

Acute liver failure - syndromes and management

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Acute Liver Failure

- Acute liver failure
 - Fulminant liver failure
- Acute liver failure with underlying cirrhosis
 - Acute on chronic liver failure (ACLF)



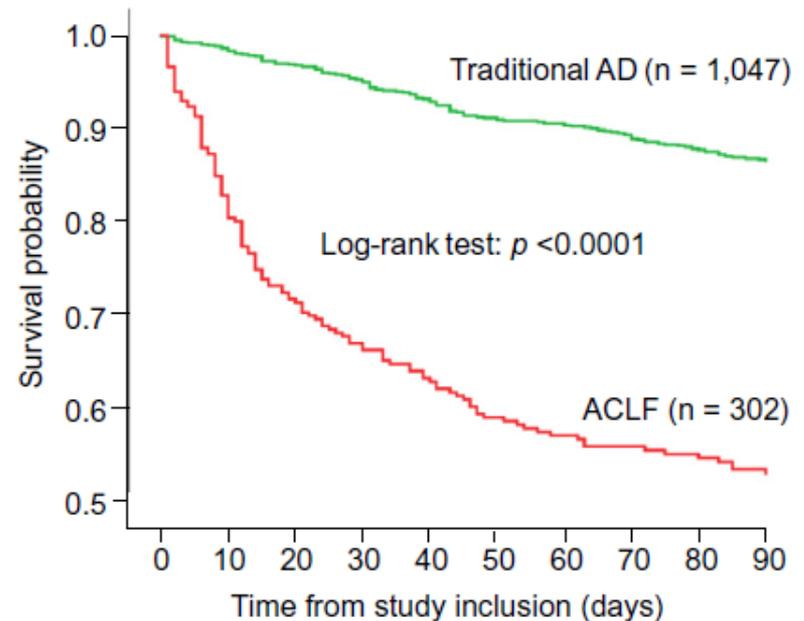
Cirrhosis progression

- Cirrhosis
 - Compensated
 - Decompensated
 - Ascites
 - Variceal bleeding
 - encephalopathy
- Decompensation associated with mortality (3-5 yrs)



Acute on Chronic Liver failure

- Decompensation associated with organ failures and poor survival
- 30d survival 25-40%



Moreau Gastroenterology 2013;144:1426–1



ACLF

- No agreed on definition
 - Western (US/Europe vs Asian)
 - Differing inclusion/ exclusion criteria
- EASL-CLIF
 - Stratification by defined organ failures
 - SOFA



