Indian National Association for the Study of Liver Consensus Statement on Acute Liver Failure (Part-2): Management of Acute Liver Failure

Anil C. Anand [†], Bhaskar Nandi [‡], Subrat K. Acharya [§], Anil Arora [‖], Sethu Babu [¶], Yogesh Batra [#], Yogesh K. Chawla [††], Abhijit Chowdhury [‡‡], Ashok Chaoudhuri [§§], Eapen C. Eapen [‖‖], Harshad Devarbhavi [¶¶], Radha K. Dhiman [##], Siddhartha Datta Gupta [†††], Ajay Duseja [##], Dinesh Jothimani [‡‡‡], Dharmesh Kapoor [§§§], Premashish Kar [‖‖‖], Mohamad S. Khuroo [¶¶¶], Ashish Kumar [‖], Kaushal Madan [###], Bipadabhanjan Mallick [††††], Rakhi Maiwall [‡‡‡‡], Neelam Mohan [§§§§], Aabha Nagral [‖‖‖‖], Preetam Nath [†], Sarat C. Panigrahi [†], Ankush Pawar [¶¶¶¶], Cyriac A. Philips [####], Dibyalochan Prahraj [†], Pankaj Puri [†††††], Amit Rastogi [‡‡‡‡‡], Vivek A. Saraswat [§§§§§], Sanjiv Saigal [‖‖‖‖‖], Shalimar [¶¶¶¶¶], Akash Shukla [#####], Shivaram P. Singh [†††††], Thomas Verghese [‡‡‡‡‡‡], Manav Wadhawan [§§§§§§] THE INASL TASK-FORCE ON ACUTE LIVER FAILURE

[†] *Department of Gastroenterology, Kaliga Institute of Medical Sciences, Bhubaneswar, 751024, India,* [‡] *Department of Gastroenterology, Sarvodaya Hospital and Research Centre, Faridababd, Haryana, India,* [§] *Department of Gastroenterology and Hepatology, KIIT University, Patia, Bhubaneswar, Odisha, 751 024, India,* [‖] *Institute of Liver Gastroenterology & Pancreatico Biliary Sciences, Sir Ganga Ram Hospital, Rajinder Nagar, New Delhi, 110 060, India,* [¶] *Department of Gastroenterology, Krishna Institute of Medical Sciences, Hyderabad, 500003, India,* [#] *Department of Gastroenterology, Indraprastha Apollo Hospital, SaritaVihar, New Delhi, 110 076, India,* [††] *Department of Gastroenterology, Kalinga Institute of Medical Sciences (KIMS), Kushabhadra Campus (KIIT Campus-5), Patia, Bhubaneswar, Odisha, 751 024, India,* [‡‡] *Department of Hepatology, School of Digestive and Liver Diseases, Institute of Post Graduate Medical Education & Research, Kolkata, 700020, India,* [§§] *Hepatology and Liver Transplant, Institute of Liver & Biliary Sciences, D-1 Vasant Kunj, New Delhi, India,* [‖‖] *Department of Hepatology, Christian Medical College, Vellore, India,* [¶¶] *Department of Gastroenterology and Hepatology, St. John's Medical College Hospital, Bangalore, 560034, India,* [##] *Department of Hepatology, Postgraduate Institute of Medical Education and Research, Chandigarh, 160 012, India,* [†††] *Department of Pathology, All India Institute of Medical Sciences, Ansari Nagar, New Delhi, 110 029, India,* [‡‡‡] *Institute of Liver Disease and Transplantation, Dr Rela Institute and Medical Centre, Chrompet, Chennai, 600044, India,* [§§§] *Gleneagles Global Hospitals, Hyderabad, Telangana, India,* [‖‖‖] *Department of Gastroenterology and Hepatology, Max Super Speciality Hospital, Vaishali, Ghaziabad, Uttar Pradesh, 201 012, India,* [¶¶¶] *Department of Gastroenterology, Dr Khuroo' s Medical Clinic, Srinagar, Kashmir, India,* [###] *Gastroenterology and Hepatology, Max Smart Super Specialty Hospital, Saket, New Delhi, India,* [††††] *Department of Gastroenterology, Kalinga Institute of Medical Sciences, Bhubaneswar, 751024, India,* [‡‡‡‡] *Hepatology Incharge Liver Intensive Care, Institute of Liver & Biliary Sciences, D-1 Vasant Kunj, New Delhi, India,* [§§§§] *Department of Pediatric Gastroenterology, Hepatology & Liver Transplantation, Medanta – the MedicityHospital, Sector – 38, Gurgaon, Haryana, India,* [‖‖‖‖] *Department of Gastroenterology, Apollo and Jaslok Hospital & Research Centre, 15, Dr Deshmukh Marg, Pedder Road, Mumbai, Maharashtra, 400 026, India,* [¶¶¶¶] *Liver & Digestive Diseases Institute, Fortis Escorts Hospital, Okhla Road, New Delhi, 110 025, India,* [####] *The Liver Unit and Monarch Liver Lab, Cochin Gastroenterology Group, Ernakulam Medical Centre, Kochi 682028, Kerala, India,* [†††††] *Department of Hepatology and Gastroenterology, Fortis Escorts Liver & Digestive Diseases Institute (FELDI), Fortis Escorts Hospital, Delhi, India,* [‡‡‡‡‡] *Department of Liver Transplantation, Medanta – the MedicityHospital, Sector – 38, Gurgaon, Haryana, India,* [§§§§§] *Department of Gastroenterology, Sanjay Gandhi Post Graduate Institute of Medical Sciences, Raibareli Road, Lucknow, Uttar Pradesh, 226 014, India,* [‖‖‖‖‖] *Department of Hepatology, Department of Liver Transplantation, India,* [¶¶¶¶¶] *Department of Gastroenterology and Human Nutrition Unit, All India Institute of Medical Sciences, New Delhi, 29, India,* [#####] *Department of Gastroenterology, LTM Medical College & Sion Hospital, India,* [††††††] *Department of Gastroenterology, SCB Medical College, Dock Road, Manglabag, Cuttack, Odisha, 753 007, India,* [‡‡‡‡‡‡] *Department of Gastroenterology, Government Medical College, Kozikhode, India and* [§§§§§§] *Institute of Liver & Digestive Diseases and Head of Hepatology & Liver Transplant (Medicine), BLK Super Speciality Hospital, Delhi, India*

Acute liver failure (ALF) is not an uncommon complication of a common disease such as acute hepatitis. Viral hepatitis followed by antituberculosis drug–induced hepatotoxicity are the commonest causes of ALF in India. Clinically, such patients present with appearance of jaundice, encephalopathy, and coagulopathy. Hepatic encephalopathy (HE) and cerebral edema are central and most important clinical event in the course of ALF, followed by superadded infections, and determine the outcome in these patients. The pathogenesis of

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Address for correspondence. Subrat Kumar Acharya, Department of Gastroenterology and Hepatology, KIIT University, Patia, Bhubaneswar, Odisha, 751 024, India.
E-mail: subratacharya@gmail.com

Abbreviations: ALF: Acute Liver Failure; ACLF: Acute on Chronic liver Failure; AST: aspartate transaminase; ALT: alanine transaminase; CNS: central nervous system; ICU: Intensive care unit; INR: International normalised ratio; NAC: N-acetyl cysteine; HELLP: Hemolysis, elevated liver enzymes, and low platelets; LT: Liver transplantation; LDLT: Living donor liver transplantation; ICP: Intracrainial Pressure; CT: Computerized tomography; ICH: Intracrainial hypertension; MAP: Mean arterial pressure; AKI: Acute kidney injury; LAD: Liver assist device; MELD: model for end-stage liver disease; WD: Wilson's Disease; PALF: Pediatric ALF; MLD: Metabolic liver disease

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encephalopathy and cerebral edema in ALF is unique and multifactorial. Ammonia plays a crucial role in the pathogenesis, and several therapies aim to correct this abnormality. The role of newer ammonia-lowering agents is still evolving. These patients are best managed at a tertiary care hospital with facility for liver transplantation (LT). Aggressive intensive medical management has been documented to salvage a substantial proportion of patients. In those with poor prognostic factors, LT is the only effective therapy that has been shown to improve survival. However, recognizing suitable patients with poor prognosis has remained a challenge. Close monitoring, early identification and treatment of complications, and couseling for transplant form the first-line approach to manage such patients. Recent research shows that use of dynamic prognostic models is better for selecting patients undergoing liver transplantation and timely transplant can save life of patients with ALF with poor prognostic factors. (J Clin Exp Hepatol 2020;10:477–517)

Acute liver failure (ALF) is a common emergency and has high short-term mortality. The term is applied to a clinical presentation of encephalopathy within a few weeks after the onset of liver disease with associated coagulopathy.[1] The overall presentation and differential diagnosis of such cases in India is different than what is described in Western textbooks. Moreover, in India, while tertiary care centers, in general, and liver transplant centers, in particular, may have protocols to optimize the management of patients with ALF, peripheral (primary and secondary care) hospitals may have neither expertise nor resources to care for such patients in an appropriate manner. Therefore, the Indian National Association for the Study of Liver (INASL) constituted a task force to prepare a position paper on management of ALF in India with clear-cut protocols to be followed.

In the first part of the consensus paper, the INASL had summarized the disease burden, epidemiology, clinical presentation, monitoring, and prognostication. It was noted that viral hepatitis is the most common cause of ALF in India, with drug hepatitis due to antituberculosis (anti-TB) drugs being the second commonest cause. The clinical presentation of ALF is characterized by jaundice, coagulopathy, and encephalopathy. It is important to differentiate ALF from other causes of liver failure including acute on chronic liver failure, subacute liver failure, as well as certain tropical infections that can mimic this presentation. ALF can have a fulminant clinical course with high short-term mortality. The unfavorable outcome is usually attributable to cerebral complications, infections, or multiorgan failure. Timely liver transplantation (LT) can change the outcome, and hence, it is important to assess prognosis to select patients who are suitable for transplantation. Several prognostic scores have been evolved over time, and their comparison shows that indigenously developed dynamic scores have an edge over scores described from the Western world. Management of ALF will be described in this document.

For the purpose of development of consensus statements, the taskforce identified the main contentious issues on various aspects of ALF management. Members of the taskforce reviewed the existing literature, especially from India, and developed consensus statements on each of these issues. The statements along with supporting literature were circulated to the group for peer review, and comments were responded to by authors. A 2-day roundtable discussion was held on 6th and 7th July 2019 at to discuss, debate, and finalize the consensus statements. Only those statements that were unanimously approved by the members of the taskforce were accepted. The evidence and recommendations in these statements have been graded in accordance with the Grading of Recommendations Assessment Development and Evaluation (GRADE) system with minor modifications (Table 1). The strength of recommendations (strong, weak) thus reflects the quality (grade) of underlying evidence (high, moderate, or low).[2]

MANAGEMENT OVERVIEW

The survival of patients with ALF has been improving over time and may reflect an improvement in the overall management of these patients.[3,4] Before the 1980s, mortality from ALF was described as 80–85%, while more recently, it has dropped down to around 55%. Even survival after LT was reported to be 58% before 1990 and has vastly improved to around 75% in recent reports. The basic concept of management in ALF revolves around the fact that ALF is a potentially reversible disease as the liver has a tremendous capacity to regenerate. There is massive necrosis of hepatocytes, which is also a stimulus for the regeneration of hepatocytes. But before recovery can take place effectively, the patient may die due to complications of liver failure. If we can keep the patient alive and stable and buy time for liver regeneration can take place, patients will survive. Hence, intensive supportive care has a central role in the management of such patients. Thus, the main principles of management are as follows: (a) aggressive supportive therapy which involves intensive care with organ support systems; (b) identification and treatment of causative factors; (c) removal of toxic agents such as ammonia; and (d) prevention and treatment of fatal complications of liver failure such as cerebral edema, sepsis, renal failure, and gastrointestinal (GI) bleeding. It is equally important to recognize situations where the

Table 1 Level of Evidence and Grade of Recommendations (Adapted From GRADE System).[2]

Level of evidence		Confidence in the evidence
1. High	Data derived from meta-analyses or systematic reviews or from (multiple) randomized trials with high quality.	Further research is unlikely to change our confidence in the estimate of benefit and risk.
2. Moderate	Data derived from a single RCT or multiple nonrandomized studies.	Further research (if performed) is likely to have an impact on our confidence in the estimate of benefit and risk and may change the estimate.
3. Low	Small studies, retrospective observational studies, registries.	Any estimate of effect is uncertain.
Recommendations – Grade		Wording associated with the grade of recommendation
1. Strong		"must", "should", or "INASL recommends"
2. Weak		"can", "may", or "INASL suggests"

GRADE = Grading of Recommendations Assessment Development and Evaluation; INASL =Indian National Association for the Study of Liver.

aforementioned measures may not save a patient's life so that LT can be considered.

MANAGEMENT AT A PERIPHERAL CENTER

Patients need immediate hospitalization when the syndrome of ALF is recognized. Doctors at a peripheral center should be aware if they have the basic facilities for the care of patients with ALF. Intensive supportive care is critical in these patients and should start at the first point of care. Measures to contact and seek advice on transfer to a specialized center/transplant center should also be initiated.

Steps to be followed remain the same everywhere.

(a) Establish diagnosis as per definition: Mostly it is a clinical process and depends on finding altered mentation in a patient with recent onset of liver disease or jaundice.[5] This will be confirmed by finding the hepatitic picture in liver biochemical tests and prolongation of prothrombin time.[1] These patients have significant morbidity and mortality and therefore should be immediately hospitalized and followed up closely.[6] Encephalopathy is an inconsistent and difficult sign to elicit in children, and its grading fraught with subjective bias (See discussion).[7]

(b) The next step is to identify etiology which is a major determinant of outcome.[8] Tests to identify acute viral hepatitis should be sought as this is the most common cause of ALF in India.[1] ALF due to hepatitis A virus (HAV) and hepatitis E virus (HEV) infection has a better outcome than ALF from hepatitis B virus (HBV) infection, Wilson disease, drug-induced liver injury (DILI), and cryptogenic.[9] In female patients, one should confirm if the patient is pregnant or not as ALF could be due to pregnancy-specific liver disease which has a modest rise in transaminase and is associated with ascites or hypertension and has a better outcome than ALF from HEV in pregnancy.[10–12] Patients who exhibit a massive rise in AST and ALT (>3000–4000 IU/L) should undergo tests to identify unusual viruses such as dengue virus and herpes simplex virus (HSV).[13] Ischemic hepatitis and paracetamol overdose can also result in very high transaminases. A detailed history of exposure to any prescription and nonprescription medication including alternative/complementary/traditional/herbal medications is obtained. The amount, duration, and timing of the last dose should be inquired about. Traditionally anti-TB drug-induced ALF has been associated with low levels of survival (<35%).[11,12] All presumed or implicated drugs including first-line anti-TB drugs should be discontinued. (b) In an Indian setting, diseases such as malaria, typhoid fever, leptospirosis, dengue, and scrub typhus may be clinical presentation of ALF.[14] These can be differentiated by distinctive clinical features (high fever), systemic examination (hepatosplenomegaly), and appropriate blood tests. Treatment at the point of care needs to be initiated: Common dos and don'ts are listed at Table 2. Intensive supportive care is the mainstay of treatment and includes good venous access for adequate hydration with intravenous (i.v.) crystalloids, particularly normal saline, with an aim of keeping serum sodium in the normal to high range (140–150 mmol/L). The patient should be nursed with the bed at 30° head end elevated position. Hypoglycemia which is common in ALF should be treated with bolus doses of i.v. 25–

Table 2 Dos and Don'ts in Managing Acute Liver Failure at a Peripheral Hospital.

Management	What to do	What not to do
Early identification of red flag signs/ symptoms	Any degree of altered sensorium in a patient with acute liver injury should be taken seriously and may indicate ALF.	
Admission to word/ICU	All patients with ALF should be hospitalized and managed in the intensive care unit	
General care	Promptly treat fever or hypothermia, ensure that patient does not develop hypoxia or hypercarbia. Minimal handling Gentle and minimal endotracheal suctioning if intubated	Avoid direct light, crowded and noisy surroundings, frequent position change, and bowel enema
Fluid and electrolyte management	Normal saline or balanced fluid, i.e., plasmalyte to be preferred. (Gradually try to achieve serum sodium between 140 and 150 meq/l by using hypertonic saline if needed)	Avoid Hartman solution or ringer lactate. Avoid hyponatremia or hypernatremia. Also avoid rapid correction of serum sodium >8 mEq/l in 24 h
Managing hepatic encephalopathy and ammonia and seizure	Ensure mechanical ventilation with worsening sensorium or in encephalopathy of grade III-IV.	Routine prophylaxis for seizure not indicated, but seizures, if occur, should be promptly treated with midazolam. Rifaximine, leomycin, and/or lactulose are ineffective and are not recommended
Management of cerebral edema and raised intracranial pressure	Hypertonic saline or mannitol to be used as bolus and not as maintenance infusion If there is a suspicion of rising ICP, mannitol 0.5 g/kg should be given. For a 70-kg man, give 175 ml of 20% mannitol or 350 ml of 10% mannitol over 10 min.	Mannitol to be avoided with serum osmolarity >320 mOsm/L or onset of AKI Invasive monitoring not indicated Avoid external stimulus which can precipitate seizures
Correction of coagulopathy	Correction needed only in case of any active bleeding or planned invasive procedure.	Routine prophylactic correction of coagulopathy with FFP, cryoprecipitate or platelet not recommended.
Prevention and treatment of renal failure	Higher level ammonia >122 meq/l to be avoided. Consider early CRRT.	Avoid nephrotoxic drugs, dehydration. Avoid SLED or HD in patients with ALF.
Prevention and treatment of infection	Prophylaxis with antibiotics and antifungals may be given in selected high-risk cases with severe liver dysfunction, mechanical ventilation, or multiorgan failure. (ceftriaxone 2 gm/50 ml, 5% dextrose every 24 h can be first-line therapy) Universal precaution, i.e., topical bacterial decontamination, with oral chlorhexidine and chlorhexidine bathing (soaked wipes), is recommended	Selective gut contamination is not required
Respiratory failure and ventilator management	Early endotracheal intubation, rapid sequence induction, low tidal volume, and low PEEP preferred	Avoid sustained hyperventilation and permissive hypercapnia
Hemodynamics and cardiovascular monitoring	Invasive monitoring with CVP line, PiCCO, or real-time monitor (FlowTrac with facility for extravascular lung water) is preferred	Pulmonary catheter to be avoided.
N-acetyl cysteine	N-acetyl cysteine (NAC) should be started in all patients at a dose of 150 mg/kg body weight in 250 ml 5% dextrose over 1 h, followed by 100 mg/kg doses every 6 h over a total of 72 h.	

