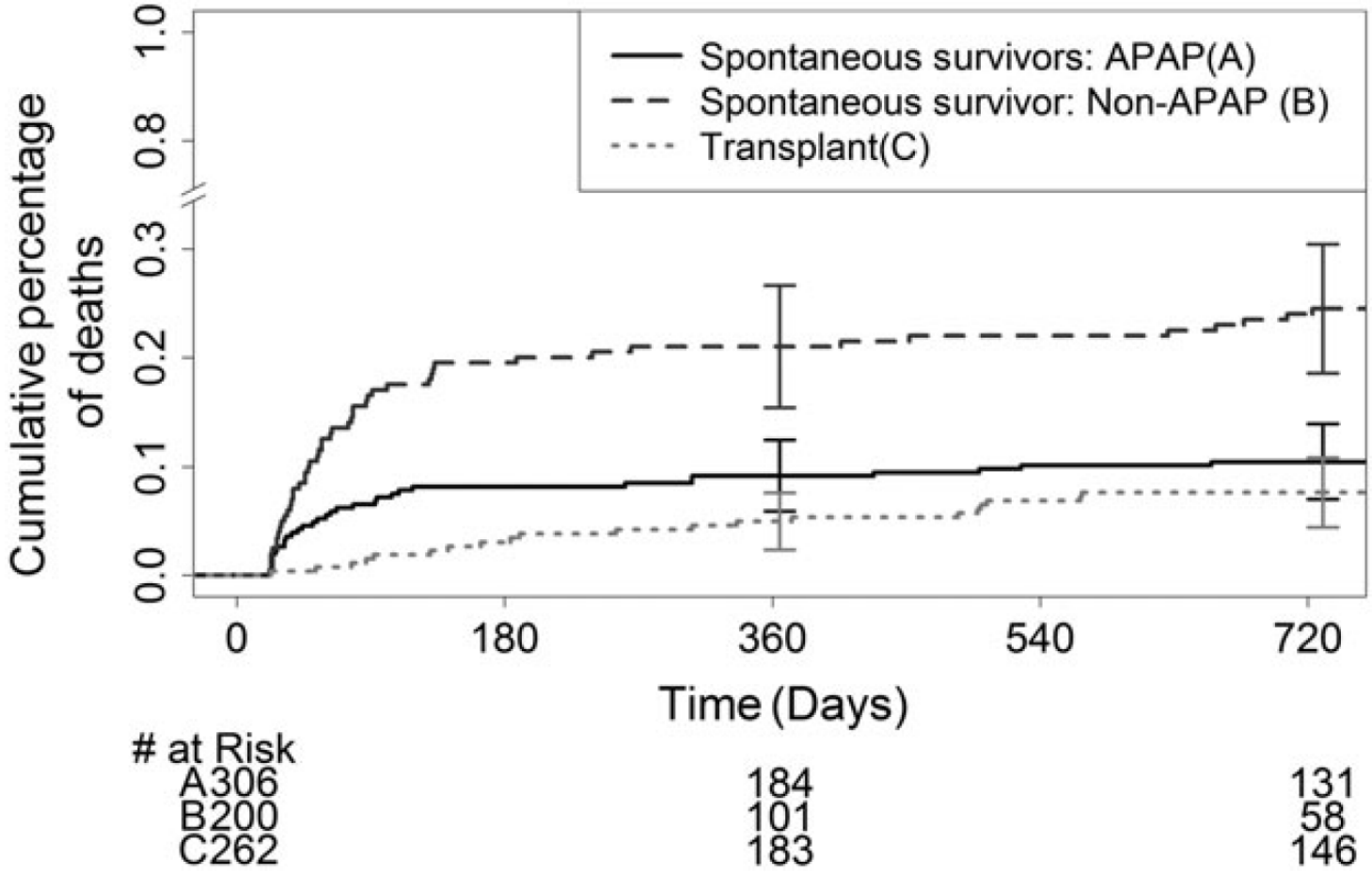
# ALF: Enormous but Finite Capacity for Recovery



