

Approach to a patient with Acute Liver Failure

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Acute liver failure (ALF)

1. Definition
2. Etiology
3. Prognosis
4. Treatment

Indian National Association for the Study of Liver (INASL) definition

		Acute liver failure (ALF)
Complication	Encephalopathy	Yes
	Coagulopathy (INR > 1.5)	Yes
	When	≤ 4 weeks after first symptom
Jaundice		Yes
Pre-existing liver disease		No

Anand AC, et al.
J Clin Exp Hepatol 2020; 10: 339-76

Indian National Association for the Study of Liver (INASL) definition

		Acute liver failure (ALF)	Acute liver injury (ALI)
Complication	Encephalopathy	Yes	No
	Coagulopathy (INR > 1.5)	Yes	Yes
	When	≤ 4 weeks after first symptom	
Jaundice		Yes	Yes
Pre-existing liver disease		No	No

Anand AC, et al.
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Spectrum of syndromes of acute liver dysfunction

		Acute hepatitis (uncomplicated)	Acute liver injury (ALI)	Severe acute liver injury	Acute liver failure (ALF)
Complication	Encephalopathy	No	No	No	Yes
	Coagulopathy	No	Yes (INR > 1.5)	Yes (INR ? > 2)	Yes (INR > 1.5)
	When	≤ 4 weeks after first symptom			
Jaundice		Yes			
Pre-existing liver disease		No			

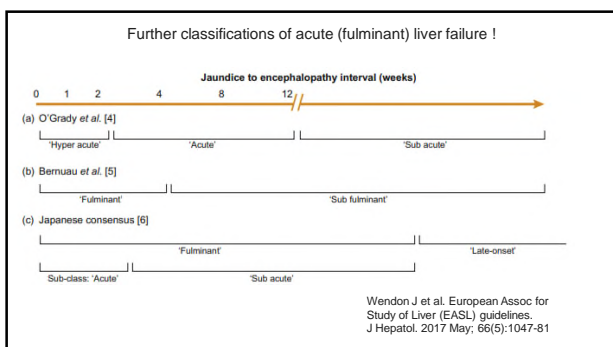
Different phenotypes of liver failure

Acute liver injury (ALI)	Severe ALI	Acute liver failure (ALF)	Cirrhosis	Acute on chronic liver failure (ACLF)

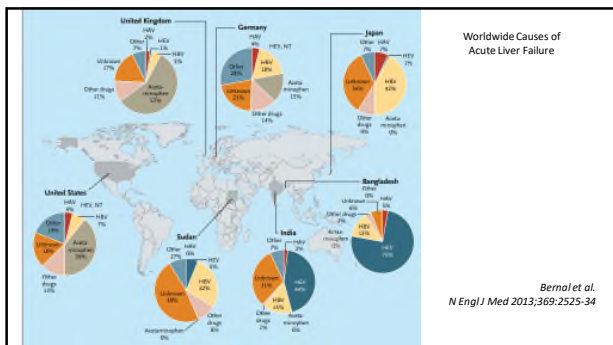
Anand AC, et al. INASL task force.
J Clin Exp Hepatol 2020; 10: 339-76

Spectrum of syndromes of acute liver dysfunction

	Acute hepatitis (uncomplicated)	Acute liver injury (ALI)	Severe acute liver injury	Acute liver failure (ALF)
Natural history			→ ALF, liver transplant or death: 23%	Death : 60 – 80%
Ref			Koch et al. Am J Gastro 2017 112(9): 1389-96	Anand AC, et al. J Clin Exp Hepat 2020; 10: 339-76



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Toxic Hepatitis :
“Rodenticide (Phosphorus) ingestion in Tamil Nadu
Equivalent to
Paracetamol Overdose in the West”

Toxic hepatitis patients across Tamil Nadu (Jan – June 2019)

Proportion of	
Rat killer: Paracetamol overdose	450 : 6
	75 : 1

Govindarajan et al. Indian J Gastro 2021; 40: 373–9

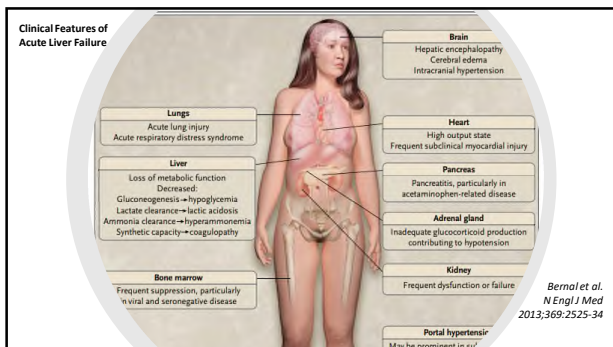
Tamil Nadu chapter – Indian Society of Gastroenterology study