Table 2 (*Continued*)

Management	What to do	What not to do
Nutrition	Nasogastric tube to be placed for feeding in patients with altered sensorium No restrictions of enteral feeding and should be started within 24 h. RBS should be maintained around 90–120 mg/dl. Avoid 5D and consider 20–25% dextrose infusion at low dose to avoid cerebral edema. If hypoglycemia detected, a bolus of 50% glucose should be given.	Protein restriction Immune nutrition with arginine or glutamine avoided Hypoglycemia.
Referral to a tertiary care hospital and risk of transportation	Early referral is recommended. Patients with encephalopathy should be transported to shorter distance, in comfortable transport, and with mechanical ventilation under medical supervision. Adequate drugs for treatment on the way should also be sent along with. Relatives should be counseled about the possible outcomes and options of treatment available	Managing a patient with ALF in a setup with no facility for intensive care

ALF = acute liver failure; AKI = acute kidney injury; CVP = central venous pressure; CRRT = continuous renal replacement therapy; SLED = sustained low efficiency dialysis; HD = henodialysis.

50% dextrose administration. Fever if present should be controlled with i.v.paracetamol. Colloids and 5% dextrose are best avoided.

(c) Cerebral edema is common in ALF and may lead to surges in raised intracranial hypertension (ICH) which can be diagnosed clinically by the presence of hypertension, bradycardia, pupillary dilatation and decerebrate rigidity. A bolus of i.v.mannitol (0.5–1.0 g/kg body weight) is recommended as first-line therapy before transfer to an advanced center for further management. The prophylactic administration of mannitol is not recommended. In patients who develop seizures as a part of raised intracranial tension, short-acting benzodiazepine such as small boluses of i.v.midazolam should be considered. The use of more potent sedatives such as propofol, although effective, cannot be recommended at a peripheral setting.

(d) Regardless of the severity of coagulopathy or thrombocytopenia, no correction of coagulopathy or thrombocytopenia is recommended. Patients seldom bleed from the aforementioned factors, and correction of coagulopathy by administering fresh frozen plasma hampers the assessment of prognosis.

(e) N-Acetylcysteine (NAC) by virtue of being an antioxidant, anti-inflammatory vasodilator has been used extensively in ALF. NAC has an established role in paracetamol toxicity (which is very rare in India). There are 3 randomized controlled trials on the use of NAC.[15,16] While one trial on ALF secondary to paracetamol showed statistically significant decrease in mortality with a risk ratio of 0.65, the other 2 trials on patients with ALF from nonparacetamol etiology showed no statistically significant effect on mortality compared with placebo.[17,18] However, a subgroup post hoc analysis in the largest trial found a statistically significant transplant-free survival in 114 patients with grade I/II encephalopathy (52% survival in the NAC group vs 30% in the placebo group; P = 0.01).[17] Based on these studies, NAC is useful in ALF from nonparacetamol cases, particularly virus- and drug-induced ALF.

(f) Patients with ALF have an increased susceptibility for infections, resulting in sepsis. Infection can further complicate prognosis by worsening cerebral edema and encephalopathy, as well as multiorgan failure. Therefore, routine microbiological cultures should be obtained from blood, urine, and respiratory secretions. A large, observational study did not find antimicrobial prophylaxis to reduce either the incidence of bloodstream infection or mortality within 21 days of ALF.[18] Most experts in India have a low threshold of starting antibiotics, especially in individuals with hemodynamic compromise or increasing grades of encephalopathy. A third-generation antibiotic (ceftriaxone) may be considered in a peripheral setting pending culture reports.

(g) Specific therapies based on etiology at point of care shiuld be initiated: virus-specific nucleos(t)ide analogues for HBV-associated ALF, ribavirin in HEV-

associated ALF (although the latter needs to be evaluated by prospective studies; it should only be considered if HEV RNA is positive and hemolysis is absent). For patients with acute fatty liver of pregnancy or hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome, expeditious delivery of the infant at point of care is critical before transfer to a higher center. Antidotes for other causes of drug- or toxin-induced ALF include cholestyramine for leflunomide DILI,[19] desferoxamine for iron toxicity, and steroids in those who exhibit hypersensitivity reaction.

TIMING OF TRANSFER TO A TRANSPLANT CENTER AND PRECAUTIONS DURING TRANSFER

Patients with ALF can have unpredictable course, and a patient with seemingly early disease may rapidly pass into grade III and IV hepatic encephalopathy (HE) and die over a time span of a few hours. Ideally, they should be treated at centers that are equipped to handle the disease in terms of hepatology and intensive care unit (ICU) care as well as the facility of LT . Relatives should be explained about these possibilities and given the option to transfer the patients as early as requisite arrangement can be made.[8,20] Shifting should be with the consent of the accepting unit and after arrangement of an appropriate bed at the receiving hospital has been made. Critical care experts, if available, should be involved in the transfer of these patients. Before shifting, the treating team must ensure that the patient is in a state that he/she can reach the destination safely; hence, there should not be active bleeding. Acidosis and hypoglycemia should be corrected, in those with deeper grades or worsening HE or pulmonary complications, and the airway should be secured with elective ventilation. At least 2 secure peripheral lines or a central line should be available for transit. Fresh frozen plasma and cryoprecipitate are avoided during line insertion as they alter the coagulation and interfere with the management of the patient. Subclavian lines should be avoided because of the higher risk of complications. If expertise is available, the arterial line should be inserted.

The transfer should be made in an ambulance having facilities for advanced life support and having medical personnel trained in intubation and resuscitation. Adequate crystalloids (normal saline (NS), 5% dextrose to dilute NAC, 25% dextrose) should be carried during transit but should be only be given to maintain adequate mean arterial pressure (MAP) to ensure cerebral perfusion and to prevent hypotension, hypoglycemia, or decreased urine output. Drugs to combat common complications, as well as vasopressors such as norepinephrine and vasopressin, should also be available. The transferring hospital should be at the shortest possible distance.[21]

Consensus statements : Management at a peripheral center

1. ***Patients with severe acute liver injury (ALI) and ALF should be hospitalized and monitored closely. Measures to contact and transfer to a specialized center/ transplant center should be initiated. (Grade of evidence: low; grade of recommendation: strong)***
2. ***Supportive care and maintenance of adequate intravascular volume with crystalloids are recommended for all patients with ALF. (Grade of evidence: moderate; grade of recommendation: strong)***
3. ***Patients who progress to (grade III or IV) encephalopathy should undergo endotracheal intubation to prevent aspiration. (Grade of evidence: low; grade of recommendation: strong)***
4. ***A prophylactic administration of mannitol is not recommended. Patients with signs of ICH may be given a mannitol bolus (0.5–1.0 g/kg body weight). (Grade of evidence: moderate; grade of recommendation: weak)***
5. ***In women with acute fatty liver of pregnancy and HELLP syndrome, prompt delivery of the baby should be undertaken. (Grade of evidence: moderate; grade of recommendation: strong)***
6. ***Platelet transfusion for thrombocytopenia or fresh frozen plasma for prolonged prothrombin time is not recommended in the absence of active bleeding or in specific situations, such as insertion of intracranial pressure (ICP) monitors or active bleeding. (Grade of evidence: moderate; grade of recommendation: strong)***
7. ***In patients presenting with ALF, NAC should be administered. (Grade of evidence: high; grade of recommendation: strong)***
8. ***Broad-spectrum antibiotics such as ceftriaxone should be routinely instituted in patients with ALF with progression of HE, clinical signs of infection, or presence of systemic inflammatory response syndrome (SIRS). Grade of evidence: low; grade of recommendation: strong]***
9. ***In the setting of drug-induced ALF, discontinue all but essential medications. (Grade of evidence: high; grade of recommendation: strong)***
10. ***Cause of ALF should be sought because of availability of etiology-specific treatment such as nucleos(t)ide analogues for hepatitis B. (Grade of evidence: low; grade of recommendation: weak)***
11. ***In patients with HEV-induced ALF, administration of ribavirin may be considered if HEV RNA is positive and evidence of hemolysis is absent. However, further studies need to be sought regarding its efficacy. (Grade of evidence: low; grade of recommendation: weak)***
12. ***Relatives should be counseled about the possible outcomes and various options of treatment. (Grade of evidence: low; grade of recommendation: strong)***
13. ***Shifting should be with the consent of the accepting unit. (Grade of evidence: low; grade of recommendation: strong)***

14. ***Critical care experts if available should be involved in directing transfer of these patients. (Grade of evidence: low; grade of recommendation: strong)***

MANAGEMENT AT A TERTIARY CARE CENTER

Once a patient with ALF has been received at a transplant center, care must be taken to explain that the option of transplant will only be considered if the ALF does not resolve on medical therapy or continues to worsen. While the patient is settled in the ICU, detailed counseling of relatives must be done side by side.

In living donor liver transplantation (LDLT) settings, which is common in India, donor workup should be started preemptively as testing and counseling may take time. Furthermore, permissions will need to be taken from the authorization committee.

Management and monitoring are continued as outlined earlier. Complications, as they arise, need to be managed as detailed in the following. Many patients may become delirious during encephalopathy. Psychomotor agitation and pain contribute to ICH in patients with ALF.[22,23] As prophylactic measures to reduce ICH, the patient should be positioned with head elevated to 30° and stimulation minimized. Adequate analgesia and judicious sedation is required in patients with grade III/IV HE before placement of invasive devices such as endotracheal tube. There are insufficient data to recommend a standard agent for sedation in patients with ALF. However, it should be recognized that both propofol and benzodiazepines may exacerbate HE.[24,25] It is postulated that the metabolism of all agents used for sedation is attenuated in patients with ALF but the recovery time from propofol is shorter than that from benzodiazepines which allows more neurological examination when the infusion is temporarily interrupted. Therefore, sedation is normally undertaken with a short-acting opiate and propofol. The dosage of propofol should be limited to approximately 80 mcg/kg per minute (5 mg/kg/h) to decrease the risk of propofol infusion syndrome.[26] An opiate infusion is an option, and agents with shorter half-life such as fentanyl are preferred. Morphine and meperidine are not recommended in patients of ALF.

PREVENTION AND MANAGEMENT OF CENTRAL NERVOUS SYSTEM (CNS) COMPLICATIONS

HE is the defining component of ALF.[27] It may progress from trivial alteration in behavior to a comatose state very rapidly. Raised ICP or ICH, the most dreadful and severe complication of ALF, is the most likely the underlying pathophysiological abnormality in encephalopathy of ALF, especially of the higher grades (grade 3 or 4). It may lead to brain herniation and accounts for 20–30% of deaths due to ALF.[28] Seizures and agitation may complicate the HE of ALF although it is rarely seen in patients with cirrhosis. Several studies[29,30] have now shown that raised ammonia levels along with severe systemic inflammatory response lead to astrocyte swelling and brain edema responsible for this complication. The degree of cerebral edema is highest in patients with shorter jaundice to encephalopathy interval, i.e., less than 7days.

The prime focus of neurologic care should be on infection prevention, maintaining stable cerebral perfusion, and reduction of circulating ammonia levels. Simultaneously, it is also of paramount importance to identify patients who will not survive without a liver transplant and offer that treatment before other organ failures set in or brain stem herniation occurs, rendering liver transplant futile.

Clinical diagnosis

The clinical signs of raised ICP may be very subtle in the beginning. These may range from increased muscle tone (early manifestation) associated with or without bradycardia, hypertension (>150/90 mm Hg) (Cushing's reflex), unequal or abnormally reacting pupils, neurogenic hyperventilation, myoclonus, and spontaneous decerebrate posturing, which are late features and may denote brainstem herniation.[31] Computerized tomography (CT) scan is relatively insensitive to diagnose ICH, and moving patients to the radiology department also carries a risk of increasing ICP. The need for performing a CT scan should be individualized based on clinical examination. An noncontrast computed tomography (NCCT) head may often demonstrate abnormalities such as symmetric effacement of sulci and ventricles and loss of gray-white matter differentiation and also can be helpful to rule out other structural causes of altered sensorium such as intracranial bleeds or hematoma.

Management of ICH

Cerebral hyperemia and subsequently cerebral edema lead to ICH. Perioperative medical management may be optimized by monitoring cerebral blood flow (CBF), oxygen consumption, and ICH (Table 3). Noninvasive measures may be inaccurate, whereas invasive ICP monitoring has its inherent risks.[32,33]

Noninvasive assessment of ICH

Apart from the clinical assessment of the patient's neurological status as outlined earlier, raised ICP can be objectively assessed by using certain noninvasive tools such as ultrasound-guided estimation of optic nerve sheath

diameter (ONSD)[34] and middle cerebral artery doppler.[35] However, these methods need further validation and do suffer from interobserver and intraobserver assay variations.

a. Optic nerve sheath diameter:

Transmission of raised ICH via subarachnoid space is the likely mechanism of distension of ONSD; thus, sequential monitoring of ONSD may be used as a surrogate marker for cerebral edema. ONSD >4.5–5.5 mm, measured 3 mm below the retina, signifies ICP >20 mmHg and may help in early recognition of ICH. The technique is an easy-to-learn, simple, bedside assessment but requires further validation.

b. Middle cerebral artery Doppler:

Few studies have shown loss of cerebral blood flow (CBF) autoregulation leading to direct transmission of raised blood pressure to cerebral circulation leading to rise in cerebral perfusion pressure and thus raised ICP. In a small study in 7 patients,[13] relative changes in cerebral perfusion were determined by transcranial Doppler–measured mean flow velocity (V_{mean}), and resistance was determined by the pulsatility index in the anterior and middle cerebral arteries. Cerebral autoregulation was evaluated by concomitant measurements of mean arterial pressure and V_{mean} in the anterior and middle cerebral arteries. However such findings need further standardization as well as validation in a larger homogenous population.

Invasive ICP monitoring

Cerebral hypoperfusion suggested by prolonged (>2 h) intracranial hypertension (ICP >25 mm Hg) or a low CPP (MAP minus ICP <40 mm Hg) portends a poor neurologic recovery and may contraindicate LT.[36] There is a 5% risk of clinically significant intracranial hemorrhage, which varies in direct proportion to the invasiveness and reliability of the monitor.[37]

In a protocol-based invasive ICP monitoring (IICPM) study on patients with ALF by Rajajee et al,[33] 37 adult patients with ALF and grade 4 encephalopathy with a reasonable likelihood of survival were considered eligible for IICPM. The coagulopathy reversal protocol included administration of recombinant Factor VIIa and desmopressin (a goal platelet count >50,000/mm^3 and fibrinogen >100 mg/dL). Intraparenchymal monitor insertion was performed within an hour of the recombinant Factor VIIa dose. CT of the brain was performed before and within 24 h of monitor placement. Twenty-four of 37 patients (65%) with ALF underwent IICPM. Four patients underwent LT. There was one asymptomatic ICH after IICPM, in a patient who had an excellent outcome. Sustained ICH occurred in 13 of 24 monitored patients (54%); 5 of 24 (21%) and required extreme measures for ICP control. Such measures were successful in 4 patients; and 12 of 24 patients (50%) died, but only 4 deaths (17%) were attributed to ICH. Six of the 8 survivors with a 6-month follow-up had good functional outcomes (Glasgow Outcome Scale > 3), suggesting that protocol-directed use of IICPM in ALF is feasible, associated with a low incidence of serious

Table 3 Management Principles to Prevent and Treat CNS Complications.

Optimization of cerebral blood flow:	a. Elevate head of bed by 20–30° b. Correct fluid balance and avoid volume overload c. Maintain MAP at ~60–70 mm Hg d. Hyperventilate to keep PCO_2 at 35–40 mm Hg
Prevent surges in ICP	a. Minimize head turning b. Avoid bilateral internal jugular vein cannulation c. Invasive ventilation for grade 3 and 4 hepatic encephalopathy with adequate sedation and analgesia (short-acting agents such as propofol and fentanyl) d. Minimize suctioning and stimulation: use lidocaine e. Treat agitation with intubation and sedation; paralyze if necessary f. Monitor for seizures: (EEG to detect nonconvulsive seizures) g. Induce hypernatremia to a sodium concentration of ~150 mmol/L Mannitol (0.5–1 g/kg body weight IV bolus) when required liver transplantation: assess need and futility
Rescue measures	a. Hypothermia b. Indomethacin c. Total hepatectomy

CNS = central nervous system; MAP = mean arterial pressure.

complications, and has a significant impact on clinical management.

However, clinical endpoints are not standardized and management needs to be protocolized along with larger data on safety before invasive intracranial monitoring can be routinely recommended. The need of the hour is to identify the subgroup of patients who will benefit the most from invasive monitoring such as patients with higher grade of HE, concomitant cardiovascular failure, or persistent rise in ammonia to >150 μg/dL, considering the risk involved.

Medical management: general measures

Measures should be undertaken to prevent unnecessary ICP increases such as the neutral position of the head with the patient elevated at 30° and avoidance of bilateral jugular venous cannulation. Fever should be vigorously treated and cause searched for, and infections ruled out as outlined earlier. Metabolic derangement such as hypoglycemia/hyperglycemia should be avoided with rigorous electrolyte monitoring and corrections as needed.

Mechanical ventilation and sedation

The medical management of ICH requires optimization of cardiorespiratory parameters. Intubation of the airway with progression to grade 3 or grade 4 encephalopathy should be undertaken with appropriate sedation and paralysis. Propofol is short-acting and reduces the ICP and should be the preferred agent for sedation.[38] Limited respiratory suctioning with instillation of 1–2 ml of lidocaine, with prior 100% oxygen before suctioning, is recommended to prevent acute surges in ICP.

Management of seizures

Patients with ALF are prone to develop seizures which may further worsen cerebral edema. Often seizures are nonconvulsive. Prophylactic use of antiepileptics has not been shown to provide benefit.[39] Phenytoin has been the traditional antiepileptic of choice; however, less hepatotoxic antiepileptics such as levetiracetam or lacosamide should be used when seizure activity is suspected on electroencephalogram (EEG).

Hyperventilation

Spontaneous hyperventilation with resulting hypocapnia may be protected by promoting cerebral vasoconstriction, controlling hyperemia, and decreasing ICP. There is no role of prophylactic hyperventilation; however, moderate reduction of pCO_2 (25–30 mmHg) may be undertaken in mechanically ventilated patients to reduce ICP, who show signs of raised ICP, although its effects are short-lasting.[40]

Hyperammonaemia

HE with hyperammonemia can be treated with bowel cleansing by lactulose or saline enema and nonabsorbable antibiotics (rifaximin); however, their role is unclear in patients with ALF.[41] Lactulose administered orally or via a gastric or jejunal tube may be problematic as it may result in gaseous distention of the bowel, which complicates transplant surgery. Role of I.V. L-ornithine L-aspartate (LOLA) in patients with ALF was refuted in a recent, double-blind, randomized, placebo-controlled study.[42]

Hypertonic saline (3%)

A prospective randomized controlled clinical trial,[43] including 30 patients with grade 3 or 4 HE, examined the effect of induced hypernatremia on the incidence of intracranial hypertension. Patients in group 1 (n = 15) received the normal standard of care. Patients in group 2 (n = 15) received standard care and hypertonic saline (30%) via infusion to maintain serum sodium levels of 145–155 mmol/L. ICP was monitored in all patients with a subdural catheter for up to 72 h after inclusion. Serum sodium levels became significantly different from the levels observed in the control group at 6 h (P < 0.01). Over the first 24 h, norepinephrine dose increased relative to baseline in the control group (P < 0.001; 13 patients) but not in the treatment group. ICP decreased significantly relative to baseline over the first 24 h in the treatment group (P = 0.003; 13 patients) but not in the control group. The incidence of raised ICH, defined as a sustained increase in ICP to a level of 25 mmHg or greater, was significantly higher in the control group (P = 0.04). It is recommended to maintain serum sodium concentration between 145 mmol/L and 150 mmol/L with an infusion of hypertonic saline.