# Prognosis of ALF

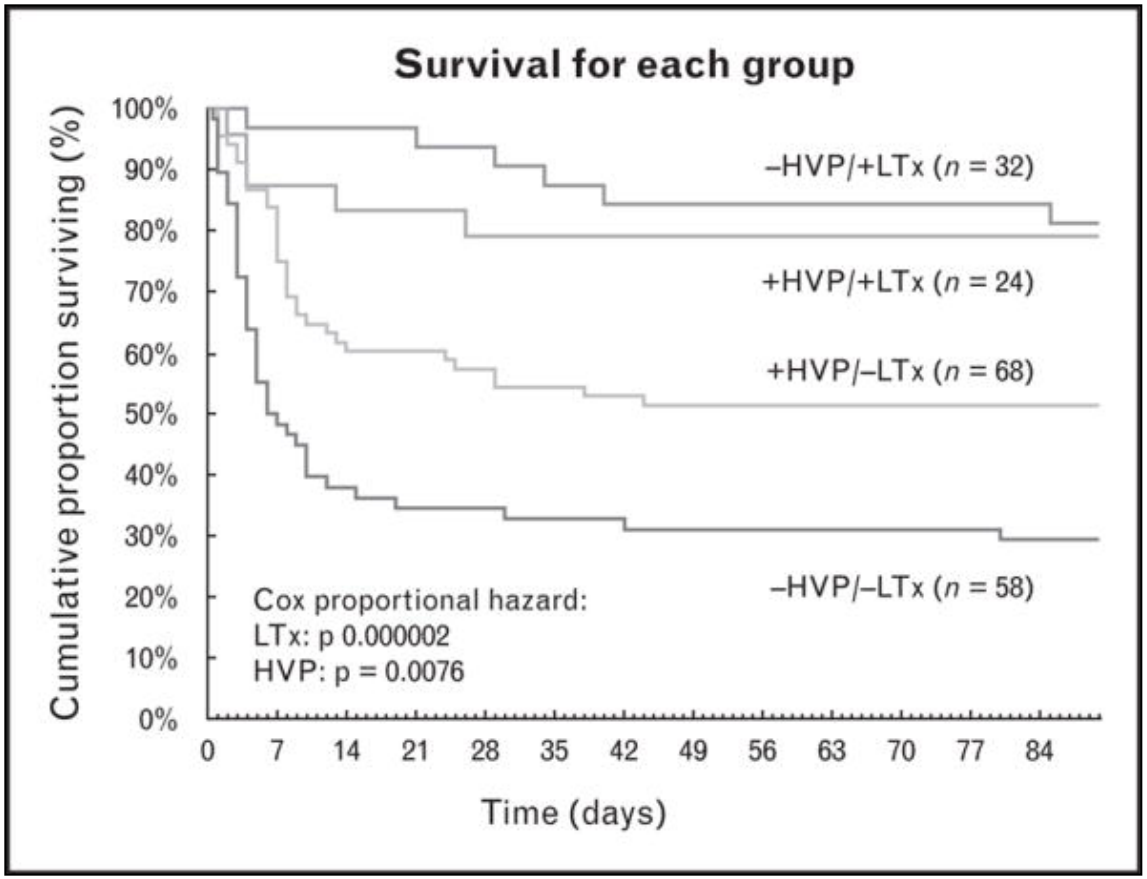
- Overall outcome of ALF is improving
- Acute Liver Failure Study Group (USA, 1300 pts)
  - Spontaneous recovery 45%
  - OLTx 25%
  - Died without OLTx 30%
- Mortality stage III/IV encephalopathy >80%

# Long-Term Outcome of Acute Liver Failure




Fontana RJ. Liver Transplantation 2015;35:370

# High-Volume Plasma Exchange in ALF




- single center study
- 11 years to complete
- 182 pts randomized
- PE 10 l FFP/d x3 d

Willars, Current Opinion in Critical Care. 2014; 20:202-9
Larsen et al, Hepatology 2010;52 S1:376A

# Criteria voor HU LTX

## 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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**High Urgency Liver**

**In case of retransplantation ≤ 14 days or > 14 days:**

Cause of graft failure:

○ PNF ○ HAT ○ Portal Vein Thrombosis ○ ITBL
○ Other

Previous transplant:

Donor ETnr: Transplant date:

○ Post-mortem ○ Living Age yrs Weight kg

CIT hrs min WIT (ice to vascularization) min

Graft quality ○ Good ○ Moderate ○ Poor

Graft type ○ Whole ○ Reduced size ○ RL (V-VIII) ○ LL (I-IV)
○ LLS (II + III) ○ ERL (I, IV-VIII)

*(Make sure the transplantation has been registered in ENIS and the recipient is put back on the waiting list)*

**In case of first transplant:**

Clichy criteria can also be used instead of King's College criteria for non-paracetamol and non- viral diseases, depending on data availability and centers possibilities.

