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# ACUTE LIVER FAILURE MANAGEMENT
## *Evidence Based Medicine Guideline*

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Approved: 10/30/2024

**SUMMARY**
Acute liver failure (ALF) is defined as impaired hepatic function following an acute insult. The associated comorbidities can be difficult to manage. This guideline serves as a template for the management of acute liver failure and its associated conditions.

**RECOMMENDATIONS**

**Level 1**

- N-acetylcysteine (NAC) should be administered for patients in ALF (except for those with ALF secondary to ischemia / shock liver).
- Plasma exchange should be considered for all patients with ALF, especially in those unresponsive to NAC.
- Thromboelastography (TEG) should be used to drive coagulopathy correction rather than PT, PTT, or INR.

**Level 2**

- Continuous renal replacement therapy (CRRT), even in the absence of other conventional indications, should be initiated early in patients with ALF.
- Glucose levels should be monitored every 2 hours and hypoglycemia should be avoided
- Hyponatremia should be corrected to maintain serum sodium concentrations of 140–150 mEq/L.
- Mannitol or hypertonic saline should be strongly considered for those with intracranial hypertension and ALF.
- Enteral feeding should be initiated as soon as possible making sure to account for increased energy expenditures and use of branched chain amino acids.

**Level 3**

- Consider prophylactic broad-spectrum antibiotics (third generation cephalosporin) and vancomycin in critically ill patients with ALF. Antifungal prophylaxis should also be considered.

## INTRODUCTION

Acute liver failure (ALF) has been characterized by a constellation of symptoms including hepatic encephalopathy, intrinsic coagulopathy, and an acute hepatic insult. Severe injury is defined as impaired hepatic synthetic function (INR > 1.5) along with altered mentation in a patient without pre-existing hepatic disease. Illness duration is commonly < 26 weeks (1).

It is vital to understand the distinction between ALF and acute on chronic liver failure (ACLF). ALF tends to occur in younger patients where there is usually an absence of chronic liver disease. ALF is typically precipitated by drugs or viruses, and liver biopsy shows necrosis. Clinically, patients have an elevated INR and demonstrate symptoms of hepatic encephalopathy. ACLF, however, tends to occur in older patients with evidence of chronic liver disease or cirrhosis. Usual triggers for ACLF are infections and alcohol use, and liver biopsy demonstrates fibrosis (2).

**LEVEL OF RECOMMENDATION DEFINITIONS**

- **Level 1:** Supported by multiple, prospective randomized clinical trials or strong prospective, non-randomized evidence if randomized testing is inappropriate.
- **Level 2:** Supported by prospective data or a preponderance of strong retrospective evidence.
- **Level 3:** Supported by retrospective data or expert opinion.

Common causes of ALF include acetaminophen toxicity, non-acetaminophen drug-induced liver injury, viral hepatitis, autoimmune hepatitis, ischemic liver injury, mushroom poisoning, Wilson disease, Budd-Chiari syndrome, and pregnancy specific liver diseases such as HELLP syndrome and acute fatty liver of pregnancy.

## LITERATURE REVIEW

### ***Central Nervous System***

Cerebral edema is a serious complication of ALF. Cerebral edema is thought to occur because of hyperammonemia which causes astrocyte swelling, thus impairing the blood brain barrier. Previous researchers have demonstrated that serum ammonia > 150-200 micromol/L has been associated with an increased risk of cerebral edema and intracranial hypertension (3). The use of CRRT to lower ammonia levels in ALF patients has also been demonstrated to be beneficial. In their prospective study, Slack et al. demonstrated a 22% reduction in median arterial ammonia concentration over 24 hours utilizing ultrafiltration (4). Cardoso et al., in conjunction with the US Acute Liver Failure Study Group, performed a multicenter cohort study of ALF patients. They studied the impact of early renal replacement therapy during the first 3 days post admission and on 21-day transplant free survival. They found that higher median ammonia levels were associated with higher grade levels of hepatic encephalopathy and increased mortality at day 21. After they adjusted for year of enrollment into the study, age, etiology, and disease severity, CRRT usage in this population resulted in a reduction in 21-day transplant free all-cause mortality (5). Because of this, the American Journal of Gastroenterology has conditionally recommended that in patients with ALF and Grade 2 (or higher) encephalopathy (defined as lethargy, behavioral changes, asterixis, or hypoactive reflexes), CRRT be initiated. They recommend administration of CRRT even in the absence of other traditional dialysis indications (2).