ACLF Grade and Outcome

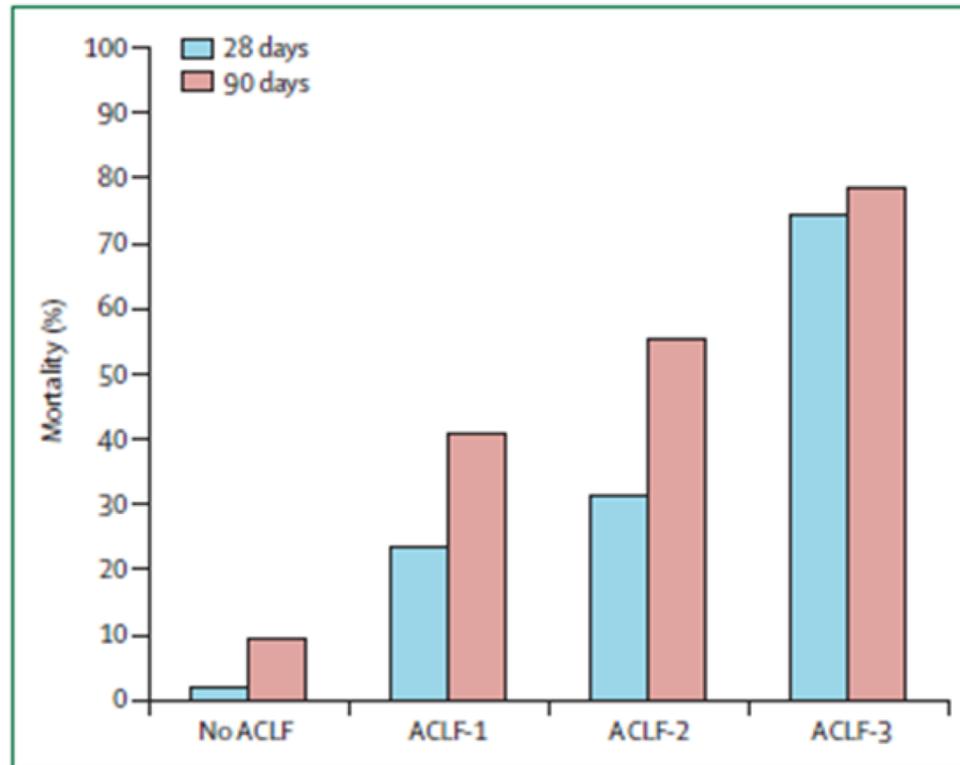


Figure 4: Mortality in patients admitted to hospital with cirrhosis, by ACLF grade

Bernal Lancet 2015; 386: 1576



ACLF - Precipitants

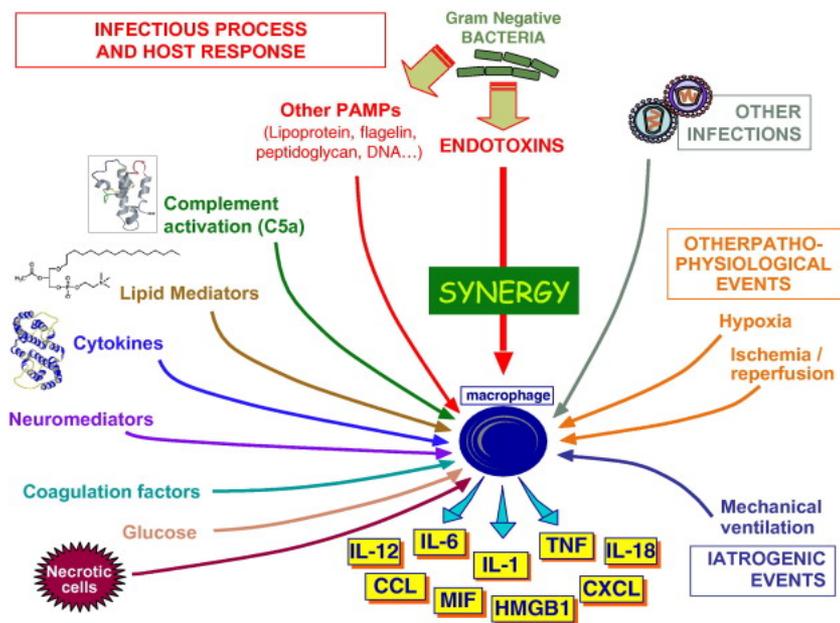
	CANONIC n=303, (9)	Shi <i>et al</i> n=405, (14)
Exacerbation hepatitis B	–	145 (35.8)
Bacterial infection	98 (32.6)	113 (27.9)
GI haemorrhage	40 (13.2)	40 (9.8)
Active alcoholism within the past 3 months	69 (24.5)	25 (6.1)
Other (TIPSS, surgery, large volume paracentesis without albumin, hepatitis, alcoholic hepatitis)	25 (8.6)	9 (2)
Not identifiable	126 (43.6)	83 (20.4)
More than one	39 (13.5)	36 (8.9)

Hernaez Gut 2017;66:541–553



ACLF - pathophysiology

- Systemic inflammation
- Degree of inflammation related to outcome



ACLF - management

- Treat precipitating process
 - Infection
 - Alcoholic hepatitis - steroids
- Organ supportive therapy
 - Standard ICU management
 - If renal failure
 - CVVH
 - Use albumin/terlipressin



ACLF - management

- Liver support therapies (e.g. MARS)
 - Improved biochemistries
 - No evidence of outcome benefit
- Transplant
 - Yes, but controversial
 - Timing
 - Outcome, esp. with MOFS
- Immunotherapies
 - GCSF
 - Stem cells



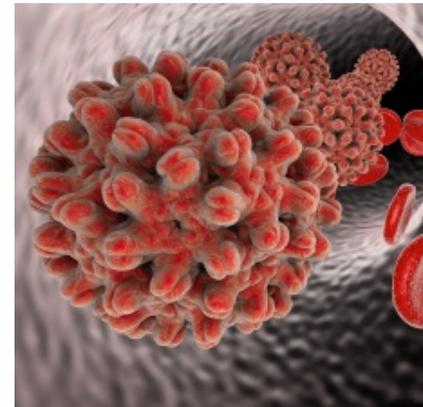
Acute Liver Failure

- Severe acute liver injury
 - Encephalopathy
 - Synthetic dysfunction (INR > 1.5)
- No pre-existing cirrhosis
 - Encephalopathy within 26 wks of illness
- Alcoholic hepatitis excluded
 - ACLF