**Cause:**

○ **Paracetamol** ***Laboratory values at time of request:***

fulfilling King's College Criteria:

☐ pH < 7.30

Or

All 3 criteria:

☐ 1) PT (Prothrombine Time) > 100 sec or INR 6.5

☐ 2) S-Creatinine> 3.4 mg/dL or >300 µmol/L mg/dL µmol/L

☐ 3) Encephalopathy III or IV Encephalopathy grade:

○ None ○ I ○ II ○ III ○ Iva ○ IVb

○ **Non-paracetamol:** ***Laboratory values at time of request :***

fulfilling King's College Criteria:

☐ PT (Prothrombine Time) > 100 sec or (INR > 6.5)

Or

At least 3 of the criteria below:

☐ 1) Age < 10 yrs or > 40 yrs

☐ 2) S-Bilirubin >17.5mg / dL (>300 µmol/L)

☐ 3) Onset jaundice > 7 days before Encephalopathy Onset clinical jaundice

Onset encephalopathy

Encephalopathy grade:

○ None ○ I ○ II ○ III ○ Iva ○ IVb



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**High Urgency Liver**

☐ 4) PT > 50sec (INR >3.5)

☐ 5) Non-paracetamol induced:

- ○ NANB hepatitis
- ○ halothane
- ○ idiosyncratic drugs
- ○ toxin induced
- ○ other

Or fulfilling Clichy Criteria:

☐ Encephalopathy gr. III or IV Encephalopathy grade:

○ None ○ I ○ II ○ III ○ Iva ○ IVb

AND

☐ FV ≤ 20% for recipients < 30 yrs Factor V %

☐ FV ≤ 30% for recipients ≥ 30 yrs

○ **Fulminant viral hepatitis:** ***Laboratory values at time of request :***

○ HAV ○ HBV ○ HCV
○ Other

fulfilling Clichy Criteria:

☐ Encephalopathy gr. III or IV Encephalopathy grade:

AND ○ None ○ I ○ II ○ III ○ IVa ○ IVb

☐ FV ≤ 20% for recipients < 30 yrs Factor V %

☐ FV ≤ 30% for recipients ≥ 30 yrs

**Other causes:**

○ Acute M. Wilson
○ Acute Budd-Chiari Syndrome
○ Unknown cause/ other life-threatening liver trauma
○ Anhepatic state secondary to toxic liver syndrome
○ Hepatoblastoma

- ☐ Recipient is <16 yrs old
- ☐ Hepatoblastoma proven in liver biopsy
- ☐ Recipient is a suitable candidate for liver transplantation after chemotherapeutical treatment Absence or complete resection of extrahepatic metastases
- ☐ Germany: not curable by partial liver resection

Proceed

- Persistence of accepted criteria associated with a poor prognosis
- Absence of co-morbidity independent of acute liver failure that would impact on survival
- Absence of complications of acute liver failure associated with reduced survival
- Absence of psychosocial profile suggestive of poor adaptation of rigour of post-transplant survival

Willars, Current Opinion in Critical Care. 2014; 20:202-9.

## Wait

- Patients showing sustained evidence of improvement of prognostic criteria in the absence of clinical deterioration
- Paracetamol induced acute liver failure patients who do not have grade 3 or 4 encephalopathy irrespective of severity of coagulopathy
- Patients with paracetamol induced acute liver failure and severe acidosis or elevated serum lactate that responds rapidly to resuscitative measures
- Most patients when the liver allocated is marginal, especially steatotic, non-ABO identical or split, ABO-incompatible or the donor is aged over 60 years