Osmotherapy

Surges of ICH despite aforementioned prophylactic maneuvers prompt urgent treatment. First-line therapy includes increasing blood osmolality with mannitol boluses (20%, 0.5–1 g/kg body weight).[44] Mannitol is ineffective in returning ICP to an acceptably low level (<25 mmHg) in individuals with severe ICH (>40 mmHg to 60 mmHg), and initial improvements in ICP usually wane, necessitating multiple doses, which can result in hyperosmolality (>320 mOsm/L). Close watch to keep serum osmolality below 320 mOsm/L should be undertaken. Mannitol will transiently expand circulating blood volume and increase central venous pressure, as well as ICP. In patients with renal failure, use of mannitol should be avoided rather ultrafiltration with continuous renal replacement therapy (CRRT) can be increased to maintain intravascular

volume and prevent increased central venous pressure. Hypertonic saline boluses (200 ml, 3% or 20 ml, 30%) can be used for established cerebral edema surges in patients with ALF,[45] although this approach lacks studies as per current literature.

Rescue therapy

Patients who break through despite osmotic therapy for ICH may succumb to brainstem herniation unless an urgent LT is performed. Rescue measures that may be considered under these conditions include the induction of deeper sedation with propofol[46] or barbiturates,[47] intravenous boluses of indomethacin,[48] and therapeutic hypothermia (TH).[28,49] Of these, only hypothermia has been studied systematically, albeit in a small number of patients. In a retrospective analysis of the U.S. Acute Liver Failure Study Group (ALFSG) registry, 97 patients in whom TH was induced were compared with 1135 controls. TH was not associated with consistent improvement in 21-day survival.[49] Spontaneous hypothermia sometimes accompanies patients with ALF and reduces ICP; hence, it should not be corrected.

Consensus statement: Prevention and treatment of CNS complications

15. ***Patients with subtle alteration in sensorium or encephalopathy grade I/II must be frequently evaluated clinically for signs of deterioration regularly. Benzodiazepines should not be used. (Grade of evidence: low; grade of recommendation: strong)***
16. ***Patients in grade 3 or 4 encephalopathy with elective intubation should be given adequate analgesia, propofol being the preferred agent. (Grade of evidence: moderate; grade of recommendation: strong)***
17. ***Noninvasive assessment by optic nerve sheath diameter and clinical parameters should be carried out in all intubated patients regularly. (Grade of evidence: moderate; grade of recommendation: strong)***
18. ***Invasive intracranial monitoring may be considered in select group of patients at high risk of ICH in centers with expertise (patients with higher grades of HE, hyperacute presentations, persistent ammonia levels >150 mcg/dl, and/or cardiovascular failure). (Grade of evidence: moderate; grade of recommendation: strong)***
19. ***Prophylactic use of antiepileptics is not recommended. If indicated, newer less hepatotoxic antiepileptic agents such as levetiracetam or lacosamide should be used based on EEG monitoring. (Grade of evidence: moderate; grade of recommendation: strong)***
20. ***Nonabsorbable antibiotics, lactulose, and parenteral LOLA have not been shown to improve survival or improvement in encephalopathy in ALF. (Grade of evidence: moderate; grade of recommendation: strong)***
21. ***Stringent infection control measures should be practiced, and regular periodic surveillance cultures should be performed in all patients with ALF. (Grade of evidence: moderate; grade of recommendation: strong)***
22. ***Empirical antibiotics should be considered in patients with clinical suspicion of infections or progressive or higher grades of encephalopathy or multiorgan failures based on local antibiograms and modified based on subsequent culture and sensitivity reports. (Grade of evidence: moderate; grade of recommendation: strong)***
23. ***Hypertonic saline infusion (3%) should be used to maintain serum sodium levels around 145–150 mmol/L. (Grade of evidence: high; grade of recommendation: strong)***
24. ***Mannitol or hypertonic saline boluses should be administered for surges of ICP, maintaining serum osmolality below 320 mOsm/L. (Grade of evidence: moderate; grade of recommendation: strong)***
25. ***Early referral for LT should be done in patients with poor prognostic factors and refractory ICP. (Grade of evidence: low; grade of recommendation: strong)***

PREVENTION AND TREATMENT OF RENAL COMPLICATIONS

Acute kidney injury (AKI) in the setting of liver cirrhosis (LC) has recently been defined by the International Club of Ascites (ICA) as either an absolute increase in serum creatinine (SCr) of ≥0.3 mg/dl in less than 48 h or an increase in SCr of ≥50% (≥1.5-fold from baseline) in less than 7 days. AKI is of four types: prerenal, hepatorenal (HRS-AKI), intrarenal (most often ATN), and postrenal (rare). The severity of AKI in LC has been staged from stages 1–3, which carry prognostic significance. Stage 1 has been subdivided into stage 1A and 1B.[8] Although it has been suggested that AKI in ALF should also be defined in the same manner,[50] no prospective study of AKI in ALF applying this definition and severity grading has been reported so far.

Frequency, risk factors, and outcomes of AKI in ALF

The frequency of AKI in ALF is high, ranging from 40 to 80% in reports from tertiary centers in the West [European Association for the Study of the Liver (EASL) guidelines]. The frequency of AKI is higher in acetaminophen-related ALF (80%) than in non–acetaminophen-related ALF (51%).[51] In a retrospective analysis of data from more than 1600 patients, the US ALFSG found that AKI developed in 70% of patients with ALF and that renal replacement therapy (RRT) was needed in 30% of these patients.[52] Interestingly, the frequency of AKI in large series reported from northern India (Delhi, Srinagar,

Table 4 Frequency of AKI in ALF in India.

Series	Number	Mortality (%)	AKI (%)
SK Acharya et al. Hepatology 1996[53]	423	280 (66)	13 (3)
MS Khuroo. J Viral Hep 2003[54]	180	131 (72.8)	54 (30)
V Bhatia. Hepatology 2008[12]	1015	575 (56.6)	94 (9.2)
R Kumar. Hepatology 2010[55]	1229	686 (55.8)	134 (10.9)

ALF = acute liver failure; AKI = acute kidney injury.

Chandigarh) has been low (3–10%), although a figure of 30% is reported in one study from Srinagar (Table 4).[53–55] This is to be expected as paracetamol-related ALF is virtually not seen in India.

Risk factors for AKI in ALF

Risk factors for AKI include increased age, paracetamol-induced ALF, hypotension, the presence of SIRS, and infection.[8] Severe kidney injury needing RRT was seen more often in patients with acetaminophen-induced ALF than in patients with other causes of ALF (34% vs. 25%; $P < 0.002$).[52] Compared with patients with ALF without AKI, those with AKI had poorer liver function (higher international normalized ratio (INR) values [$P < 0.001$] and a higher proportion with coma grades 3 or 4 [$P < 0.001$]) or presented more often with hypotension requiring vasopressor therapy ($P < 0.001$).[52]

The occurrence of AKI is a harbinger of poor outcome in patients with ALF as it results in prolongation of hospital stay (11 days vs. 6 days in the non-AKI cohort), as well as reduced spontaneous survival (36% vs. 84% in the non-AKI cohort).[51] Significantly fewer patients with ALF and AKI survived for 1 year. Survival was better in patients with acetaminophen-associated or ischemic ALF, even in those needing RRT, than in patients with ALF attributed to other causes (transplant-free survival > 50% vs. 19%; $P < 0.001$). Only 4% of patients requiring RRT became dependent on dialysis.[52]

Prevention of AKI in ALF

Steps to prevent the development of AKI in ALF include correction of hypotension, prompt treatment of infection, avoidance of nephrotoxic medications, and intravenous contrast agents. The risks and benefits of contrast radiology and aminoglycoside use must be balanced in the given clinical context.[8]

Renal replacement therapy

RRT entails replacement of the renal filter function by filtering blood through a semipermeable membrane, which may be intracorporeal (peritoneal dialysis) or extracorporeal (hollow-fiber dialyzers). The process involves the removal of fluid and solutes from the blood and replenishment with bicarbonate buffer.Ultrafiltration (UF) removes fluid by the application of negative pressure outside the hollow fibers. Solute removal is achieved by hemofiltration (HF), hemodialysis (HD), or a combination, i.e., hemodiafiltration (HDF), while circulating blood volume is maintained by replenishment with bicarbonate buffer. Characteristics of intermittent continuous renal replacement therapy (ICRRT) and continuous modes of RRT (CRRT) are summarized in Table 5.[56]

Various forms of CRRT (CVVH/CVVHD/CVVHDF) are preferred to IRRT for patients with ALF as these therapies avoid the large metabolic and hemodynamic fluctuations associated with intermittent dialysis, which can precipitate episodes of raised ICP.[8,56] Slow/sustained low-efficiency

Table 5 RRT Modalities and Their Characteristics.[56]

Modality	Duration	Clearance mechanism		Replacement fluid
		Convection	Diffusion	
Continuous renal replacement therapy (CRRT)				
Continuous venovenous hemofiltration (CVVH)	≥24 h	++++	–	+++
Continuous venovenous hemodialysis (CVVHD)	≥24 h	+	++++	+
Continuous venovenous hemodiafiltration (CVVHDF)	≥24 h	+++	+++	++
Slow continuous ultrafiltration (SCUF)	≥24 h	+	–	0
Intermittent renal replacement therapy (IRRT)				
Intermittent hemodialysis (IHD)	4–6 h	+	++++	+
Sustained low efficiency dialysis (SLED)	6–12 h	+	++++	+

RRT = renal replacement therapy.

Table 6 Conventional Indications for RRT in ALF With AKI.[56]

Indications	Cutoffs
Uremic complications	Pericarditis, uremic bleeding
Fluid overload	Diuretic-resistant organ edema in the presence of AKI
Acidosis	Serum pH £ 7.15
Hyperkalemia	K^{+3} 6.0 mmol L^{-1} and/or EKG abnormalities
Hypermagnesemia	$Mg^{+2\ 3}$ 4.0 mmol L^{-1} and/or anuria or absent DTR
Oligoanuria	Urine output < 200 mL.12 hr^{-1} or anuria

ALF = acute liver failure; AKI = acute kidney injury; DTR = deep tendon reflexes; EKG = electrocardiogram; RRT = renal replacement therapy.

dialysis (SLED), a modification of IHD with decreased blood flow rate, dialysate rate, and increased duration, is a reasonable alternative, with better cardiovascular tolerability than IHD and is less complicated and less expensive than various forms of CRRT. However, there are no data comparing it with the established forms of CRRT.[57] Good results have been reported with the use of high-flow continuous hemodiafiltration (HFCHDF) with or without slow plasma exchange (SPE) from Japan.[58] Lactate-free buffers accelerate correction of acidosis. Adequate serum sodium and serum osmolarity levels should be maintained during CRRT because hyponatremia (Na+ ˜140 mmol/L) can worsen ICH and has been shown to independently increase mortality in patients with ALF. Higher CRRT dose (40 mL/kg/hr) is not better than low-dose CRRT (25 mL/kg/hr) in terms of benefit in mortality reduction.[59]

Anticoagulation during CRRT

Although patients with ALF often have coagulopathy, they need some form of anticoagulation (AC) to prevent circuit clotting, unless there is evidence of active bleeding. Various options for AC are standard unfractionated heparin (UFH), half-dose UFH ('tight' heparin), heparin free with saline flushes, and regional citrate anticoagulation (RCA). Although RCA is tolerated by patients with liver cirrhosis, close monitoring of citrate levels, as well as total and ionized calcium levels, is needed in patients with ALF owing to the risk of citrate accumulation. Only a few studies report its use in ALF.[60,61]

Indications and timing of initiation of CRRT for AKI in ALF

There is little disagreement that 'rescue RRT' should be initiated in patients with ALF if conventional indications for RRT (Table 6) are present.[56] However, early initiation of CRRT, even in the absence of conventional indications, is being used increasingly for patients with ALF and AKI to treat hyperammonemia and thus prevent and control cerebral edema and HE. CRRT has been shown to increase ammonia clearance in parallel with creatinine clearance.[62,63] A recent multicentre cohort study involving 1186 consecutive patients with ALF found an association between higher serum ammonia level at admission and deeper grade of HE, as well as poorer 21-day transplant-free survival. In a smaller cohort (n = 340), CRRT achieved greater lowering of serum ammonia level (P < 0.007) compared with no-RRT group and was associated with a decreased 21-day transplant-free all-cause mortality (odds ration [OR], 1.68 [95% confidence interval {CI}, 1.04–2.72]), while IRRT failed to achieve reduction in serum ammonia compared with no-RRT group and was associated with increased mortality.[63] Early initiation of RRT should be considered for patients with ALF with markedly elevated ammonia and/or progressive HE. However, more studies are needed to establish timing, duration, and intensity of CRRT for management of hyperammonemia in ALF. RRT may be offered to manage sodium imbalance and facilitate temperature and metabolic control.[8]

Combination of CRRT (CVVH/CVVHD/CVVHDF/HFCHDF) with liver support therapies (HVPE) or liver assist devices, e.g., molecular adsorbants recirculation system (MARS), single-pass albumin dialysis (SPAD), fractional plasma separation and adsorption (FPSAPrometheus), HepatAssist, Dialive, bioartificial liver, etc. are being used for ALF in research settings.

Consensus statement: Prevention and treatment of renal complications

26. ***AKI is common and is present in 40–80% of patients with ALF, 30–40% of whom are likely to need RRT. AKI is less common in ALF in India (10–30%). (Grade of evidence: moderate)***
27. ***AKI is more common in paracetamol-induced ALF, in severe forms of ALF (with higher INR values and deeper grades of coma), and in patients presenting with hypotension needing vasopressor support. (Grade of evidence: high)***
28. ***Development of AKI in patients with ALF is associated with poorer outcomes, including prolongation of hospital stay, reduced spontaneous survival, and reduced survival at one year. (Grade of evidence: high)***
29. ***The INASL recommends that RRT for ALF with AKI should be initiated as per standard indications, e.g., fluid overload, hyperkalemia, metabolic acidosis, uremia, etc. (Grade of evidence: moderate; grade of recommendation: strong)***
30. ***The INASL recommends that continuous RRT should be preferred over intermittent HD as it is better tolerated with lower chances of raised intracranial pressure. (Grade of evidence: moderate; grade of recommendation: strong)***

31. ***The INASL suggests that early institution of CRRT should be considered for persistent hyperammonaemia, hyponatraemia, and other metabolic abnormalities, as it may reduce mortality. (Grade of evidence: low; grade of recommendation: weak)***
32. The ***INASL suggests use of half dose of UFH or heparin-free RRT with saline flushes for anticoagulation during CRRT and also suggests close monitoring if RCA is used during CRRT for AKI in ALF. (Grade of evidence: low; grade of recommendation: weak)***
33. ***The INASL suggests further studies of combinations of CRRT with liver support therapies or liver assist devices to improve outcomes in patients with AKI in ALF. (Grade of evidence: low; grade of recommendation: weak)***

PREVENTION AND MANAGEMENT OF INFECTIONS

Spectrum and diagnosis of infections in patients with ALF

Compromised natural defenses and stay in the critical care unit with a number of interventions such as central lines, endotracheal intubation, and urine catheters predispose to development of infections in these patients. The incidence of bacterial infections varies based on the region. Infections may lead to further rise in ICP and increased mortality.[64] Rolando et al[65] reported that infection-causing organisms were bacteria in 80% and fungi in 32%. Acharya et al[66] reported the prevalence of microbial infections in 52%, of which 43% were secondary to gram-negative bacteria while 25% were secondary to fungal organisms. Gram-negative organisms have been more frequently reported in more recent studies. Karvellas et al[18] evaluated 1551 patients with ALF; 34% of whom had infections of which 14% had bloodstream infections (BSIs) or bacteremia. They noted a significantly reduced 21-day survival with BSI mostly in patients in the nonacetaminophen group. The survival rates were however not different in patients who underwent LT irrespective of the presence of BSIs. Furthermore, there was no benefit noted from antimicrobial prophylaxis. Therefore, currently the role of antimicrobial prophylaxis remains controversial. The diagnosis of infection in these patients is also extremely challenging as classical signs such as fever and leukocytosis can be absent in 30% of the cases.[65] The hemodynamic and biochemical alterations in ALF also pose a challenge to the clinician to diagnose infection as these are very similar to those seen in septic shock. In patients with ALF, any unexplained hypotension or renal failure, worsening grade of encephalopathy, and a new onset of metabolic acidosis could be considered as signs of sepsis. Fungal infections are seen in almost one-third of these patients and are detrimental. Fever, leukocytosis, worsening grade of encephalopathy, and renal failure could all be considered as early markers of fungal infections in these patients.[64] Biomarkers such as C-reactive protein (CRP) and procalcitonin fail to provide reliable prediction of the patient outcome.[67]

Treatment of infections in ALF

The majority of infections in ALF occur within 72 h of admission, and it is suggested that one should have a low threshhold for starting antimicrobial therapy. There is a lack of prospective studies and randomized controlled trials examining the impact of infections or of antimicrobial prophylaxis in these patients. In different studies, pneumonia has been reported as the most frequent infection in 50% followed by bacteremia and urinary tract infections in 20–25% of patients.[68] The challenge is to choose the most appropriate antibiotic regimen which has to be guided by the local institutional and microbiological profile, the decision of including empirical antifungals in patients with risk factors, and diagnosis of infection in patients wherein the organism cannot be speculated. Furthermore, each center also has its own practice of preventing BSI and ventilator-associated pneumonia, making it difficult to extrapolate the results of clinical studies performed in this context.[69,70] In addition, with the recent surge in multidrug-resistant infections in countries such as India as compared with the West, the policy and choice of empirical antibiotics would be different. The choice is pertinent as an inappropriate initial antibiotic is associated with worse outcomes in patients with infections.The ALFSG has recommended the use of antimicrobial prophylaxis in patients with ALF and advanced HE, refractory hypotension, and presence of systemic inflammatory response syndrome components and for patients listed for LT. However, this recommendation remains questionable in view of lack of adequately powered controlled trials.[71]