450 rodenticide hepatotoxicity patients
 75% : 15 – 34 years old
 35%: died / discharged in moribund state

Only 1 patient had liver transplant

Urgent liver transplant is not feasible for most patients in Tamil Nadu at present

Gastro Hepat Endosc Pract [GHEP] 2022; 2: 1 - 6



ALF-mimics: ALF – like presentations caused by tropical infections

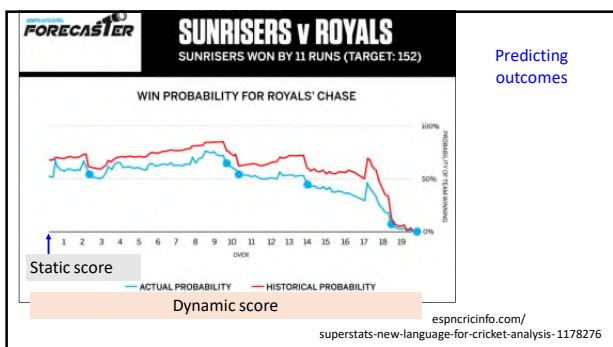
Severe falciparum malaria	Fever, chills, hepatosplenomegaly, altered sensorium, anemia,
Dengue	Fever, headache, retro-orbital pain, myalgia, rash,...
Leptospirosis	Fever, headache, myalgia, abdo pain, conjunctival suffusion, transient skin rash. If severe: acute kidney injury, pulm hemorrhages, ARDS, myocarditis, hepatomegaly
Scrub typhus	Fever, headache, myalgia, breathing difficulty, delirium, cough, jaundice. Hepatomegaly+

Anand AC, et al. J Clin Exp Hepat 2020; 10: 339-76

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Scores to predict survival in acute liver failure

Static score	Dynamic score
?	?




Experts opine at the start of the game: who will win ?
Static score



Predicting outcomes


Can the crowd predict who will win ?

Start of the match



Static score

[Home] team about to lose



Dynamic score

Predicting outcomes

Prospective derivation, validation of ALF early dynamic [ALFED] score to predict outcome in ALF

Static score	Dynamic score	
MELD score	ALFED score	}
King's college hospital criteria		

Encephalopathy

INR

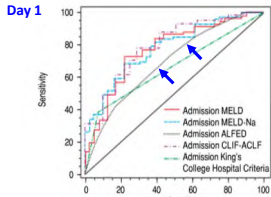
Arterial ammonia

Serum bilirubin

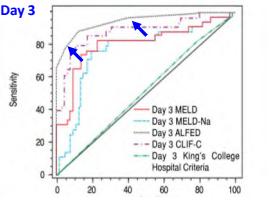
Kumar R, et al. Gut. 2012 Jul;61(7):1068-75.

AUROC of prognostic models in ALF patients caused by hepatitis viruses

Day 1



Day 3



Hospital stay	MELD	MELD-Na	ALFED	King's College criteria
Day 1	0.77	0.77	0.68	0.65
Day 3	0.81	0.77	0.95	0.52

Acharya SK. Clin Liver Dis 2021 Jul 22; 18(3):143-9

Acute liver failure (ALF)

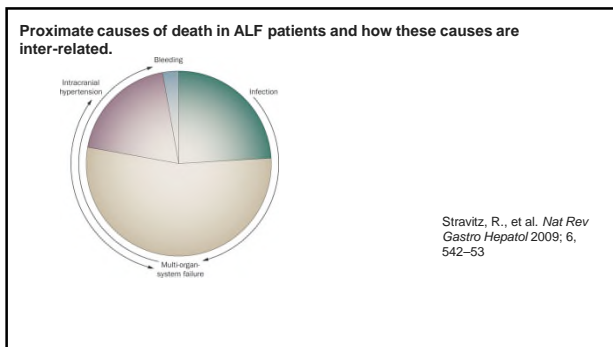
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 - a) Etiology specific
 - b) Cerebral edema
 - c) Liver transplantation
 - d) New therapies: Plasma exchange

Treatment of patient with ALF

1. Look for the cause. Treat appropriately
2. Managing a critically ill patient
3. Urgent liver transplantation
4. Newer non – transplant therapies: Plasma exchange

Acute liver failure (ALF)