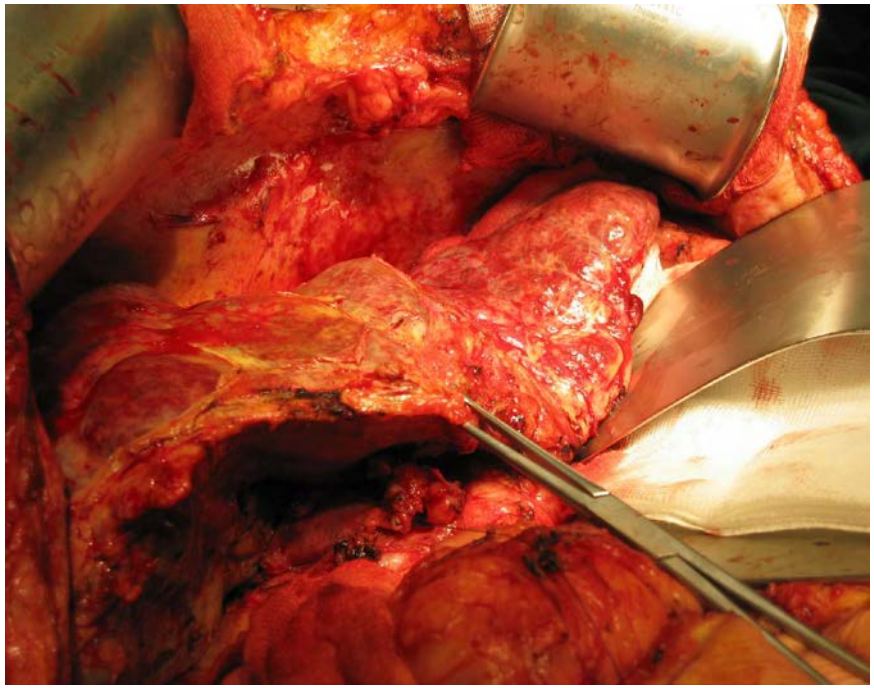
Willars, Current Opinion in Critical Care. 2014; 20:202-9.

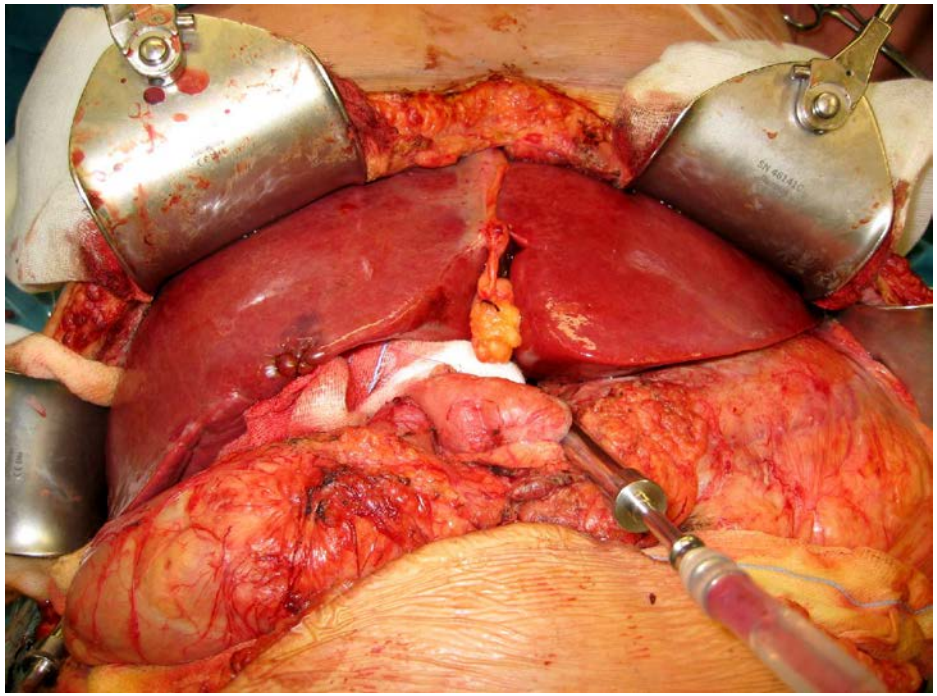
Stop

- Evidence of compromised brainstem function, especially fixed and dilated pupils
- Invasive fungal infection
- Rapidly escalating inotrope requirements
- Severe pancreatitis [usually in paracetamol-related ALF]

Willars, Current Opinion in Critical Care. 2014; 20:202-9.

# Liver transplantation





# Clinical case ALF

- 12-08 heartbeating donor liver
- Difficult operation (KIT 9h 11min)

- Hemodialysis
- Positive sputumcultures Aspergillus
- IC acquired weakness
- Compartment syndrome: transgenual amputation left and fasciotomy right
- Non-anastomotic stricture
- Post ERCP pancreatitis

# Handbike Battle Austria

# Take home message

- ALF is a rare clinical syndrome
- Identification aetiology and estimate prognosis
- High mortality due to multi-organ failure
- Increased survival due to supportive care on ICU

# Guidelines for the Management of ALF

- https://easl.eu/publication/management-of-acute-fulminant-liver-failure/

- http://www.aasld.org/practiceguidelines/Documents/AcuteLiverFailureUpdate2011.pdf

- http://www.internisten.nl/uploads/Jx/g9/Jxg9lbR739EcLass3lxKIQ/richtlijn_2010_Acuut-leverfalen.pdf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