Consensus statement: Prevention and treatment of infections

34. ***Infections are commonly seen in patients with ALF and associated with worse outcomes. (Grade of evidence: moderate; grade of recommendation: strong)***
35. ***Diagnosis of infection is challenging and mostly relies on clinical signs. Worsening hypotension or encephalopathy, renal failure, or development of metabolic acidosis could suggest sepsis in patients with ALF. (Grade of evidence: low; grade of recommendation: weak)***
36. ***Pneumonia and bacteremia are the most common infections reported in patients with ALF. (Grade of evidence: moderate; grade of recommendation: strong)***

37. ***One should have a low threshold for starting antibiotics on clinical suspicion of infection. (Grade of evidence: low; grade of recommendation: strong)***
38. ***Although there is scarce evidence to support prophylactic antibiotics in ALF, the treating unit may institute such therapy where the risk of infection is considered high. (Grade of evidence: low; grade of recommendation: strong)***
39. ***The choice of empirical antibiotics should be guided by local microbiological profile. (Grade of evidence: moderate; grade of recommendation: strong)***

PREVENTION AND MANAGEMENT OF RESPIRATORY COMPLICATIONS

To protect the airway, better control of oxygen and carbon dioxide levels, and to facilitate the general care, endotracheal intubation should be considered in all patients with ALF progressing to ≥ grade 3 encephalopathy (West Haven). (EASL Guideline) Sedation and intubation also help in controlling the agitation, which can lead to surges in ICP. Intubation may be done with rapid sequence induction (RSI) techniques which minimize the increase in ICP.[72] Sedation with a short-acting sedative alone or in combination with a short-acting narcotic is suggested. Recent evidence supports the use of propofol (5–50 μg/kg/min) which may even have an independent beneficial effect on ICP and has anticonvulsant properties. (Widjik Propofol) Since neuroparalytics can mask the seizure activity, these can be avoided, but if required (if sedation alone is not enough), neuromuscular blockade with nondepolarizing agents such as cis-atracurium (not dependent on hepatic and renal metabolism) is preferred for this purpose.[73] Controlled mechanical ventilation (CMV) with low tidal volume (6–8 ml/kg predicted body weight) is preferred as a lung-protective strategy once the patient is mechanically ventilated.[74] Minute ventilation is titrated to get a target pCO_2 of 30–40 mmHg and to allow hyperventilation at the time of the transient increase in ICP; however, sustained hyperventilation should be avoided.[75,76] Even though mild levels of positive end-expiratory pressure (PEEP) may not lead to an increase in ICP, it is best to either avoid PEEP or keep it to the minimum. In general, noninvasive ventilation should be avoided in patients with ALF because of poor compliance, high risk of neurological deterioration, and aspiration.[77]

Common respiratory issues which can affect patients with ALF include pleural effusion, atelectasis, ascites, and impaired respiratory compliance due to raised intra-abdominal pressure or chest wall edema. Intrapulmonary shunting has been reported in uncommon ALF due to ischemic hepatitis.[78] The occurrence of acute lung injury (ALI) and ARDS was reported more commonly earlier in around 33–37% of patients with ALF. However, with the improvement in critical care, ALI and ARDS occur less frequently with recent series reporting it to be around 21% in ALF and may not significantly affect the outcome.[79,80] Patients with raised ICP, those on vasopressor therapy and heavy sedation, and those in whom bronchial toilette is being avoided are at increased of developing pulmonary and extrapulmonary sepsis and ARDS. ARDS should be managed with standard ventilator techniques, keeping in mind an appropriate monitoring for increased ICP with increased PEEP and other special techniques such as prone ventilation and oscillation. There are no data on the utility of extracorporeal membrane oxygenation (ECMO) in patients with ALF.

Special care of the airway to avoid ventilator-associated pneumonia in patients with ALF include proper position and physiotherapy, endotracheal lidocaine for suction, and regular sampling of secretions for culture.[1] Percutaneous tracheostomy, if required during weaning, is usually safe and tolerated even in the presence of severe coagulopathy.[81]

Consensus statement: Prevention and treatment of respiratory complications

40. ***Sedation with propofol, low tidal volume (6–8 ml/kg predicted body weight), and minimum PEEP is the preferred lung-protective strategy in mechanically ventilated patients with ALF. (Grade of evidence: moderate; grade of recommendation: strong)***
41. ***Minute ventilation should be titrated to get a target pCO_2 of 30–40 mmHg with avoidance of hypocarbia and hypercarbia. (Grade of evidence: moderate; grade of recommendation: strong)***
42. ***ALI/ARDS is not very common in ALF and should be managed with standard ventilator techniques. (Grade of evidence: moderate; grade of recommendation: strong)***
43. ***Percutaneous tracheostomy, if required during weaning, is usually safe and tolerated even in the presence of severe coagulopathy. (Grade of evidence: moderate; grade of recommendation: weak)***

PREVENTION AND MANAGEMENT OF CARDIOVASCULAR COMPLICATIONS

Cardiovascular assessment is important for the initial management of ALF. Apart from clinical assessment, one should also perform chest X-ray, electrocardiogram (EKG), and baseline echocardiography. Hemodynamic instability threatens life by reducing CPP as well as by compromising tissue perfusion elsewhere. Myocarditis as

a complication of ALF secondary to hepatitis A has been described.[82] It is due to an immune response to myocyte infiltration of the virus. It may present like myocardial infarction with angina, arrhythmias, ECG changes, and troponin elevation.

ALF is usually associated with hemodynamic derangements which contribute to multiorgan failure. ALF is characterized by hyperdynamic circulation with high cardiac output, low MAP, and low systemic vascular resistance through increased NO production and alterations in cyclic GMP. As ALF progresses, there is progressive decrease in systemic vascular resistance.[83–85] This systemic vasodilation leads to relatively insufficient circulating blood volume and end organ dysfunction. Hypovolemia is also aggravated by poor oral intake of these patients and transudation of fluid into extracellular space. It manifests as oliguria, acidosis, or renal failure. SIRS – an essential component of ALF – also plays an important role in the pathogenesis of systemic vasodilation.

Proper fluid administration is necessary to improve tissue perfusion. Hyperlactatemia occurs in ALF as a consequence of decreased volume, which gets corrected with volume supplementation, but if it persists, then it indicates the severity of the underlying liver failure.[86] Volume repletion is best done by giving normal saline or balanced plasmalyte solution. Hypochloremia and hypoglycemia should be avoided. Volume overload also should be avoided as the positive balance is associated with increased tissue edema and greater impairment of microcirculatory flow secondary to raised right-sided cardiac pressure affecting liver venous outflow and hence liver function, regeneration, and gut integrity.[87] Volume overload should also be avoided in patients with rare ALF with ascites for which an ascitic tap may help in improving venous return and cardiac index.[88] In case cerebral edema or raised ICH is suspected, colloid administration with concentrated albumin can be considered.[89]

If hypotension persists after volume repletion and treatment of potential sepsis, norepinephrine at a dose of 0.05ug/kg/min should be given up to a maximum dose of 0.2–0.3ug/kg/min. Norepinephrine augments peripheral organ perfusion while minimizing tachycardia and preserving splanchnic and hepatic blood flow.[90] MAP should be between 60 and 75 mmHg. If this is not achieved by the aforementioned measures, terlipressin could be added, which helps in decreasing the dose of norepinephrine. A recent study has shown that it also increases CPP without increasing ICP.[91] A higher MAP of >75 mmHg may be associated with an increased risk of atrial fibrillation.[92] More than 50% of patients with ALF may have adrenal dysfunction.[93] A recent study has suggested that steroids decreased vasopressin requirements and prolong time to death providing time to obtain a suitable liver for transplantation. There however may be an increased risk of sepsis and reactivation of viruses.[94]

Consensus statement: Prevention and treatment of cardiovascular complications

44. ***Patients with ALF are volume-depleted requiring crystalloid volume repletion. (Grade of evidence: moderate; grade of recommendation: strong)***
45. ***If hypotension persists, norepinephrine should be administered. (Grade of evidence: moderate; grade of recommendation: strong)***
46. ***Volume overload is detrimental; hence close monitoring is important. (Grade of evidence: moderate; grade of recommendation: strong)***
47. ***Ideal MAP should be between 60 and 75 mm/hg. Higher MAP may be detrimental. (Grade of evidence: moderate; grade of recommendation: strong)***
48. ***Hydrocortisone 200 mg/day in divided doses is indicated if hypotension persists. It does not reduce mortality but decreases vasopressin requirements. (Grade of evidence: moderate; grade of recommendation: strong)***

MANAGEMENT OF COAGULOPATHY

Prolonged prothrombin time is integral to the definition of ALF and has prognostic significance.[95] Recent studies have suggested that despite the frequently intimidating elevation of the INR and moderate thrombocytopenia, global hemostasis in most patients with ALF remains normal or rebalanced. This is related to significant increases in endogenous heparinoids, procoagulant microparticles, von Willebrand factor and factor VIII, reduced procoagulant and anticoagulant factors, and release of "younger" more reactive platelets in patients with ALF. Bleeding complications in patients with ALF are markers of severe systemic inflammation rather than of coagulopathy and so portend a poor prognosis.[96] Incidence of clinical bleeding or its contribution to the morbidity and mortality of patients with ALF is uncommon, leading to a perception that bleeding complications are not an important determinant of outcome. In one of the largest series of reported patients with ALF, bleeding was not mentioned as a complication of ALF or a cofactor in the poor outcome.[97] Therefore, it is suggested that "no routine correction of coagulation abnormalities" is warranted in patients with ALF.[98] Monitoring of coagulation in patients with ALF requires standard and extended laboratory techniques (thrombin generation, factor VIII, etc.), and thromboviscous technology (thromboelastography) should increasingly become a standard additional measure.

Prophylactic fresh frozen plasma (FFP) does not reduce the risk of significant bleeding; rather, it may increase the

risk of volume overload and may obscure the trend of prothrombin time as a prognostic marker. However, such corrections are attempted in patients with clinically significant bleeding or before placement of invasive devices such as ICP monitoring. The exact goal of treatment with FFP is not evident. However, replacement with FFP may be considered in an occasional patient with clinically significant bleeding or while performing invasive high-risk procedures by giving approximately 3–5 mL/kg/h. A rough target would be to correct the INR to approximately 1.5 and platelet count to approximately 50,000/mm^3.[99,100]

Vitamin K deficiency may contribute to the coagulopathy of ALF in a minority of patients. The administration of vitamin K is recommended empirically. The cryoprecipitate is recommended in patients who have significant hypofibrinogenemia (<100 mg/dL) and are bleeding. Antifibrinolytic agents such as aminocaproic acid should be considered in patients with diffuse mucosal and puncture wound oozing. Recombinant factor VIIa (rFVIIa) administration may be considered in circumstances where FFP has failed to correct INR. Because the use of rFVIIa may increase the risk of thrombotic complications, it should not be given to patients with a history of myocardial infarction, stroke, or unstable angina within 2 weeks, or in patients with deep venous thrombosis, those who are pregnant, or those with Budd-Chiari syndrome. In subjects with persistent coagulopathy despite FFP who have contraindications to rFVIIa, plasma exchange is effective and should be considered.

The incidence of upper GI bleeding in patients with ALF has been shown to be related to coagulopathy and decreased by gastric acid suppression.Using intravenous proton pump inhibitors is recommended. The risk of bleeding from stress ulceration of gastric mucosa is reduced by the prophylactic use of sucralfate. Although indications in the specific setting of ALF are not available, it seems reasonable to target plasma fibrinogen levels of 1.5–2 g/L by infusing fibrinogen concentrate at an initial dose of 25–50 mg/kg body weight and a platelet count >60,000/ll. The role of additional supportive therapies such as tranexamic acid should also be considered in this context.[8]

Consensus statement: Prevention and treatment of hematological abnormalities

49. ***Hemoglobin target for transfusion is 7 g/dl. Venous thrombosis prophylaxis should be considered in the daily review. (Grade of evidence: moderate; grade of recommendation: strong)***

PREVENTION AND MANAGEMENT OF METABOLIC COMPLICATIONS

ALF is often complicated by metabolic complications such as hypoglycemia, hyponatremia, metabolic acidosis especially lactic acidosis, hypocalcemia, hypomagnesemia, and hypophosphatemia. Hypoglycemia is common and may worsen sensorium. It is often associated with AKI and carries higher mortality.[101] The prevalence of hypoglycemia is higher in patients with paracetamol-induced ALF and AKI (55%) when compared with patients without AKI (22%).[102]

Blood glucose should be monitored every 2 hourly. When hypoglycemia is detected, it should be promptly treated with an intravenous bolus of 50% dextrose which can be repeated. Too many boluses of hypertonic solutions may cause changes in osmolality of blood and may adversely affect cerebral functions in the presence of cerebral edema. Hyperglycemia, if it occurs, should be treated with infusion of insulin with a target level of blood glucose between 150 and 180 mg/dl.[103]

Hyponatremia is another common complication that may result from poor oral intake and due to vomiting. The targeted value of 145–150 mEq/l should be maintained by constant monitoring and continuous infusion of hypertonic saline (3%). Prophylactic administration of hypertonic saline in the first 36 h of admission to the ICU has been shown to reduce the incidence of raised ICP and the need for vasopressors to maintain adequate blood pressure. Changes in serum sodium levels should be gradual (<10 mEq/L in 24 h) to avoid central pontine myelinolysis and additional neurological deterioration. Care should also be taken to avoid infusion of large boluses of hypertonic saline as it may adversely affect the management of cerebral edema.[104–106]

Metabolic acidosis especially due to increased lactate is common in hyperacute ALF owing to paracetamol overdose. Lactic acidosis is an important marker for poor prognosis and should be promptly treated with RRT. In lesser grades of metabolic acidosis, intravenous infusion of sodium bicarbonate is recommended. Blood tests should also be conducted to check for hypophosphatemia, hypomagnesemia, and hypocalcemia, and these should be corrected promptly. Hypophosphatemia is considered a favorable prognostic sign which is associated with liver regeneration.[107]

Consensus statement: Prevention and treatment of metabolic abnormalities

50. ***ALF can be complicated by metabolic complications such as hypoglycemia, hyponatraemia, metabolic acidosis especially lactic acidosis, hypocalcemia, hypomagnesemia, and hypophosphatemia. They should be monitored for these complications. (Grade of evidence: high; grade of recommendation: strong)***
51. ***Hypoglycemia is common in patients with ALF, and it is associated with increased mortality. Blood sugars should be monitored every 2 h, and hypoglycemic episodes should be managed promptly by i.v. boluses of glucose (50%) taking care not to cause hyperglycemia. (Grade of evidence: moderate; grade of recommendation: strong)***

52. ***Hyponatremia is common in ALF denoting a bad outcome, and it should be corrected to maintain concentrations of 145–150 mmol/L. (Grade of evidence: moderate; grade of recommendation: strong)***
53. ***Elevated blood lactate due to increased production and decreased clearance is a major problem in ALF especially in paracetamol overdose, and it denotes poor prognosis. RRT is recommended to correct the acidosis and metabolic disturbances. (Grade of evidence: moderate; grade of recommendation: strong)***

PREVENTION AND MANAGEMENT OF GI COMPLICATIONS

Spontaneous GI bleeding occurs in about a tenth of patients with ALF, although clinically significant bleeding is not common. According to the ALFSG Registry data, overall all-site bleeding occurred in about 11% of patients with ALF, and upper GI bleeding accounted for 94% of these episodes. Red blood cell transfusion was rarely necessary in these cases. In the ALFSG, GI bleeding accounted for only 30% of the deaths due to bleeding (remaining 70% were due to intracranial bleeding).[108] Older studies report GI bleeding to be much more common.[109–112] In the large ALF series published from India by Acharya et al,[53] GI bleeding was the cause of death in only 1.4% of patients. One can say that the incidence of bleeding complications as well as mortality due to the bleeds seems to be decreasing in patients with ALF, and there is an emerging consensus that patients with ALF are not at risk of major bleeding complications despite the presence of prolonged prothrombin time.[113]

Spontaneous and procedure-related bleeding in patients with ALF are markers of severe systemic inflammation rather than of coagulopathy and therefore herald a poor prognosis. In most patients with ALF and upper gastrointestinal (UGI) bleeding, the likely source is the stress-related mucosal disease, a manifestation of critical illness characterized by intense systemic inflammation.[114] In a recent study involving more than 1000 patients with ALF, clinically significant UGI bleeding occurred in only 2.6%, and the major risk factors for bleeding were the three integral features of the ALF syndrome: liver disease (OR, 7.6), coagulopathy (OR, 5.2), and RRT (OR, 6.9).[15] The responsible lesion, subepithelial hemorrhage, is caused by gastric mucosal ischemia proportional to the severity of underlying illness, rather than defective hemostasis.[113] Consequently, prophylaxis with acid suppression has not been universally shown to decrease its incidence.[115]

The association of acute pancreatitis (AP) with ALF was first recognized in an autopsy study that reported various severities of AP in 35% of patients with ALF.[116] Since then, several studies have reported this association in 6–41% of cases of ALF.[117–120] In the ALFSG report, 12% of 622 patients with ALF developed hyperamylasemia (HA), while only 9% of those with HA had clinical AP.[121] The elevation in serum amylase levels commonly occurs in the absence of clinical pancreatitis[122–124] especially in the presence of renal dysfunction. HA appears to be related to renal dysfunction and multiorgan failure. Although the presence of HA in ALF is not an independent predictor of mortality and can be present in ALF of all etiologies, it is associated with diminished overall survival.[121]

The pathophysiology of AP in fulminant hepatic failure (FHF) is not yet clear. The proposed mechanisms implicated in the development of pancreatic damage include hypoperfusion or hemorrhage from coagulopathy, as well as direct injury from the etiologic agents, such as HBV or drug/toxins, especially acetaminophen.

There is scanty information on the impact of AP in patients with ALF undergoing LT. Kuo et al[117] have reported a lower 1-year post-transplant survival of 50% in patients with ALF complicated by AP undergoing LT compared with 86% in recipients without AP, suggesting that AP adversely impacts survival. However, it would not be fair to adjudicate the indication for LT in this setting based on their limited results.