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Grade of HE	Level of consciousness	Personality, intellect	Neurologic signs	EEG	West Haven criteria to grade hepatic encephalopathy (HE)
0	Normal	Normal	None	None	
Sub-clinical			Abnormal psychometric test		
1	Day / night sleep reversed, restless	Forgetful, mild confused	Tremor, apraxia	Triphasic waves	
2	Slow response	Not oriented : time, place, person	Asterixis, dysarthria		
3	Confused, drowsy				
4	Coma	None	Decerebrate	δ slow waves	

Clinical signs of intracranial pressure (ICP)

↑ muscle tone (early), bradycardia, hypertension, unequal pupils, neurogenic hyperventilation, myoclonus, decerebration (late)

Anand AC, et al. *J Clin Expt Hepatol* 2019; 9 (1) : 99 - 108

Management principles : Prevent, treat CNS complications in ALF patient

Optimise cerebral blood flow	Raise head of bed by 20 - 30° Correct fluid balance, avoid volume overload Maintain MAP ~ 60 – 70mm Hg Hyperventilate (aim to reduce PCO2)
Prevent surges in intracranial pressure	Minimise head turning Gd 3 /4 HE: invasive ventilation with adequate sedation, analgesia. Minimise suctioning, stimulation Osmotherapy: IV 3% saline (target serum sodium : 145 – 150 mmol / L;) or Mannitol

Anand AC, et al. *INASL J Clin Exp Hepatol* 2020;10:477–517

INASL Consensus statement:
Prevention and treatment of CNS complications

1. gd I or 2 HE : frequently monitor for signs of deterioration.
Do not use sedatives like benzodiazepines.
2. gd 3 or 4 HE: elective intubation (to prevent aspiration) with adequate analgesia, [propofol preferred].
3. Noninvasive tests: optic nerve sheath diameter can be used.
4. Prophylactic antiepileptics is not recommended. If indicated, less hepatotoxic drugs ex: levetiracetam preferred
5. Nonabsorbable antibiotics, lactulose : not shown to improve survival or HE in ALF.

Anand AC, et al. J Clin Exp Hepatol 2020;10:477–517

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Listing criteria for urgent liver transplantation in ALF patients

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:
 - o Hepatic encephalopathy ≥grade 3
 - o Serum creatinine >300 µmol/L
 - o INR >6.5

ALF not due to paracetamol

- INR >6.5 or
- 3 out of 5 following criteria:
 - o Aetiology: indeterminate aetiology hepatitis, drug-induced hepatitis
 - o Age <10 years or >40 years
 - o Interval jaundice-encephalopathy >7 days
 - o Bilirubin >300 µmol/L
 - o INR >3.5

Wendon J et al. J Hepatol. 2017 May; 66(5):1047-81

Criteria for the Selection of Patients with Acute Liver Failure for Transplantation.*			
Factor	King's College Criteria	Clichy Criteria	Japanese Criteria
Age†	Yes	Yes	Yes
Cause	Yes	No	No
Encephalopathy†	Yes	Yes	Yes
Bilirubin level	Varies	No	Yes
Coagulopathy†	Yes	Yes	Yes

Varies indicates that the criterion is used only in cases not associated with acetaminophen. † This factor is common to all prognostic models.

*Bernal et al.
N Engl J Med 2013;369:2525-34*

Living Donor Liver Transplantation [LDLT] for Acute Liver Failure [ALF]

Aim : to donor safety and recipient outcomes after LDLT for ALF.

410 patients who had LDLT [2011 – 2018] → 61 (15%) for ALF.

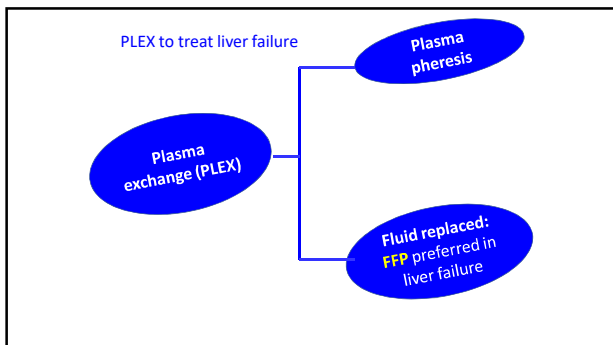
All met King's College criteria.
MELD score : 37 (32-40), > 2/3rd had grade 3 / 4 HE, 70% mech. ventilated.
Most common etiology : viral (37%).

No donor mortality.