ALF - etiology

- **Drugs**
- **Viral**
- Autoimmune
- Vascular
- Toxins
- Shock liver
- HELLP
- Wilson disease
- Heat stroke



Etiology

- Geographic differences in most common causes
- Acetaminophen (paracetamol)
 - US, UK (approx 50%)
- Viral (Hep B)
 - France, Japan (45%)



Diagnosis

- Consider ALF if:
 - Mental status changes
 - Jaundice
 - RUQ pain
- LFTs
- If abnormal INR
- ABG, ammonia, lactate
- History important
 - Particularly for acetaminophen



Outcomes

- Dependent on etiology
- Improved outcomes in recent years
- Overall survival 75%
 - Transplant 96%
 - Without Tx 56%
- Acetaminophen more favorable outcomes

Reuben Ann Intern Med. 2016;164(11):724



Management

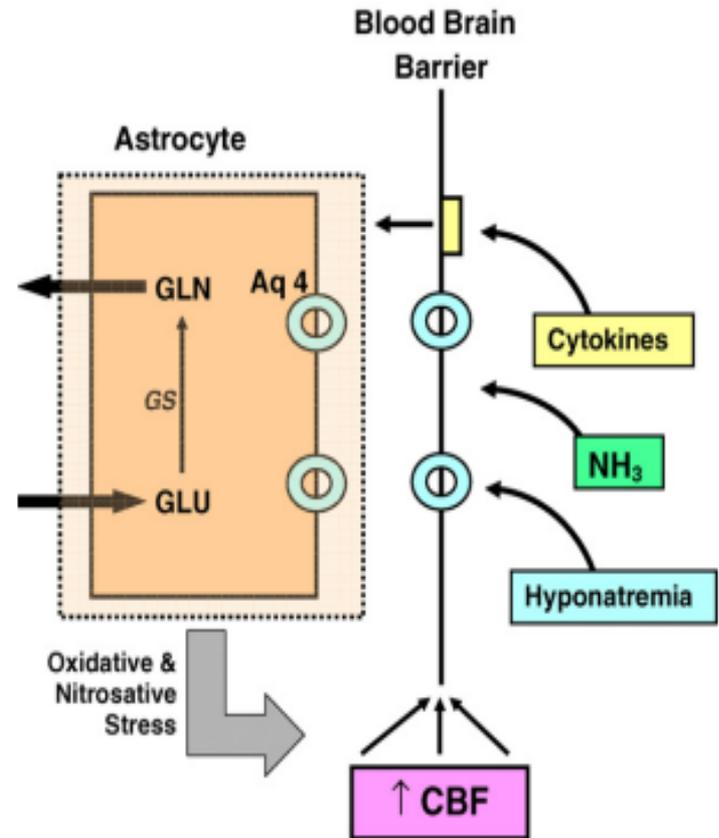
- Specific treatment
 - n-acetyl cysteine
- Early referral to specialist center
- Medical support
 - Recovery
 - Transplant
 - Death



Specific Concerns

Cerebral Edema

- Glutamine production
- Oxidative stress
- hyponatremia
- Astrocyte swelling
- ↑ CBF



Blei Journal of Hepatology 46 (2007) 553–582



Specific Concerns Cerebral Edema

- Uncommon in HE grade 1 & 2
- Grade 3 30%
- Grade 4 75%
- Higher risk
 - Higher ammonia (> 150)
 - Rapid rise in ammonia



Clemmesen Hepatology 1999;29:648–653



Cerebral Edema Management

- As for other raised ICP
- Intubation, ventilation for grade 3 HE
- ICP monitoring
 - Controversial
 - No outcome benefit shown



Cerebral Edema Management

- Treat exacerbations (or high risk)
 - hyperventilation
 - Osmotic therapy (hypertonic saline vs mannitol)
 - Barbiturate coma
- Consider mild hypothermia (32-35C)
 - Success in resistant ICP elevation
 - Or not

Jalan Gastroenterology. 2004;127(5):1338

Karvellas Liver Transpl. 2015;21(1):4.