Furthermore, postoperative AP can also develop after orthotopic liver transplantation (OLT). Krokos et al at Pittsburgh conducted a retrospective analysis of 1832 patients undergoing 2161 OLTs and reported a 16.4% incidence of postoperative AP.[125] While the mortality was no different in those with merely biochemical pancreatitis (elevated amylase levels) compared with control OLT population (23%), in patients with clinical pancreatitis, mortality was a high 64%. In another study by Camargo et al, the mortality rate was 40% in 10 patients who developed clinical features of AP.[126]

Consensus statement: Prevention and treatment of GI complications

54. ***The two major GI complications of ALF are GI bleeding and AP. They are infrequently seen although GI bleeding has been reported in about 10% and AP in up to one-third of patients with ALF in some reports. (Grade of evidence: moderate)***
55. ***Both GI bleeding and AP are markers of severe systemic inflammation and portend poor prognosis. (Grade of evidence: moderate)***

NUTRITION IN ALF

There is very little information on the subject of nutrition in ALF, and there is no consensus regarding the amount of nutritional support, use of supplements, and method of delivery of nutrition support. A European survey of 33 hepatology units evaluated the practice of nutritional support

of patients with ALF in 11 different European countries and found a lot of heterogeneity with regard to use of enteral versus parenteral nutrition, amount of glucose and fat infusions in patients receiving parenteral nutrition, the amount of protein that should be supplied, and the type and amount of amino acid supplementation.[127]

Low glycogen stores, glucose intolerance, insulin resistance, increased protein turnover, and an imbalance between branched-chain amino acid (BCAA) and aromatic amino acids (AAA) characterize the physiologic derangements of ALF. In addition, ALF results in circulatory dysfunction, initially due to poor oral intake and increased fluid loss leading to hypovolemia. In addition, hypoglycemia and electrolyte abnormalities remain important complications of ALF. The main mechanisms contributing to hypoglycemia in ALF include impaired gluconeogenesis and decreased insulin uptake by dysfunctional hepatocytes.[128] This increased level of insulin in the peripheral circulation results in severe hypoglycemia. Electrolyte abnormalities including hyponatremia, hypokalemia, hypophosphatemia, and acid-base imbalances are common. Hyponatremia is commonly caused by hypervolemia.[129,130] CNS-induced hyperventilation precipitates a respiratory alkalosis, in turn causing the kidneys to exchange hydrogen ions for potassium, resulting in hypokalemia. Fortunately, these electrolyte abnormalities rarely result in cardiac arrhythmias.[98]

ALF is an acute condition, and patients with normal nutrition before liver failure may not be considered candidates for malnutrition. However, in India, good nutrition cannot be taken for granted and a thorough nutritional assessment is important to unmask signs of malnutrition in patients with ALF. Subjective global assessment is often used to assess nutritional status in patients with various liver diseases and may also be used in ALF. Objective measurements such as body mass index (BMI), mid-arm muscle circumference, and triceps skin fold thickness have also been used as part of a nutritional assessment.

In patients with ALF, oral feeding should not be interrupted if safe and feasible. Enteral feeding is preferred over total parenteral nutrition (TPN); hence, nasogastric or nasojejunal feeds should be attempted before starting TPN. However, if fluid overload is an issue or if ensuring euglycemia is not possible with enteral feeding, supplemental parenteral nutrition may be necessary to provide maximal calories with minimal volume. Patients with ALF are likely catabolic and will require more calories than basal needs. The recommended energy intake is 35–40 kcal/kg body weight/day. Consider using more concentrated high-energy formulas in patients with ascites.

Restriction of protein is not advisable, even in the presence of hyperammonemia. Recommended protein intake is 1.2–1.5 g/kg body weight/day. Whole-protein formulas are generally recommended. The results of the studies comparing formulas enriched with BCAA versus standard amino acid formulas have been variable. A recent Cochrane review showed that there was modest improvement in HE but no improvement in mortality or adverse events in the BCAA-supplemented group.[131] Hence, use of BCAA-enriched formulas is recommended in patients with HE arising during enteral nutrition. Lipids can be started unless suspected disorder of fatty acid oxidation or mitochondrial disease.

Consensus statement: Nutrition in ALF

56. ***Oral and enteral nutrition are preferred over TPN. (Grade of evidence: moderate; grade of recommendation: strong)***
57. ***The recommended energy intake is 35–40 kcal/kg body weight/day and protein intake is 1.2–1.5 g/kg body weight/day. (Grade of evidence: moderate; grade of recommendation: strong)***
58. ***Use of BCAA-enriched formulas may have some benefit in patients with hepatic encephalopathy. (Grade of evidence: moderate; grade of recommendation: strong)***

LIVER ASSIST DEVICES IN ALF

Liver assist device (LAD) or extracorporeal liver support (ECLS) system is a platform that allows the function of the liver to be taken up by the device until it regenerates or is replaced.

Traditionally, LADs have been classified as artificial or bioartificial. The former uses a column chromatography with different membrane pore size and adsorbent resins to remove specific toxins from the blood which accumulate in ALF. The latter is a hybrid platform which has active hepatocytes in addition to the components of artificial LAD. Most artificial LADs are based on the principle of albumin dialysis. It has been known for long that in liver failure, hydrophobic toxins accumulate in the plasma, which cannot be removed with conventional RRT. Many of these toxins are albumin bound and therefore can be removed if there is a higher concentration of albumin on the dialysate side. The main LADs based on the principle of albumin dialysis are MARS, SPAD, and FPSA.

Molecular adsorbent recirculating system

This is the LAD with which there is maximum clinical experience. The MARS LAD has a blood circuit through which the patient's whole blood is passaged. The membrane pore size is 50 kDa, which is less than the size of albumin. The membrane is preimpregnated with 600 ml of 20% human albumin, and this constitutes the albumin circuit. The protein-bound toxins bind to albumin on the membrane, which is at a higher concentration than that of the patient's plasma. The albumin is passaged over an anion-exchange resin and activated charcoal in the

albumin circuit and thus regenerated on-line to get attached to the membrane for binding more toxins from the circulating blood. The albumin circuit is dialyzed against a standard high flux dialyzer to remove the water-soluble toxins such as urea, creatinine, lactate, and ammonia.

The substances removed from the blood of patients with ALF result in an improvement in hemodynamic status, HE grades, liver biochemistry, and possibly systemic inflammatory response (Table 7).[132–134] However, the studies in this cohort of patients have been poorly conducted with respect to etiology of ALF (paracetamol vs nonparacetamol), type of ALF (hyperacute, acute, or subacute), randomization, and dosing. The largest (n = 103) and most recent French multicentric trial (fulminant MARS – FULMARS) suffered from serious drawbacks: only patients eligible for LTx were included, most patients received an organ within less than 48 h of randomization and listing, and some patients randomized to the MARS arm did not receive even a single session of MARS therapy. The study failed to show any benefit of MARS therapy over standard medical treatment [SMT]. The incidence of new-onset infections, including invasive fungal infections was higher in the MARS arm than in the SMT arm.

Single-pass albumin dialysis

The patient's blood is passed through a standard polysulfone dialyzer and dialyzed against 4.5% human albumin, with dialysate flow ranging from 700 to 1000 ml/h. The dialysate is discarded and not regenerated online, as in MARS. Therefore, the device utilizes large volume of albumin. There are no well-conducted studies on the use of SPAD in patients with ALF. There are no published studies describing the use of SPAD in patients with ALF in the past 5 years.

Fractionated plasma separation and adsorption

FPSA or Prometheus requires patient plasma to be fractionated and then passaged through an albumin-permeable membrane (pore cutoff: 250 kDa). Native albumin and other serum proteins cross this membrane and are passed in series across a neutral resin adsorber and an anion-exchange column (Prometh 1 and 2) to remove serum toxins. The cleansed albumin-rich plasma fraction is then returned to the standard blood circuit, which is subsequently filtered against a conventional high-flux HD system. There are no published studies on the use of FPSA in patients with ALF in the last 5 years.

Bioartificial LADs

The two bioartificial LADs for which published studies are available are described in Table 8.[135,136] There are no recent studies performed in the setting of ALF, which have utilized these devices. The principle concerns are as follows: (1) source of the hepatocytes – BAL (porcine, risk of zoonotic transmission) or extracorporeal liver assist device (ELAD) (human hepatoblastoma cell line, potential of carcinogenesis); (2) critical mass of hepatocytes; (3) bioreactor 3D design; and (4) survival of hepatocytes. Therefore, in spite of huge theoretical promise, these devices have failed to make an impact.

Future directions

The reason why LADs have failed to make an impact are nature of therapy (intermittent rather than continuous), finite life span of the platforms, whether artificial or bioartificial, short filter life due to nonstandardized anticoagulation practices, cost, heterogeneous patient population in which the LADs have been used, and frequent listing of patients treated with LADs for LTx, thus preventing any meaningful conclusions to be drawn.

Consensus statement: LADs in ALF

59. ***Patients with ALF who fail to respond to standard liver intensive care have high liver transplant-free mortality. (Grade of evidence: moderate; grade of recommendation: strong)***
60. ***The available LADs (artificial or bioartificial) have failed to either make an impact as a bridge to LT or improve transplant-free survival. (Grade of evidence: moderate; grade of recommendation: weak)***

ROLE OF PLASMAPHERESIS

Apheresis is a form of extracorporeal therapy where in the patient's blood is taken out and passed through a centrifuge and the components of the blood (WBCs, RBCs, and platelets) are separated and selectively removed and the blood is then pumped back into the circulation. During plasmapheresis, the plasma is removed with the premise that the disease-causing element (immune complexes, antibodies, activated lymphocytes) would be removed and the blood is returned to the circulation after replacement of a replacement fluid, which may be albumin or FFP.

A recent large randomized trial demonstrated that patients with ALF who underwent high-volume plasmapheresis had a better transplant-free survival than those who got standard medical treatment (HR for transplant-free survival of 0.56; 95% confidence interval (CI) = 0.36–0.86; p = 0.0083). For patients who underwent LT, presurgery plasmapheresis did not improve survival. In part B of the study (proof of concept study in 12 patients undergoing HVP and 11 undergoing SMT), the HVP group demonstrated reduced levels of damage-associated molecular patterns (DAMPs) (histone associated DNA), inflammatory cytokines such alfa-tumor necrosis factor and interleukin (IL)-6.[137] This could be responsible for patients with

Table 7 Use of Artificial ECLS in Patients With ALF.

Author [Ref]	N	ECLS type	Biochemical improvement	Hemodynamic improvement	Improved gd of HE	Survival benefit
Schmidt et al[132]	13	MARS	Yes	Yes	N/A	No
El Banayosy et al[133]	27	MARS	No	N/A	N/A	Yes
Saliba et al[134]	102	MARS	Yes	N/A	N/A	No

ECLS = extracorporeal liver support; ALF = acute liver failure; MARS = molecular adsorbants recirculation system.

HVP having higher MAP and lower vasopressor requirements.[138] It is proposed that these beneficial effects are related to removal of a multitude of toxins along with the plasma.[139,140]

Consensus statement: Role of plasmapharesis

61. ***For patients with ALF not undergoing an LT (nonavailability of donor), high-volume plasmapheresis may be considered as a treatment option for improving survival. (Grade of evidence: high; grade of recommendation: weak)***
62. ***Based on the antiinflammatory and ammonia-lowering effect, plasmapheresis may be recommended as a bridge for patients undergoing LT if the transplant is going to get delayed. (Grade of evidence: moderate; grade of recommendation: weak)***
63. ***Based on the current evidence, standard volume plasmapheresis can at best be recommended only as a bridge to transplant. (Grade of evidence: moderate; grade of recommendation: weak)***

AMMONIA-LOWERING STRATEGIES

Ammonia plays a key role in the complex pathophysiology of encephalopathy in ALF. It increases the osmotic pressure and oxidative stress within the astrocytes, causing it to swell and leading to cytotoxic cerebral edema. In addition, hyperammonemia modulates inflammatory and signal transduction pathways, gene expression, and neurotransmitter release, as well as posttranslational protein modifications.[141–144] Arterial ammonia correlates with severity and is of prognostic value in ALF. It predicts the occurrence of ICH and death from cerebral edema.[145,146] Arterial ammonia is included in the ALFED score to define severity and need for transplantation in ALF.[147] Lowering of ammonia levels is thus a logical strategy in management of ALF.

Strategies to lower ammonia in liver failure

Systemic hyperammonemia can be reduced by either reduction of intestinal ammonia production or its removal from systemic circulation (Table 9). Many drugs and measures have been tried in the treatment of encephalopathy, but only a few have entered clinical trials in ALF (Table 10).[137,148–151] In the absence of proven ammonia-lowering strategies, treatment of encephalopathy in ALF has centered on neuroprotective strategies and organ failure support. Possible reasons for lack of trials include the fulminant clinical course, complex pathophysiology of encephalopathy, and increasing access to LT.

Among drug therapies, there are data only for lactulose and LOLA in ALF. Both the drugs have proven efficacy in overt and/or minimal HE in cirrhosis but have failed to show any benefit in ALF.[42,152] L-Ornithine and L-aspartate are both substrates of urea cycle and lower ammonia by activating ureagenesis in residual hepatocytes. In addition, LOLA lowers ammonia by stimulating glutamine synthesis in skeletal muscles. In this reaction, ornithine and aspartate are transaminated with alpha ketoglutarate to glutamate which in turn is metabolized to glutamine. As the ornithine-derived glutamine is reconverted back to ammonia in the gut and kidneys, there is negligible reduction in net ammonia. Fusion ammonia scavengers such as ornithine phenylacetate have the potential to circumvent this problem. Phenylacetate conjugates with glutamine to form phenylacetylglutamine which is excreted in urine as it cannot be metabolized by glutamine synthetase to generate ammonia. Currently the drug is undergoing phase 2 clinical trials in ALF.

Other than pharmacotherapy, ammonia-lowering strategies tried in ALF are RRT

Hypothermia and plasma exchange

RRT and plasmapheresis have been discussed earlier. TH has also been evaluated in ALF. In a study of seven patients with ALF and poor prognosis criteria including ICH refractory to mannitol, TH (target cooling 32–33*C) showed improvement in CBF, arterial ammonia, and CPP.[144] The same group in subsequent studies showed that TH restored cerebral autoregulation and reduced proinflammatory cytokines. In contrast, retrospective study from US-ALFSG registry (n-92) showed TH failed to improve overall or transplant-free survival at 21 days.[150] While there was no therapeutic benefit, the study did show that TH was safe with no increase in infections and bleed hepatic regeneration. Survival benefit was also not found when TH was done as prophylaxis to prevent cerebral edema.[151]

Table 8 Use of Biortificial ECLS in Patients With ALF.

Author [Ref]	N	ECLS type	Cell type	Survival benefit
Ellis et al[135]	24	ELAD	Human hepatoblastoma [C3A]	No
Demetriou et al[136]	171	HepatAssist	Porcine	No

ECLS = extracorporeal liver support; ALF = acute liver failure.

FECAL MICROBIOTA TRANSPLANTATION

Microbiota has a complex role in hepatic regeneration. Studies on small-animal models have demonstrated that germ-free rodents developed more acute toxic liver injury than conventional controls after treatment with toxic drug agents. Hepatic regeneration after partial hepatectomy was markedly reduced in germ-free mice in relation to conventional controls, possibly due to the lack of endogenous lipopolysaccharide stimulated liver regeneration. Multiple studies have shown that antibiotic treatment generally results in an improved hepatic phenotype in a multitude of experimental liver diseases including ALI.[153–159] Sepsis-induced liver injury, an acute phenomenon, is commonly seen in ICUs. Gut microbiota in mice resistant to sepsis generated more granisetron, a 5-hydroxytryptamine 3 (5-HT3) receptor antagonist, which protected against liver injury and death, than the microbiota from those sensitive to sepsis, demonstrating that gut microbiota played a key role in the sensitization of sepsis-induced liver injury.[160] A reduction in ALI from concanavalin-A in a mouse model was found to be linked to enrichment of commensal *Lactobacillus* in the gut. It was associated with activated-classical dendritic cells–produced IL-10 and tumor growth factor (TGF)-beta, which prevented further liver inflammation. These indicate that beneficial gut microbes influence tolerogenic immune responses in the liver and that the modulation of the gut microbiota might be a potential option to regulate liver tolerance to reduce ALI.[161]

A recent study showed that the gut microbial metabolite 1-phenyl-1,2-propanedione (PPD) was associated with the diurnal variation of hepatotoxicity induced by acetaminophen by decreasing glutathione levels. *Saccharomyces cerevisiae*, with the potential to reduce intestinal PPD levels, was able to significantly reduce acetaminophen-induced liver injury.[162] In an animal model of acetaminophen liver toxicity with add-on fructose supplementation, Cho et al found that the abundance of several bacterial taxa including the genus *Anaerostipes* was found to significantly correlate with hepatic levels of Cyp2e1, Cyp1a2-mRNA, and glutathione, suggesting that the fructose-supplemented diet decreased acetaminophen-related liver injury by reducing metabolic activation of the drug and inducing detoxification of toxic metabolites, potentially through altering the composition of gut microbiota.[163] Mice treated with carbon tetrachloride (CCl4) and fed goat milk had enrichment in carbohydrate and amino acids metabolism compared with controls not on goat milk. The differential gut microbial metabolism was probably due to bacterial content in the goat milk group, with higher degradation of lipopolysaccharide and lower degree of liver injury. Furthermore, the gut microbiota of the goat milk–fed group was abundant in drug metabolism-cytochrome P450 than that of the untreated group. This demonstrates the role of gut microbiota and its metabolic function in amelioration of ALI.[164] Elfers et al[165] found that intestinal dysbiosis seen in Nlrp6−/− mice was transferable to healthy mice through fecal microbiota transfer. This aggravated liver injury upon acetaminophen administration by promoting proinflammatory macrophage polarization. Another study[166] showed that, in a rat model of acute HE established with carbon tetrachloride treatment, healthy human donor fecal transplant improved rat behaviors, HE grades, and spatial learning capability. Healthy donor FMT ameliorated hepatic necrosis, reduced intestinal permeability, and improved ammonia clearance. Toll-like receptor 4 and 9, two potent mediators of inflammatory response, were significantly downregulated in rat livers after FMT. Furthermore, loss of tight junction proteins (claudin-1, claudin-6, and occludin) was restored in intestinal tissues of rats after FMT treatment There are no human studies on the role of FMT in ALF and associated treatment outcomes, although this is a potential area for further studies.

Consensus statement: Ammonia-lowering strategies

64. ***Lactulose and LOLA do not change the clinical outcome in ALF and hence are not recommended. (Grade of evidence: moderate; grade of recommendation: strong)***
65. ***No recommendation can be made about newer potential ammonia-lowering agents such as ornithine phenylacetate, sodium benzoate, sodium phenylacetate, L-acetylcarnitine BCAAs, carbon microspheres, and probiotics as they are still under investigation. (Grade of evidence: moderate; grade of recommendation: weak)***

COUNSELING FOR TRANSPLANTATION

LT in ALF is a lifesaving intervention if done in time. At the time of admission, it is often not possible to predict which patient will require a transplant. Hence, the counseling of relatives for possible need for transplant should begin at the time of admission. Each patient's family should be explained in detail that the individual patient may improve or deteriorate over the next few days. It is imperative to explore the option of liver transplant at the time of

Table 9 Ammonia-Lowering Strategies in Hepatic Encephalopathy.