127 patients who met King's college criteria, but did not have LT, survival : 23%.
5-year post-LT actuarial survival : 66 %

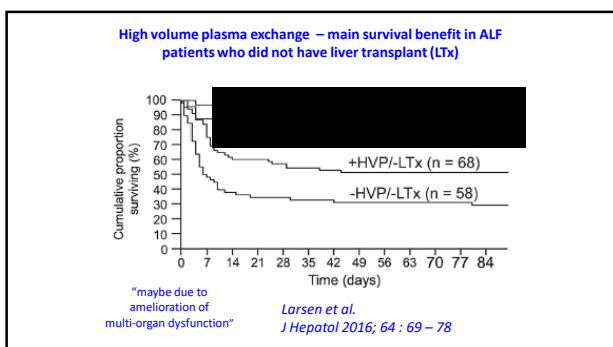
*Pamecha et al. Liver Transpl.
2019; 25(9): 1408-21*

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PLEX to treat ALF / ACLF	Volume of plasma exchanged per PLEX session		
High volume	4 X	8 – 12 litres	Larsen et al. <i>J Hepatol</i> 2016; 64 : 69 – 78
Standard volume	1.5 – 2 X	2.2 litres	Maiwall et al. <i>Clin Gastro Hepatol</i> 24 Jan 2021
Low volume	0.5 X	1.2 – 1.4 litres	Alexander et al. <i>Curr Med Issues</i> 2020; 18: 77 - 82 Zachariah et al. <i>GHEP</i> 2021; 2: 47 - 54

Adult: Blood volume: 5 litres Plasma volume: 2.5 litres



Guidelines: PLEX in clinical practice

for acute liver failure	Category	Grade (Quality of evidence)	Recommendation
High-volume PLEX	I 1 st -line Rx alone / with other Rx	IA RCT	Strong
PLEX	III Decide case by case	IIB RCT : major limitations+	Weak

Padmanabhan A, et al. American Society for Apheresis J Clin Apher 2019; 34:171-354

[Standard volume PLEX improves outcomes in ALF: RCT](#)

40 ALF patients
 ↳ standard medical treatment
 ↳ PLEX (target : 1.5 - 2 X plasma vol. exchanged per session)

Results:

PLEX arm : better 21-day transplant free-survival [75% vs. 45%; P = .04]

Conclusion:
 In ALF pts with cerebral edema, PLEX is safe, effective, improves survival, probably by ↓ing cytokine storm.

Maiwall R, et al. Clin Gastro Hepatol. 2022 Apr;20(4):e831-54

[Access to urgent liver transplants: for only a minority in India at present](#)

1000 liver transplants / year being done in India [mainly living donor].
 5% - 7.5% for acute liver failure, survival rate : 80% at 1 year.

Acharya SK. Clin Liver Dis. 2021 Jul 22; 18(3):143-9

Estimated: 1584 (95% CI: 265–6119) patients with **rodenticidal hepatotoxicity with poor outcome** in 35% (554 patients) in 2019 in Tamil Nadu

Govindarajan et al. Indian J Gastro 2021; 40: 373–9

(Kochi) listing criteria for urgent liver transplantation in patients with rodenticide (phosphorus) induced liver damage

1. MELD \geq 36

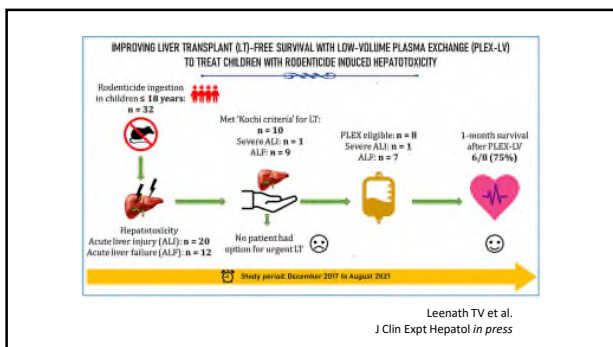
or

2. Baseline INR \geq 6 and encephalopathy

*Saraf et al.
Indian J Gastro. 2015; 34 : 325-9*

Phosphorus poison patients who met listing criteria for urgent liver transplant			
	Kochi criteria met	Treatment	Survival
AIMS Kochi	all ages	Standard medical care (n = 8)	0 (0%)
		Liver transplant (n = 14)	12 (86%)
CMC Vellore	all ages	PLEX (n = 26)	16 (62%)
	\leq 18 yrs old	PLEX (n = 8)	6 (75%)

Saraf et al. *Ind J Gastro.* 2015; 34 : 325-9
Thomas et al *JCEH* in press



Editorial

Low-Volume Plasma Exchange to Treat
Children With Acute Liver Failure

Larsen FS.
J Clin Expt Hepatol 2023 (in press)
<https://doi.org/10.1016/j.jceh.2023.01.015>