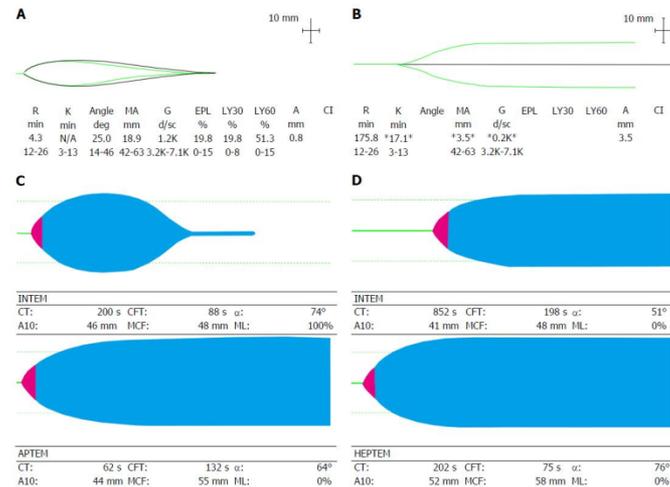
Specific Concerns Infection

- High risk for infection
- Prophylactic antimicrobials
- *or* treat at initial suspicion of infection



Specific Concerns Coagulopathy

- PT/INR very high
- Normal thrombin generation
- No indication for prophylactic management
- Viscoelastic testing



ALF – prognostication Transplant Benefit

- King's College Criteria (1989)
- Still used
- May need revision in modern era

O'Grady Gastroenterology. 1989 Aug;97(2):439-45.



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 $\mu\text{mol/L}$
 - 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 $\mu\text{mol/L}$
 - INR >3.5



Improved Outcomes Acetaminophen OD

- 64 patients 2010 – 2016
- N-acetyl cysteine
- Prophylactic antimicrobials
- “4H” management
 - Mild hyperventilation
 - High-dose ultrafiltration
 - Hypothermia
 - hypernatremia
- No ICP monitoring
- **No transplantation**

Porteous Liver Transplantation 2019;25: 35–44



Improved Outcomes Acetaminophen

- 80% survival
- 70% meeting KC criteria
- UK Registration criteria for super-urgent transplant
 - More accurate than KC criteria

Porteous Liver Transplantation 2019;25: 35–44



UK Registration Criteria for Super-Urgent Liver Transplantation

Category	Etiology	Criteria
1	APAP	pH < 7.25 more than 24 hours after overdose and after fluid resuscitation
2	APAP	Coexisting PT > 100 seconds or INR > 6.5 and serum creatinine > 300 μ mol/L or anuria, and grade 3-4 encephalopathy
3	APAP	Significant liver injury and coagulopathy following the exclusion of other causes of hyperlactatemia after adequate fluid resuscitation: arterial lactate > 5 mmol/L on admission and >4 mmol/L 24 hours later in the presence of clinical HE
4	APAP	2 of the 3 criteria from category 2 with clinical evidence of deterioration (eg, increased ICP, FiO ₂ > 50%, increasing inotrope requirements) in the absence of clinical sepsis
5	Favorable non-APAP (eg, viral hepatitis, cocaine)	The presence of clinical HE is mandatory and PT > 100 seconds or INR > 6.5, or any 3 of the following: age > 40 or < 10 years; PT > 50 seconds or INR > 3.5; any grade of HE with jaundice to encephalopathy time >7 days, serum bilirubin > 300 μ mol/L
6	Unfavorable non-APAP (eg, indeterminate ALF, DILI)	(1) PT > 100 seconds or INR > 6.5 or (2) in the absence of HE then INR > 2 after vitamin K repletion is mandatory and any 2 of the following: age > 40 or < 10 years; PT > 50 seconds or INR > 3.5; if HE is present, the jaundice to encephalopathy time was >7 days; serum bilirubin > 300 μ mol/L
7	Acute Wilson's disease or Budd-Chiari syndrome	A combination of coagulopathy and any grade of encephalopathy

NHS Blood and Transplant Super-urgent Liver Recipient Registration.

http://www.odt.nhs.uk/pdf/Super_Urgent_Liver_FRM4324_

DRAFT_v2.pdf.



ALF – future directions

- Liver replacement devices
 - No evidence of benefit
- GCSF/Stem cells
 - Experimental
 - Small series in ACLF



Acute Liver Failure Summary

- ACLF
 - Recent concept
 - Developing understanding
- ALF
 - Improving outcomes
 - Re-addressing outcome prediction





<https://youtu.be/Ydw2Mk-r2kw>