Reduction of intestinal ammonia production and absorption	Lactulose, lactitol, polyethylene glycol, antibiotics (rifaximin, meomycin)
Nutritional and micronutrient supplementation	Zinc, L-carnitine, branched-chain amino acids (BCAAs)
Plasma ammonia–lowering devices (removal of ammonia from systemic circulation)	CRRT, high-volume plasma exchange, MARS,
Reduction in brain energy metabolism and cerebral blood flow (reduced ammonia uptake in the brain)	Hypothermia
Alternative pathway/ammonia scavengers	L-Ornithine L-aspartate, sodium benzoate, phenylacetate, ornithine phenylacetate
Liver transplantation	

See text for detailed discussion on efficacy of these measures.
CRRT = continuous renal replacement therapy; MARS = molecular adsorbants recirculation system.

admission. It should be explained to them that evaluation for transplant does not necessarily mean that the patient is going to require a transplant as up to 50% patients may improve on SMT. Some families would refuse the transplant option at the outset. In such scenarios, a detailed documentation in the file is important for the patient as well as the treating doctor. Those willing for transplant (if the need arises) should be asked to identify a potential healthy donor shortly after admission in the LDLT setting. The donor workup should be done in the next 48 h. Usually 48–72 h would be enough to see the clinical trend of the patient. Those improving would go off the list for transplant. A worsening patient can then be transplanted if the donor workup is completed by that time. As patients with ALF have a very narrow window of stability for transplant, starting a donor workup late can jeopardize the possibility transplant. The workup of the donor is per standard criteria for liver donation.[167] The only difference in ALF is the rapidity of evaluation in view of a critically sick patient.

Consensus statement: Counseling for transplantation

66. ***Counseling of relatives regarding possible need of transplant should be done as early as feasible after admission to hospital. (Grade of evidence: low; grade of recommendation: strong)***
67. ***Donor workup should be expedited in potential transplant recipients with ALF. (Grade of evidence: low; grade of recommendation: strong)***

Table 10 Ammonia-Lowering Strategies: Clinical Trials in ALF.

Strategy	Remarks	Reference
Continuous renal replacement therapy (CRRT)	Small prospective study. ALF (acetaminophen) n = 10. 24-hr CRRT; 22% reduction in ammonia Retrospective study. US-ALFSG registry (1998–2016). n = 1186. 37.9% reduction in ammonia. Improved 21-day transplant-free survival (TFS)	148
Plasma exchange (high volume)	RCT involving ALF; n = 180. Standard medical treatment (SMT) vs SMT plus HVPE. Improved TFS (58.7% vs 47.8%). Significant reduction in arterial ammonia (D1-D3)	137
Therapeutic hypothermia (TH)	N-7(ALF with poor prognosis). TH improved cerebral blood flow, cerebral perfusion pressure, and arterial ammonia. Retrospective study. US-ALFSG(n-92).No overall or transplant-free survival at 21 days. TH has no prophylactic role in prevention of cerebral edema or intracranial hypertension	149, 150, 151
Lactulose	US-ALF SG data. N = 70. Lactulose mean = 3.45 days. No difference in clinical outcome, ICU stay, grade of coma.	152
L-Ornithine L-aspartate (LOLA)	RCT: LOLA vs placebo. N-201. LOLA 15 g/d x3 days. No reduction in mortality. Decline in ammonia similar in both groups.No difference in encephalopathy grade, survival time, consciousness recovery time, or complications.	42

US-ALFSG = US Acute Liver Failure Study Group; RCT = randomized controlled trial.

SPECIAL SITUATIONS

Transplantation in autoimmune hepatitis

There are few published series, mostly retrospective on acute severe autoimmune hepatitis, and usually these include AIH-ALF as part of the spectrum, where the latter is characterized by the presence of encephalopathy. No exclusive studies on AIH-ALF are available. The US ALFSG showed improved survival with steroids in a retrospective analysis of 66 patients, all of whom had encephalopathy. They reported a high risk of mortality in those with highest model for end-stage liver disease (MELD) scores. They recommended prophylactic use of antibiotics and antifungals in those being treated with steroids.[168] In a large multicenter French study,[169] of 121 patients with acute severe autoimmune hepatitis (INR of ≥1.5 and/or bilirubin ≥200 μmol/L), 110 patients received corticosteroids, whereas 11 patients did not. Encephalopathy was present in all 11 nontreated patients and in 8 of 110 patients who received corticosteroids. Only 1 patient of the 8 with encephalopathy responded to steroids. The presence of encephalopathy and nonresponse to steroids at day 7 and high INR with low platelets were measures of poor response to steroids. In the absence of encephalopathy two thirds (67%) responded to steroids with a drop of more than four MELD points. Another observational French study on 16 patients with severe AIH found corticosteroids to be not beneficial and increased the risk of septic complications.[170] A retrospective series of acute severe autoimmune hepatitis of 32 patients compared outcomes among those treated with steroids (23 patients) versus those who were not given steroids (9 patients).[171] Ten patients (48%) receiving steroids needed a liver transplant versus all who did not (p = 0.01). However, mortality in steroid vs. no steroid group was comparable. In another retrospective analysis[172] of 40 patients with AIH-ALF from 6 centers in Argentina, 20% survived without a transplant. They suggested that patients with an initial MELD score of less than 27 and low-grade HE might benefit from the administration of corticosteroids. Similar suggestions were made in another retrospective analysis of 20 patients from the U.S. In this study, low MELD, presence of response to steroids within 4 days, and absence of submassive necrosis on biopsy were significantly higher in the responders than in the nonresponders.[173]

Corticosteroids should be started as soon as the diagnosis of ALF-AIH is made, and a workup for LT initiated in all patients with ALF-AIH and urgently in those with high-grade encephalopathy. A thorough workup for sepsis needs to be undertaken simultaneously. Rahim et al[174] from the UK recommend that steroids may be stopped in those patients in whom there has been no improvement by day 7. Total plasma exchange (TPE) has been anecdotally found to be successful in a patient unresponsive to steroids (Yeoman 2011). As most series are retrospective in nature, there are no clear guidelines on the steroid dose that needs to be started. Some experts recommend a dose of 1 mg/kg of prednisolone (EASL G). Azathioprine is avoided in the presence of significant cholestasis and altered drug metabolism related to the disease. In the absence of good prospective trials of steroids in AIH-ALF, one may consider patients with low MELD scores on admission, low-grade encephalopathy, absence of massive hepatic necrosis on histology, and improvement of bilirubin within 7 days of therapy to be associated with higher response rates to corticosteroids.

Consensus statement: Special situations – autoimmune hepatitis

68. ***On diagnosis of ALF-AIH, treatment with corticosteroids should be started and preparation for transplantation and a thorough workup for sepsis initiated. (Grade of evidence: moderate; grade of recommendation: strong)***
69. ***Prophylactic antibiotics and antifungals may be started in ALF-AIH treated with steroids to reduce the risk of septic complications. (Grade of evidence: low; grade of recommendation: weak)***
70. ***Presence of high-grade hepatic encephalopathy, high MELD scores, or lack of an improvement within seven days of corticosteroids implies poor prognosis and necessitates a liver transplant. (Grade of evidence: moderate; grade of recommendation: strong)***

Transplantation in Wilson disease

D-Penicillamine or trientine should be started in patients as soon as the diagnosis of WD-ALF is suspected. HE and rapidly increasing bilirubin should be considered for urgent LT. The New Wilson Index (NWI) has been conventionally used to predict mortality without transplantation and recommends that a patient with a score of ≥11 has a low chance of survival without a transplant.[175] The NWI includes the initial Nazer score (viz serum bilirubin, INR, and serum albumin) with AST and white cell count added later (Table 11). In a study from St John's hospital Bangalore,[176] regression analysis based on HE and bilirubin was used in predicting outcomes and seems to be more accurate than the NWI, pediatric end-stage liver disease (PELD), and MELD. Besides, other researchers have also not been able to validate these scores.[177]

MARS andTPE have been used to rapidly remove copper in patients with ALF-WD. These modalities help break the cycle of hemolysis and ongoing liver damage. They mainly serve as a bridge to transplant rather than a cure, although there are anecdotal reports from China and Japan on TPE being able to salvage and avoid a liver transplant all

together.[178,179] TPE is preferable to MARS as is more widely available and less expensive.[180,181]

Siblings or parents may be carriers (heterozygous donors) or even have the disease. They need to be screened for the disease. Studies suggest that liver grafts from heterozygous donors are safe for both recipient and donor, and there is no risk of recurrence in the long term.[182,183] This is especially relevant in countries such as India where the majority of the transplants are living related. The patient with ALF-WD is also considered for a super urgent listing in the deceased donor situation.

A large French multicenter study of 75 adults and 56 children (53% had ALF-WD) revealed on Kaplan-Meir survival analysis a 5-year survival of 86–96% depending on whether the transplants were performed before or after the year 2000.[184] The improved results in the latter group were attributed to improvement in the operative techniques. The European Liver Transplant Registry looked at the survival of 338 children with WD transplanted before the age of 18 years from 1968 to 2003. The survival was 87% (1-year survival), 84% (5-year survival), and 81% (10-year survival), with improvement in survival in the later years, and was similar to other etiologies of liver disease needing transplantation. Early age at LT, living donation, and HTK preservative solution were identified as risk factors for poor patient survival in the multivariable analysis.[185]

Thirty-nine patients of ALF older than 8 years from the National transplant Registry of Uruguay were studied retrospectively; 6 (15%) of these had WD, and all were females with a mean age of 18 years and mean MELD score of 36. Three of the 6 survived – 1 without and 2 with a liver transplant. The referral time to the transplant program and the total time (referral plus waiting list time) were longer for nonsurvivors than for survivors. The authors concluded that early referral was the determinant of prognosis.[186]

Consensus statement: Special situations – Wilson disease

71. ***The NWI ≥ 11 has been used as a predictor of death in those without a liver transplant. Rising bilirubin, advancing HE, and acute hemolysis have been suggested as better predictors for LT than the NWI, MELD, and PELD, although it needs validation. (Grade of evidence: moderate; grade of recommendation: strong)***
72. ***MARS and TPE are newer modalities which rapidly remove copper and can be used as a bridging therapy to LT. (Grade of evidence: moderate; grade of recommendation: strong)***
73. ***TPE has the potential to help improve survival with native liver and avoid LT. (Grade of evidence: moderate; grade of recommendation: strong)***
74. ***LT for ALF-WD has good long-term outcomes including those from heterozygous donors. (Grade of evidence: moderate; grade of recommendation: strong)***

TRANSPLANT IN A PATIENT WITH ALF AND HIV

People living with human immunodeficiency virus (PLWHIV) and decompensated cirrhosis are undergoing liver transplants with the same efficacy as those without. This has been made possible because of the excellent efficacy of antiretroviral therapy (ART). The first such series from the USA compared outcomes in 24 HIV-infected transplant recipients with a cohort of 5225 age- and race-matched HIV-uninfected recipients and found similar cumulative survival in the HIV-infected patients (87%, 73%, and 73% at 1, 2, and 3 years, respectively) and matched controls (87%, 82%, and 78%).[187] The subgroup of HIV-infected recipients who had lower survival were those who could not tolerate HIV medications after transplantation and those with CD4+ T cell counts <200 at the time of LT. In the modern transplant era, risk for death (HR: 1.11; 95% CI: 0.52–2.35, p = 0.79) and graft loss (adjuted hazard ratio [aHR]: 0.89; 95% CI: 0.42–1.88, p = 0.77) were found to be similar between HIV monoinfected and uninfected LT recipients.[188] In a meta-analysis of liver transplant outcomes in HIV-infected patients of 15 cohort studies and 49 case series, the 1-, 3-, and 5-year survival was 85%, 66%, and 64%, respectively. Decreased survival was found in patients with detectable HIV viral load at the time of transplantation (OR: 2.89 [95% CI: 1.41–5.91]).[189]

LT has been done successfully in patients with ALF and HIV. In a series of 6 patients with ART-related ALF, four patients underwent a liver transplant, and after 21 months, 3 of the 4 were alive and doing well.[190] Another study from France reported 80% survival at 24 months. Of the 15 patients with HIV and ALF, 7 patients were listed for emergency LT. Two patients died before LT, and 5 patients received a liver transplant. One patient died 40 days after LT due to severe sepsis, one patient had hemicolectomy for ischemic colitis, and one patient experienced seizures. No opportunistic infections were seen in these four patients, and their last mean CD4 count was 530 giga/L [270–731] and HIV viral load <20 cp/ml on ART.[191]

Consensus statement: Special situations – transplant in patients with ALF and HIV infection

75. ***HIV is not a contraindication to liver transplant in patients with ALF. Patients with ALF due to ART can safely undergo LT. The indications for LT are similar to those in HIV-negative patients with ALF. (Grade of evidence: moderate; grade of recommendation: strong)***
76. ***PLWHIV having CD4 count less than 200 and those with detectable HIV RNA at the time of transplantation have worse outcomes after LT. (Grade of evidence: moderate; grade of recommendation: strong)***

Table 11 New Wilson's Index for Predicting Death Without Transplantation.

Score	Bilirubin (mg/dl)	INR	AST (IU/L)	WCC (10^9/L)	Albumin (g/dl)
0	0–5.8	0–1.29	0–100	0–6.7	>4.5
1	5.9–8.7	1.3–1.6	101–150	6.8–8.3	3.4–4.4
2	8.8–11.6	1.7–1.9	151–200	8.4–10.3	2.5–3.3
3	11.7–17.5	2.0–2.4	201–300	10.4–15.3	2.1–2.4
4	>17.6	>2.5	>300	>15.4	0–2.0

AST = aspartate transaminase; INR = international normalized ratio; WCC = white cell count.
Modified from the study by Dhawan A et al[175]

LT IN A PATIENT WITH ALF AND DENGUE

In a recent case report published in *Hepatology*, LT was performed successfully in a 49-year-old previously healthy woman of Jamaican origin with severe ALF due to dengue.[192] She had an INR of 7.2 and serum lactate of more than 10 mmol/L. The authors concluded that LT may be considered as a treatment option for patients presenting with ALF secondary to dengue virus infection. This patient was on hemodialysis with no mention of the involvement of any other organs. The encephalopathy was mild in this patient. There are no other reports or recommendations for the management of ALF due to dengue with a liver transplant.

Consensus statement: Special situations – transplant in patients with ALF and dengue infection

77. ***There is insufficient evidence to recommend LT in patients with dengue-related ALF. (Grade of evidence: low)***
78. ***In a rare patient with dengue-related ALF, where death is imminent due to liver failure and other organs are not affected/recovered/recovering/likely to recover, LT may be considered. (Grade of evidence: low; grade of recommendation: weak)***

LT FOR ALF AND HSV

In a multicentric retrospective, registry-based study over 22 years,[193] 30 patients were listed for LT due to HSV hepatitis–related ALF. Seven had recovery with medical therapy, and 5 died. Recovery was better in children (7/9) than in adults (0/3, p = 0.017). Eighteen patients (10 children and 8 adults) underwent LT. The survival was comparable with other etiologies among children (5-year survival: 69 vs. 64%, log-rank p = 0.89. However, survival was very poor in adult HSV recipients, with 1-year mortality of 63% and 5-year survival of 13% (vs. other etiologies 59%, log-rank p = 0.006). In another study of three patients from France who underwent LT due to HSV-related ALF, all died, although two died due to unrelated reasons.[194] As the diagnosis is frequently delayed in HSV ALF, and chances of improved outcomes with medical therapy, some authors recommend empiric acyclovir therapy for patients presenting with ALF of unknown etiology until HSV hepatitis is excluded.[195]

Consensus statement: Special situations – transplant in patients with ALF and HSV infection

79. ***Children listed for HSV hepatitis have a better survival than adults after LT. While HSV fulminant hepatitis is an appropriate indication for LT in children, it should only be performed in very selected adult patients. (Grade of evidence: low; grade of recommendation: weak***)

TRANSPLANTATION IN A PREGNANT LADY

Pregnancy-related liver diseases include pre-eclampsia and HELLP syndrome. Pre-eclampsia presents with systemic hypertension, leg edema, and proteinuria, occurring at the second or third trimester. Headache and jaundice are also commonly present; transaminases can be elevated up to fivefold. The involvement of the liver in pre-eclampsia is an indication of disease severity. In 10% of women, pre-eclampsia can progress to HELLP syndrome, characterized by microangiopathic hemolytic anemia. Presentation is hemolysis, elevated transaminases, and low platelets due to consumption. Presence of fragmented RBCs (microangiopathic) and hemolysis with low or undetectable haptoglobin is the clue for diagnosis. Liver histology shows hepatic necrosis with fibrin deposition. Serious complications such as disseminated intravascular coagulation (DIC), placental abruption, hepatic rupture, and hepatic failure can occur.

AFLP is a rare but serious disease occurring in the second or third trimester. Prevalence may vary from 5 to 30 per 100, 000 pregnancies.[196] Nulliparous, twin pregnancies are more vulnerable for AFLP. Pathogenesis involves severe mitochondrial dysfunction leading to impaired beta-oxidation of fatty acid, leading to microvesicular steatosis. Patients usually present in the second or third trimester with jaundice, encephalopathy, coagulopathy, and very high transaminases (>1000 U/L). Treatment of this life-threatening condition involves a multidisciplinary approach between obstetricians, hepatologists, and intensivists. Owing to high maternal and fetal mortality, 10% and 50%, respectively, immediate delivery of the fetus or termination of pregnancy should be considered.

Delivery of the fetus is the only effective treatment for pregnancy-induced ALF. It should be a multidisciplinary team approach involving an obstetrician, hepatologist, intensivist, and surgeon. AFLP is mostly reversible after fetal delivery. In the largest series from Xiong et al,[197] 25 patients with AFLP were followed up for 54 months from their index presentation. LFTs normalized in all patients

with completely normal health with no long-term consequences. LT should be considered only in patients with no resolution of liver failure (persistent hepatic coma, DIC, or liver rupture) despite delivery of the fetus. In the largest case series by Zarrinpar et al,[198] 8 patients underwent cadaveric LT over 20-year period, with an 88%, 88%, and 65% 1-, 5-, and 10-year survival, respectively.

Diseases unrelated to pregnancy can be caused by all other causes of ALF including hepatitis E which is more common and more severe in pregnancy.[199] It also carries high mortality and poor prognosis, particularly in the second or third trimester.[53] ALF unrelated to pregnancy may not resolve after fetal delivery and therefore should be managed like any other liver failures. Indications to transplant these patients should be based on ALF severity scores discussed in part 1 of this article.

LT in pregnancy is challenging as it deals with two lives. Sporadic cases were reported around the world where LT was performed on pregnant women. HBV-related ALF remains a common indication for LT in pregnancy.[200] A case report from Italy showed a successful maternal and fetal outcome of LT for patients with ALF, where lower segment Caesarean section (LSCS) was performed before LT for favorable fetal outcome.[201] In another report, LDLT was performed in a 15-week pregnant lady with ALF; the patient survived after the surgery, but the fetus had to be aborted.[202] Similar cases have been reported elsewhere with successful maternal and fetal outcomes.[203,204]

A retrospective data from King's College Hospital studied 54 patients with pregnancy-induced liver disease: 44 patients survived with medical management, 6 died without transplantation, and 4 underwent LT. Patients who underwent LT and/or died had a higher incidence of HE ($p = 0.04$) and high lactate ($p = 0.03$). Serum lactate 2.8 mg/dl was the best discriminant factor of mortality (area under the receiver operating characteristic [AUROC] curve: 0.84).[205]

Consensus statement: Special situations – transplant in a pregnant lady

80. ***Pregnant women with ALF should be managed by a multidisciplinary team involving an obstetrician, hepatologist, liver surgeon, anesthetist, and intensivist. (Grade of evidence: moderate; grade of recommendation: strong)***
81. ***ALF directly due to causes related to pregnancy is likely to recover after delivery of the fetus, and LT may be considered only if patients do not improve after delivery. (Grade of evidence: moderate; grade of recommendation: weak)***
82. ***Decision to transplant ALF unrelated to pregnancy should be based on the existing dynamic criteria such as ALFED or MELD. (Grade of evidence: moderate; grade of recommendation: strong)***

WHEN NOT TO TRANSPLANT IN ALF

LT for ALF has evolved as an established treatment in selected cases of ALF and has led to a reduction in mortality from 80% to 30%.[206] The selection of patients for this treatment has been discussed in part 1 of this article. The available criteria used to select patients for LT are limited by their sensitivity and specificity. Low sensitivity would leave out those who would have benefited by LT and die without it. Low specificity would provide livers to those who would have survived otherwise. It has been reported that as many as 20% patients of ALF may be transplanted unnecessarily.[207] Patients in the other end of the spectrum are also ineligible because they are too sick to undergo LT or no sustainable improvement is expected after LT. Concurrent medical or psychiatric comorbidities are deemed relevant if they are severe enough to affect the patient's prospects for survival after transplantation or likelihood of compliance with medical therapy or outpatient follow-up. Irreversible brain injury, evidence of compromised brain functions, and brain death are absolute contraindications. Brain death is defined, in a patient who has not received barbiturates, as the presence of bilateral nonreactive pupils with no spontaneous ventilation and two consecutive electroencephalograms without cerebral activity.[208] Other contraindications include severe uncontrolled septic shock, invasive fungal infection, uncontrolled acute respiratory distress syndrome, unstable hemodynamics, rapidly escalating inotrope requirement, and severe coexisting medical disease.[209] In terms of psychosocial disease, contraindications to transplantation include multiple previous episodes of self-harm (>5), refractory or resistant mental illness, active i.v. drug use or polydrug or alcohol use in a severe and chaotic fashion, and a consistently stated wish to die in the absence of established mental illness. In particular, predicting compliance with the intensive posttransplant immunosuppression and follow-up regimen in those patients with psychiatric comorbidity can be very difficult to assess within the time constraints available to assess the patient with ALF.[210] This explains prognostic scoring systems cannot and should not be used in isolation to identify patients who could and should be listed for emergency LT. In addition, with the changing spectrum of etiology, management, and prognosis of ALF, there is an ever-growing need of modification of prognostic criteria for more pragmatic allocation of liver grafts.

Consensus statement: When not to transplant in ALF

83. ***LT should not be performed in case of improving clinical status, and criteria for eligibility of LT should be reviewed regularly; role of dynamic model should be considered. (Grade of evidence: low; grade of recommendation: weak)***
84. ***Patients of ALF with more than three organ failures, circulatory failure with the requirement of two vasopressors, both with limited responses to further dose***

escalation, severe respiratory failure requiring maximum ventilator support (FiO_2>0.8, high PEEP), or on ECMO should be considered as contraindications for LT. (Grade of evidence: low; grade of recommendation: strong)

85. *Ongoing severe sepsis and tissue invasive fungal infection are relative contraindications of LT. However, it can still be considered after controlling the infection. (Grade of evidence: low; grade of recommendation: weak)*
86. *Brain death and absence of brainstem reflexes are absolute contraindications of LT. (Grade of evidence: low; grade of recommendation: strong)*

MERITS OF VARIOUS TECHNIQUES OF LT FOR ALF

Three techniques are currently used for the treatment of ALF – deceased donor liver transplantation (DDLT), LDLT, and auxiliary partial orthotopic liver transplantation (APOLT). The main hurdle to DDLT is the timely availability of a liver graft. Owing to time constraints, marginal grafts are often accepted with one or more of the following factors: elderly donor, steatotic liver, long ischemia times, donor on high inotropes, and ABO-incompatible graft. This may compromise posttransplant graft and patient survival. However, because most well-developed DDLT systems can usually get a liver within 72 h for ALF recipients, the need to consider live donors is low. Such teams are reluctant to subject live donors to the emotional pressure of making a quick decision. Even from the logistic point of view, these systems lack well-oiled rapid donor evaluation protocols owing to low volumes.

The results of LDLT in patients with ALF in Asia are good and similar to those of DDLT in Europe and the USA.[211] Several other studies including 2 Indian reports have shown good outcomes of LDLT for ALF.[212–216] Yamashiki et al[214] reported survival rates of 79%, 74%, and 73% at 1, 5, and 10 years, respectively, in a nationwide survey from Japan. Outcomes of ALF with LDLT and DDLT are similar. Jin et al[217] compared 36 patients with DDLT with 124 patients with LDLT and reported similar 1- and 3-year graft and patient survival.

Indian experience from two centers showed that a total of 106 adults underwent LDLT for ALF. The commonest etiologies were virus, Wilson Disease, and cryptogenic and drug-induced liver injury. The survival varied from 79% to 80.5% at 5 years.[218,219]

Special considerations in LDLT

Donor selection criteria are as for standard LDLT,[220] i.e., 18- to 55-year-old, blood group–matched relatives with BMI <33. All donors have systemic, liver, psychiatric, pulmonary, cardiac, and anesthesia evaluation divided in 4 phases. The limitations in the emergency live donor setting are limited choice of donors, risk of inadequate counseling, and logistic issues with urgent biopsy evaluation and documentation for the authorization committee. It is common practice in Indian centers to counsel the family to prepare themselves psychologically, financially, and with 1–2 live donors at the time of referral along with legal documents even before admitting the patient. The prospective donors undergo noninvasive phase 1 and 2 evaluation, once the patient is admitted. A liver biopsy if needed, and the final phases 3 and 4 are, however, are done only after the decision for transplant is confirmed.

Except as a last resort, ABO-incompatible LT cannot be recommended at present because it results in higher rates of rejection, infectious complications, graft loss, and mortality than ABO-matched LT.[221]

A third, much less often used option is APOLT. This involves orthotopic transplantation of a partial liver (usually left lobe or left lateral sector graft) after partial (left) hepatectomy of the native liver of the recipient. This can be done in selected cases of viral hepatitis or acetaminophen poisoning in young recipients, with the aim of providing adequate overall liver volume and a rapid recovery. There is an underlying hope of native liver recovery and regeneration so that immunosuppression can eventually be withdrawn and the transplanted liver can atrophy. This may happen in two-thirds of the cases. While earlier evidence[222] suggested inferior outcome compared with standard orthotopic transplantation, recent reports of small case series[223,224] suggest that in experienced centers, APOLT may result in good outcomes. However, with high success rates of standard LT, the overall experience and acceptance of the procedure remain limited, especially if the liver graft is of adequate quality and volume.

Consensus statement: Merits of various techniques of LT for ALF

87. *Both DDLT and LDLT result in good outcomes and are accepted as viable treatment options for those who meet the criteria for transplant. DDLT is suited to countries with good deceased donation rates where ALF receives allocation priority, whereas LDLT is better suited for experienced centers with limited access to deceased donor organs. (Grade of evidence: moderate; grade of recommendation: strong)*

POSTTRANSPLANT PROBLEMS AMONG PATIENTS WITH ALF

Patients transplanted for ALF frequently have unique challenges in the posttransplant period in relation to neurological status, sepsis, immunosuppression, and renal, cardiovascular, and psychological issues. These patients frequently need longer ICU stay and ventilatory support.

Neurological complications, especially after LT, include HE, seizures, posterior reversible encephalopathy syndrome, and intracerebral bleeds.[225] They require a high

index of suspicion with repeated clinical evaluations, correction of electrolytes, and neuroimaging as and when required. Management protocols pertinent to cerebral edema should remain in place for initial 24–48 h. Invasive ICP monitoring is seldom done in the Indian setting. Noninvasive monitoring of ICP including pupillometry, optic nerve sheath diameter, transcranial doppler, and bispectral index can reliably detect ICP elevations and may serve as a substitute for invasive monitoring.[226]

Bacterial or fungal sepsis causes almost one-third of deaths after transplantation for ALF.[227] Antimicrobial regimens in ALF include broad-spectrum antibiotics with longer duration and addition of systemic antifungals as compared with transplants for non-ALF indications. This approach is largely empirical, reactive, and institution-specific.

Immunosuppressive strategies should balance the risk of rejection characteristic of this younger patient population against the need for recovery from infections and renal failure. Standard immunosuppression includes a triple regimen comprising CNI, MMF, and steroids. However, immunosuppression modulation may be required in the context of neurological complications (substitution of tacrolimus with cyclosporine) and in case of renal dysfunction (use of basiliximab [IL-2 receptor antagonist] for delayed CNI introduction).

Patients with ALF, particularly with viral hepatitis, may have associated viral myocarditis. This may cause problems in management in the pretransplant period, or it may unmask in the posttransplant period necessitating close cardiopulmonary monitoring.

Psychological and psychiatric issues after transplantation include anxiety and mood disorders, posttraumatic stress disorder, adjustment disorder, and delirium. Transplant recipients have to deal with the knowledge that their bodies contain an organ that previously belonged to a now-dead stranger or a still-living relative, friend, spouse, or altruistic donor. Beliefs about the donor are sometimes incorporated into the delusions and hallucinations of delirium.[228] A dedicated transplant psychiatrist often needed to deal with these issues.

Consensus statement: Merits of various techniques of LT for ALF

88. ***Repeated clinical evaluations along with imaging as and when required should be done to rule out neurological complications after transplantation for ALF. (Grade of evidence: moderate; grade of recommendation: strong)***
89. ***Noninvasive monitoring to detect ICP elevations should be performed in the early posttransplant period. (Grade of evidence: moderate; grade of recommendation: strong)***
90. ***Bacterial and fungal sepsis are an important cause of mortality in the posttransplant period. Antibiotic and antifungal regimens should be broad-spectrum and guided by the institutional antibiotic policy. (Grade of evidence: moderate; grade of recommendation: strong)***
91. ***Psychological counseling should be done in the early posttransplant period. (Grade of evidence: moderate; grade of recommendation: strong)***

NOVEL AND FUTURE THERAPIES OF ALF

Patients with ALF either improve or die within the first 7 days.[9,229] For a potential treatment to be effective, it should prevent further damage to the liver, reverse the cascade of events due to liver failure, e.g., cerebral edema and HE secondary to hyperammonemia, prevent the occurrence of infections, and have the potential to promote the regeneration of hepatocytes.[100] Novel therapies need to be very effective to be of potential clinical use. Such innovative and ideal treatments are not yet available, although there are case reports describing the utility of some potential therapies, and ideally, randomized control trials are needed to evaluate their efficacy better.

Hepatocyte transplantation

OLT is the definitive treatment for ALF. Shortage of organs, high cost, and need for lifelong immunosuppression limit the routine use of LT. Hepatocyte transplantation is a potential alternative, which, when compared with LT, is less invasive, less costly, and not limited by organ availability. There are case reports of successful treatment of patients with ALF using hepatocyte transplantation.[230,231] Hepatocyte transplantation aims to bridge patients with ALF to recovery through regeneration or OLT. The exact volume of cells required, the optimal route of transplantation – via portal vein, intraperitoneally, or intrasplenic – is unclear. Further studies are needed to explore the potential of hepatocyte transplantation.

Mesenchymal stem cells

Human mesenchymal stem cells (MSCs) (hMSCs) are multipotent stem cells that can differentiate into mesodermal lineages such as osteocytes, adipocytes, and chondrocytes, as well as ectodermal (neurocytes) and endodermal lineages (hepatocytes). hMSCs have immunomodulatory properties as they secrete certain cytokines and immune relevant receptors to modify the host immune environment. All these properties of MSCs make them distinct from other stem cells and can be used in future cell replacement therapy. Importantly, before MSCs can be used for routine clinical use, issues that need to be addressed include safety in the form of side effects, quality control, and clinical-grade produced cells. Another potential therapy is reprogramming of differentiated somatic cells to induced pluripotent stem cells (iPSCs), which can potentially differentiate into a variety of cells of any germ cell layer.

Liver scaffolds and organoids

An interesting concept is to generate bioartificial organs, which can be a simple alternative to the donor human liver.

A recent study evaluated the role of the human placenta as a scaffold for hepatic tissue. In an animal model (using sheep), transplantation of hepatized placenta containing autologous tissue led to better outcomes in a partial hepatectomy model of ALF.[232] Although presently experimental, the development of liver scaffolds can potentially solve the problem of organ shortages. Organoids are "microscopic tissues" formed by culturing stem cells in a unique 3D culture system. Importantly, their structure and function are similar to those in vivo. Hepatic organoids consist of a spherical monolayer epithelium and have physiological features of the liver. They are obtained through isolation and expansion of stem and progenitor cells from hepatic stem cell niches. At present, hepatic organoids are in the nascent stages of development; they may evolve in the future.

PEDIATRIC ALF

Burden and etiology

ALF in infants has a different definition as encephalopathy is challenging to assess in this age group. Pediatric ALF is diagnosed when there is biochemical evidence of ALI, no known evidence of chronic liver disease, and coagulopathy (corrected with vitamin K) defined as the INR $\geq$ 1.5 in the presence of clinical HE or INR $\geq$2.0 regardless of HE.[233] Neonatal liver failure is defined as the failure of the synthetic function of the liver within 4 weeks of birth.[234] In children with metabolic liver disease and ALF, there is often a preexisting liver disease. These patients are always included in the pediatric acute liver failure (PALF) studies considering their phenotypic presentation such as ALF. Determination of the etiology of PALF is critical as the disease in some patients may be managed by dietary interventions (e.g., galactosemia) or specific medications (e.g., tyrosinemia). Similarly, a disease where a transplant is unlikely to be of benefit needs to be identified, e.g., a disease with multisystem involvement (e.g., mitochondrial hepatopathy). Besides, a diagnosis of a genetic disorder is important in advising prenatal screening in subsequent pregnancies.

The etiological spectrum of PALF differs from that in adults and also varies with the age of presentation.[235] In India and developing countries, viral hepatitis is the cause of ALF in up to 90% of adults,[9,31,236] whereas in the West, drugs and toxins are the most common cause of ALF. The Pediatric Acute Liver Failure Study Group (PALFSG) was set up in 1999 to study the pathogenesis, treatment, and outcomes of PALF. It included 24 centers from the UK, the USA, and Canada). In the first analysis of 348 children, the etiology in half the patients was termed "indeterminate."[233,237] The reasons for this could be nonavailability of diagnostic tests, incomplete workup, and financial constraints in performing a battery of tests for diseases that were thought to be untreatable. In fact, it is now being recognized that younger children especially infants often have metabolic liver disease as the underlying etiology.[238] Metabolic liver disease (MLD) is suspected when there is a history of consanguinity, affected sibling or sibling death due to liver disease, recurrent vomiting, diarrhea, seizures, or developmental delay. In addition, when MLD was diagnosed as an etiological factor, the number of indeterminate cases was much lower, implying that most of the "indeterminate" cases in older studies may have had an MLD which was not looked for. This is supported by the fact that studies with a higher prevalence of MLD among patients with PALF had a much smaller proportion of indeterminate cases.[239,240]

For the etiology of PALF, diagnostic algorithms have been formulated to narrow down the diagnosis and hence limit the tests to be performed for that age group as was documented in a recent study by Narkewicz et al where age-specific diagnostic algorithms were integrated with the electronic medical records. With this approach, the number of indeterminate cases reduced to 31%[237] compared with 49% in the preliminary PALFSG data.[233]

In India, most of the published data on PALF are from individual centers, some of which are centers of excellence or transplant centers and are likely to have a referral bias and may not represent the true prevalence of ALF. It is also likely that viral hepatitis–related diseases get diagnosed and managed at local hospitals and the indeterminate or metabolic diseases get referred to the higher centers. Nevertheless, given these limitations, a literature search was made to determine the etiology of PALF in India (Table 12)[241–246] and the West (PALFSG)[233,237] (Table 13). In general, in India, the commonest cause of PALF was viral hepatitis followed by indeterminate and MLD, whereas in the West, the largest group was indeterminate followed by drug acetaminophen and MLD.

Among the hepatotropic viruses, HAV was the commonest virus, followed by HEV and mixed infections (Table 14).[241–246] HBV was not reported in the largest and most recent study of 109 patients (Alam 2017) as a cause of ALF as these patients were included in the ACLF and not ALF group unlike older Indian studies where all patients with HBsAg positivity were included. Among the nonhepatotropic viruses, HSV can occur across all age groups (although commonest in infancy), enteroviruses in younger infants, adenovirus, Ebstein Barr Virus (EBV), and Varicella zoster are causative etiology of ALF. Some viruses such as parvovirus B19, human herpesvirus 6, and cytomegalo virus (CMV) may be associated rather than causative causes of ALF.[247]

Dengue fever by itself can cause ALF[248] and was the etiology of ALF in 12 of 40 Thai children from 14 centers in the country.[249] In the Indian series of 109 children, five of the eight hemophagocytic lymphohistiocytosis (HLH) cases were secondary to dengue and HAV infections, and the other three were thought to have primary HLH.[246] Devarbhavi et al[250] studied the effect of drug-induced ALF among 128 patients including 21 children and found that anti-TB

drugs were the commonest drug class for DILI-induced ALF followed by first-generation anticonvulsants followed by dapsone both in adults as well as in children. Two patients with acetaminophen overdose (both children) and two with ferrous sulfate toxicity (1 child) died. In the West, the most commonly implicated drug is acetaminophen. Besides, recreational drugs such as ecstasy (an amphetamine compound) and cocaine have been associated with PALF in teenagers. More than a quarter of patients in the PALSG registry had positive autoimmune markers, and the authors concluded that the presence of these markers did not eliminate the need to rule out other etiologies.[251]

Although there are some data on the etiology of PALF in infants and young children,[252] there is no systematic analysis of age-wise distribution from Indian studies or guidelines[253] from the PAFLSG group. Of the 148 children younger than or equal to 3 months of age,[254] common etiologies of ALF were indeterminate (38%), gestational alloimmune liver disease (GALD) (14%), and HSV (13%), whereas an Indian study of 30 children younger than 3 years (Alam 2015) showed MLD and HLH accounting for half the cases, other common ones being DILI, HAV infection, GALD, and HSV infection. There is thus a pressing need to have an Indian registry of PALF, especially with the age-wise and region-wise distribution to enable an algorithmic and economical approach to diagnostic testing for etiology of PALF.

Consensus statement: Pediatric ALF – burden and etiology

92. ***The exact burden of PALF in India is unclear. Viral hepatitis A is the commonest cause of PALF in India. (Grade of evidence: moderate; grade of recommendation: strong)***
93. ***In infants and younger children, metabolic liver diseases occur with a higher frequency than in older children. (Grade of evidence: moderate; grade of recommendation: strong)***

PRESENTATION OF PALF

Presentation at birth suggests congenital infection, neonatal hemochromatosis, or mitochondrial disorders. A later presentation may be related to a viral hepatitis or a metabolic condition unveiled by the introduction of feeding (i.e., galactosemia, hereditary fructose intolerance, or hereditary tyrosinemia type 1).[255]

Inborn errors of metabolism (IEM) may present in young children with jaundice, hypoglycemia, and ALF. There should be a high index of suspicion for IEM if there is family history of consanguinity, recurrent abortions, or sibling deaths or history of recurrent diarrhea, vomiting, failure to thrive, or developmental delay. Neurological involvement in the form of hypotonia, myopathy, seizures, ophthalmoplegia, psychomotor dysfunction, or presence of multisystem involvement should raise the suspicion of a mitochondrial depletion syndrome.[256]

Classical galactosemia may present early soon after birth and initiation of milk feeds. However, onset of symptoms after introduction of foods containing fructose or sucrose or aversion of sugars and sweet foods in points toward hereditary fructose intolerance. Patients with Wilsons disease may have KF ring on slit-lamp examination, Coomb's negative hemolytic anemia, low serum uric acid levels (<2.5 mg/dL), low serum alkaline phosphatase (SAP) activity (SAP-to-bilirubin ratio <4), and increased AST-to-ALT ratios. Patients with metabolic liver disease have a longer interval from jaundice to encephalopathy. Children with metabolic liver disease tend to have a much higher bilirubin but lower transaminases, gamma glutamyltransferases (GGT), and INR than the viral causes of ALF.[240] A young age, high bilirubin, synthetic dysfunction, low sugar, and non–glucose-reducing substances in urine indicate metabolic liver disease as a cause in children.[252]

ALF should be considered in any young infant with a coagulopathy as transaminases, and/or bilirubin levels can be near normal at presentation. The PALFSG enrolled children with ALF which also included those with severe coagulopathy without encephalopathy. The enrollment criteria of PALF study group were as follows: (i) the presence of severe hepatic dysfunction occurring within 8 weeks of onset of illness, (ii) no known underlying chronic liver disease, and (iii) a liver-based coagulopathy (not corrected with vitamin K) with an INR $\geq$ 1.5 in patients with encephalopathy or an INR $\geq$ 2.0 in patients without encephalopathy.[257]

HE may be subtle and difficult to recognize in young children unless it is advanced. Because it is difficult to stage encephalopathy in infants and children as compared with adults, the Pediatric Gastroenterology Chapter of the Indian Academy of Pediatrics has recommended the following grades: grades I and II are indistinguishable with clinical features of inconsolable crying, inattention to task, with normal or exaggerated deep tendon reflexes; grade III encephalopathy manifests as somnolence, stupor, combativeness, and hyperreflexia; and in grade IV encephalopathy, the child is comatose (arousable with painful stimuli [IVa] or no response [IVb]) with absent reflexes and decerebration or decortication.[253]

Consensus statement: Pediatric ALF – clinical presentation

94. ***The clinical features of ALF in children vary depending on the age and etiology. IEM should be suspected in young children if there is family history of consanguinity, recurrent abortions, or sibling deaths or history of recurrent diarrhea, vomiting, failure to thrive, or developmental delay. (Grade of evidence: low; grade of recommendation: strong)***
95. ***The recognition of encephalopathy may be difficult in children, and ALF should be considered in a young child with***

coagulopathy which is not correctable with vitamin K. (Grade of evidence: low; grade of recommendation: strong)

PALF MANAGEMENT: DIFFERENCES FROM ADULTS

Management of ALF in pediatrics is based on the same broad principles of management in adults such as management of HE, cerebral edema, coagulopathy, hemodynamics, renal and respiratory care, fluids, electrolytes, and glucose monitoring with prophylaxis/treatment of infection. However, pediatric liver failure management requires delicate fluid balance, more vigorous monitoring as it has a narrow margin of safety. The clinical course of PALF can be rapid, dynamic, and unpredictable. The interval between presentation and outcome, such as liver transplant (LTx), death, or spontaneous recovery can be as short as a few hours or days in some children.[258]

Prompt referral or at least contact with a pediatric liver transplant center is essential as early referral is known to improve outcome. Guidelines are available for transportation of critically sick children.[259] There should be decisive, frequent, and clear communication among the teams involved. Any child who has grade III or IV encephalopathy should preferably be intubated and airway secured before transport. A continuous monitoring of heart rate, rhythm, pulse oximetry, and blood pressure should be available. Facilities for infusion of vasoactive drugs, with spare supplies, should be available during transport. Well-secured vascular access must be assured before the transfer.

Management of ALF in young infants is very challenging. Neonatal hepatitis, tyrosinemia, glactosemia, urea cycle disorder, mitochondrial hepatopathies, and respiratory chain defects are common in this age group and deserve an early recognition for efficient management and improved outcome. Specific therapy is available for certain etiologies such as galactose-free diet in galactosemia, NTBC in tyrosinemia, NAC in paracetamol poisoning, acyclovir in herpes infection, steroids in autoimmune disease, and special regimes in milder cases of neonatal hemochromatosis or gestational allo-immune liver injury. The most severe form of the latter, however, is universally fatal without liver transplant. As it has a high recurrence rate (80%) in subsequent pregnancies, it is more important to remember that antenatal treatment with immunoglobulins beginning at 14–18 weeks of gestation can prevent recurrence. One has to identify occasional cases of recurrent ALF in infancy and young children secondary to mutation in NBAS and SCYL1 gene.[260] Mitochondrial disorders presenting with ALF are considered as contraindication by most centers because of high risk of extrahepatic manifestations.[261] Similarly, neonatal HLH presenting as ALF is a contraindication of liver transplant by most and treatment includes immunosuppression with corticosteroids, ATG, etoposide, IVIG, and bone marrow transplant (BMT).[262]

Renal insufficiency in PALF is a result of AKI, the etiology of which is acetaminophen toxicity, nephrotoxic medications, infection, and hypovolemia.[263] Early CRRT in is are now recommended if there is renal dysfunction, rising ammonia levels, grade 3 or 4 encephalopathy, and acidosis or electrolyte disturbances. Liver support therapy in children – unfortunately including MARS fall short of the mark or have been underpowered to assess benefit; therefore, they cannot be recommended in children.

INDICATIONS OF LT IN CHILDREN

LT has dramatically improved survival in children with ALF. However, there is no consensus on when to list for LT. With advances in medical treatment, the chances that the child may survive with the native liver are increasing.[264] Improvements in the management of the critically ill patients and newer treatments such as therapeutic plasma exchange[137] are expected to reduce the need for LT for ALF in the coming years. Hence, avoiding unnecessary LT in children with ALF is a possibility. On the other hand, LT, if needed, should be performed, before worsening complications make transplantation a futile venture.[265]

As survival in children with ALF is determined by etiology and age of the child,[253] these have to be factored in when deciding on listing for LT. Children with ALF with grade III or IV HE or worsening coagulopathy need to be considered for LT. Grading severity of HE is different in children compared with that in adults.[265]

Prognostic scores for ALF in children are not satisfactory. Most studies of these prognostic scores have combined death and LT as a single outcome. When death and LT are taken as separate outcomes, King's College criteria and Liver Injury Unit score are not good predictors of outcome in children with ALF.[266–268] Presence of ≥3 King's College criteria for nonacetaminophen liver failure have been used as criteria to list for LT.[269] PELD score for children aged <12 years and MELD score for children aged >12 years are also used to assess disease severity. Serial rise in PELD/MELD scores or in prothrombin time[246] have been used as listing criteria for LT. Dynamic scoring of disease severity in ALF, as done in adults,[270] needs to be developed in children.

Current practice is to have serial clinical assessment done by an experienced multidisciplinary team to analyze the course of the illness in the child with ALF and decide on listing for LT. Subsequent observations may change the decision maybe to wait, proceed, or stop.[271] In a patient with sustained clinical improvement, the team can wait before listing for LT; in a patient meeting the listing criteria with no contraindications, the team can proceed with LT; and in a patient with contra-indications, the team can stop and not proceed with LT.

Table 12 Indian Studies on Pediatric Acute Liver Failure.

First author, center, city	Year published	Number of patients	Viral, N (%)	Metabolic, N (%)	Drug, N (%)	HLH, N (%)	Indeterminate, N (%)	Other, N (%)
Arora NK ([241]) AIIMS, Delhi	1996	44	30 (68%)	2 (4.5%)	3 (7%)	0	5 (11%)	4 (9%)
Bendre SV ([242]) KEM, Pune	1999	36	22 (61%)	2 (5.5%)	2 (5.5%)	0	8 (22%)	2 (5.5%)
Poddar U ([243]) PGIMER, Chandigarh	2002	67	63 (94%)	–	0	0	4 (6%)	–
Samanta T, ([244]) NRS Medical college, Kolkata	2007	45	30 (67%)	–	0	0	10 (22%)	5 (11%)
Kaur S, ([245]) Kalawati Saran Childrens' Hospital, Delhi	2013	43	33 (77%)	5 (12%)	0	0	4 (9%)	1 (2%)
Alam S, ([246]) ILBS, Delhi	2017	109	50[a] (46%)	14 (13%)	12 (11%)	8 (7%)	16 (15%)	9 (8%)

HLH = hemophagocytic lymphohistiocytosis.
[a]Only study to test for non hepatotropic viruses: HAV- 43, HEV- 2 Parvovirus- 3 EBV- 1, VZV- 1.

Any medically treatable cause of ALF in children, if identified, may avoid the need for LT, for example, herpes simplex, gestational alloimmune liver disease/neonatal hemochromatosis, paracetamol overdose, autoimmune hepatitis, Wilson disease, HLH.[265] Metabolic liver diseases such as galactosemia, tyrosinemia in younger children, and Wilson's disease in older children are treatable causes which may present as ALF.[240] The New Wilson predictive index (bilirubin/INR/AST/WBC/Albumin) has 93% sensitivity, 98% specificity, and a positive predictive value of 93% in children. Patients with Wilson disease present as ALF with encephalopathy mortality as 100%, and they should be considered for urgent liver transplant. Other models using the trajectory of data collected over time

Table 13 Etiology of Pediatric Acute Liver Failure as per Age Group

	All age groups	0–3 months	>3 months–3 years	>3–17 years
Total number of patients (N)	986	181	274	531
Indeterminate (%)	45	35	59	41
Metabolic (%)	10	17[a]	11[b]	7[c]
Acetaminophen (%)	12	1	4	21
Other drugs	3	15	1	5
Virus (%)	8	20 (HSV, enterovirus)	5(EBV, influenza)	5(HAV, EBV, adenovirus)
Autoimmune (%)	7	0	7	9
Ischemia (%)	3	3	3	3
GALD (%)	3	3	0	0
HLH (%)	3	1	4	2
VOD (%)	1	0	2	1
Multiple	2	0	2	2
Other (%)	3	4	2	3

Modified From Pediatric Acute Liver Failure Study Group, 2000 to 2012; Narkewicz et al[251]
HSV = Herpes simplex virus; EBV = Ebstein Barr Virus; HAV = hepatitis A virus; GALD = gestational alloimmune liver disease; HLH = hemophagocytic lymphohistiocytosis; VOD = veno-occlusive disease.
% represents percentage of total in the respective group.
[a]Galactosemia > mitochondrial hepatopathy > Niemann Pick type C > tyrosinemia > urea cycle defect.
[b]Mitochondrial hepatopathy > tyrosinemia > fatty acid oxidation defect > urea cycle defect.
[c]Wilson's disease.

Table 14 Viral Infections in Indian Children With Acute Liver Failure.

Author	Number of patients	Hepatitis A	Hepatitis E	Hepatitis B	Mixed infections	Other Viruses
Arora NK([241])	30	4 (10%)	6 (20%)	6 (20%)	15 (50%) 9 (A + E), others 6	–
Bendre SV([242])	22	12 (54%)	–	3 (14%)	7 (32%) 2 (A + B) 4 (A + E) 1(Enteric fever + E)	–
Poddar U([243])	63	34 (51%)	17 (23%)	5 (7.5%)	7(A + E) (10%)	
Samanta T([244])	30	9 (30%)	7 (23%)	6 (20%)	8 (27%)	
Kaur S ([245])	33	25 (76%)	2 (6%)	2 (6%)	2 (A + E) (6%)	2 (6%)
AlamS ([246])	50	46 (92%)	–	–	–	Parvovirus-3 EBV 1, VZV- 1

suggest dynamic models hold some promise.[270,272] Contraindications to LT in children with ALF include irreversible cerebral edema, uncontrolled sepsis, and severe multisystem mitochondrial disease, especially if associated with valproate toxicity.[265]

Consensus statement: Indications of LT in PALF

96. ***Currently available prognostic scores in children with ALF are not accurate. Dynamic scores of disease severity need to be developed and validated, to support clinical decision-making in this regard. (Grade of evidence: low; grade of recommendation: strong)***
97. ***Children with severe disease (who meet any of the listing criteria) and have worsening disease severity (such as rising PELD score in a child aged < 12 years and rising MELD score in a child aged > 12 years) need to be considered for LT. (Grade of evidence: low; grade of recommendation: strong)***

OUTCOME OF PALF

In the scenario of DDLT, the shortage and unpredictability of donor organ availability compounds the risk. The clinical team may feel compelled to proceed to transplantation even when suboptimal graft organ is offered. Unsurprisingly, the outcome of transplantation of ALF is inferior to that of chronic liver disease in such scenarios.[273]

Data from the PALFSG in North America and Europe revealed that 21-day outcome varied by diagnosis, age, and degree of encephalopathy. Spontaneous survival was highest amongst those with liver failure due to acetaminophen (94%), and it was lower among those with liver failure due to metabolic disease (44%), for those with nonacetaminophen drug–induced disease (41%), and for those with an indeterminate diagnosis (45%).[233] For children with an established diagnosis, between 20 and 33% received an LT. In comparison, among patients with a diagnosis of indeterminate PALF, 46% underwent LT. The major causes of death for children with PALF who do not receive LT are multiorgan system failure, cerebral edema, herniation, and sepsis.

In India, similar to Japan and Korea, it is common to predominantly offer living-related liver transplant (LRLT). Experience from one of our centers on outcome of 200 LRLT in children showed that 57 patients (28.5%) underwent LT for ALF. One-year and 3-year survival in these patients were 94% and 91%, respectively, which was statistically and not different from patients with chronic liver disease.[269] In a multicentric data on more than 2000 pediatric LT patients from Japan registry, 192 (8.6%) were indicated for ALF. Fifteen-year survival was 67% in the ALF group which was statistically inferior to 84% in cholestatic liver diseases. Among the patients with ALF, those younger than 1 year exhibited a decreased survival rate of 54.2%.[274]

A recent good comparison of LRLT (n = 24) vs DDLT (n = 39) for ALF in children from a single center in Poland showed 15-year actuarial survival rate of 84% in LRLT vs 74.4.% in the DDLT group, which was not significantly different, probably because of a relatively small group of patients.[275]

ALF is not an uncommon emergency characterized by recent development of jaundice and altered level of consciousness (HE) in the background of deranged prothrombin time (INR >1.5) in the absence of underlying chronic liver disease. It often leads to a severe and rapidly progressive multiorgan failure with unpredictable complications. The most frequent cause of ALF in India is viral hepatitis followed by DILI related to anti-TB therapy. Several critical management decisions are required by the treating doctor from the time of presentation to avoid high mortality associated with this condition. It is crucial to assess prognosis in a given case so as to consider emergency LT. In those not transplanted, spontaneous survival with good long-term

prognosis is possible with good critical care management. Plasma exchange and other extracorporeal therapies are also being utilized and hold promise for such patients. Meanwhile prevention and treatment of cerebral edema, infections, and critical care support for organ failure are the mainstay of treatment.

CONFLICTS OF INTEREST

Dr Subrat K Acharya Has nothing to declare.

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CREDIT AUTHORSHIP CONTRIBUTION STATEMENT

Anil C. Anand: Writing - review & editing. **Bhaskar Nandi:** Writing - review & editing. **Subrat K. Acharya:** Writing - review & editing. **Anil Arora:** Writing - review & editing. **Sethu Babu:** Writing - review & editing. **Yogesh Batra:** Writing - review & editing. **Yogesh K. Chawla:** Writing - review & editing. **Abhijit Chowdhury:** Writing - review & editing. **Ashok Chaoudhuri:** Writing - review & editing. **Eapen C. Eapen:** Writing - review & editing, Writing - review & editing. **Harshad Devarbhavi:** Writing - review & editing. **Radha K. Dhiman:** Writing - review & editing. **Siddhartha Datta Gupta:** Writing - review & editing. **Ajay Duseja:** Writing - review & editing. **Dinesh Jothimani:** Writing - review & editing. **Dharmesh Kapoor:** Writing - review & editing. **Premashish Kar:** Writing - review & editing. **Mohamad S. Khuroo:** Writing - review & editing. **Ashish Kumar:** Writing - review & editing. **Kaushal Madan:** Writing - review & editing. **Bipadabhanjan Mallick:** Writing - review & editing. **Rakhi Maiwall:** Writing - review & editing. **Neelam Mohan:** Writing - review & editing. **Aabha Nagral:** Writing - review & editing. **Preetam Nath:** Writing - review & editing. **Sarat C. Panigrahi:** Writing - review & editing. **Ankush Pawar:** Writing - review & editing. **Cyriac A. Philips:** Writing - review & editing. **Dibyalochan Prahraj:** Writing - review & editing. **Pankaj Puri:** Writing - review & editing. **Amit Rastogi:** Writing - review & editing. **Vivek A. Saraswat:** Writing - review & editing. **Sanjiv Saigal:** Writing - review & editing. **Shalimar:** Writing - review & editing. **Akash Shukla:** Writing - review & editing. **Shivaram P. Singh:** Writing - review & editing. **Thomas Verghese:** Writing - review & editing.

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SUPPLEMENTARY DATA

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