Beyond CRRT, other adjuncts have been studied to decrease ammonia levels. Ornithine phenylacetate (OPA) theoretically works by stimulating glutamine synthetase in muscle leading to trapping of circulating ammonia as glutamine. This is then excreted in the urine as phenylacetylglutamine (6). Stravitz et al., in conjunction with the Acute Liver Failure Study Group (ATLSG), analyzed 47 patients and their ammonia levels over time after receiving one of three dosages of OPA. They found that OPA is effective as an ammonia scavenger regardless of the degree of liver injury in ALF patients. They concluded that a dosage of 20 g / 24 hours can lower serum ammonia in ALF patients (7). Rahimi et al. performed a multi-center, randomized, double-blind study of 231 patients assigned to receive either placebo or OPA (8). They found that patients who received OPA demonstrated clinical improvement in hepatic encephalopathy 21 hours sooner compared to placebo with no statistical significance regarding adverse events. They concluded that in patients with Grade 2 encephalopathy or greater with elevated ammonia levels, OPA demonstrated an ammonia scavenging mechanism with an improvement in encephalopathy (8).

Hepatic encephalopathy secondary to ALF can increase intracranial pressure (ICP). Rajajee et al. studied 37 patients with ALF and Grade 4 encephalopathy implementing a protocol for coagulopathy reversal and ICP monitoring (9). They found ICP monitoring is feasible, has a positive impact on clinical management, and has a low incidence of serious complications. The American Association for the Study of Liver Disease (AASLD) recommends ICP monitoring in ALF patients with high grade encephalopathy, those awaiting transplant, or in those in centers with ICP monitoring expertise.

In patients with ALF and elevated ICP, data has also emerged regarding the use of mannitol to decrease intracranial hypertension. These effects may be transient but have been demonstrated in small series to correct episodes of elevated ICP and improve survival. Canalese et al. performed a controlled trial of 44 patients with acute fulminant hepatic failure (10). They randomly assigned patients to either receive mannitol or dexamethasone and measured ICP. They found that ICP fell in monitored patients in those receiving mannitol ($p<0.001$). Murali et al. demonstrated a similar benefit of mannitol in both reducing cerebral edema and improving clinical outcome with a dose of 0.5-1.0 g/kg IV (11). Kahal et al., in the 'MAHAL Study', demonstrated that both mannitol and hypertonic saline can reduce ICP and mortality in ALF patients; however, they found that there was a rebound increase in ICP in those who had stopped mannitol vs. hypertonic saline ($p<0.05$) (12).

There is limited data on the use of lactulose and rifaximin in the ALF population. Rifaximin works by inhibiting bacterial protein synthesis by irreversibly binding the beta subunit of bacterial DNA dependent RNA polymerase. Lactulose works by decreasing intestinal production and absorption of ammonia. Cutler et al. performed a

retrospective single center observational study evaluating the impact of lactulose in ICU patients with hyperammonemia without chronic liver disease (13). They found no significant improvement in outcomes following treatment of mild to moderate hyperammonemia with lactulose. The Acute Liver Failure guidelines do not recommend the use of lactulose or rifaximin in the treatment of hepatic encephalopathy in ALF patients (2).

**Metabolic / Nutrition**

ALF poses a unique challenge regarding metabolism and nutrition. ALF is associated with severe loss of hepatocellular function with concomitant abnormal protein, carbohydrate, and lipid metabolism. At the same time, energy expenditure in ALF has been reported to increase by 18-30% (14). ALF causes impaired gluconeogenesis, decreased hepatic glycogen storage, and increasing insulin resistance. The Acute Liver Failure guidelines recommend a constant 10% dextrose infusion as needed to maintain a blood sugar between 150-180 mg/dL (2). Caution must be taken to balance the need for euglycemia, hypotonicity, and cerebral edema as excess hypotonic solutions may result in worsened cerebral edema (12). Murali et al. recommend early initiation of enteral feeding as soon as possible (11). Anand et al. recommend that blood sugars be checked every 2 hours given the associated increase in mortality (15). They recommend prompt IV boluses of glucose (50%) taking care to avoid hyperglycemia.

Abenavoli et al. performed a meta-analysis regarding ALF and nutrition (16). They studied 262 manuscripts including 24 randomized clinical trials. They recommended amino acid supplementation, specifically branched chain amino acids (BCAA), including leucine, isoleucine, and valine. BCAA promote anabolism, reduce cachexia, and help to prevent hepatic encephalopathy. They also recommended enteral feeding as the preferred nutrition route to preserve gut microbiota. They noted that an increased resting energy expenditure of 18-30% must be accounted for in calculating appropriate feeding regimens.

**Coagulopathy**

The intricate pathophysiology of coagulopathy in ALF remains a subject of ongoing exploration. Existing evidence underscores a complex interplay involving diminished synthesis of both procoagulant and anticoagulant factors, compromised fibrinolytic systems, platelet dysfunction, and thrombocytopenia. This delicate equilibrium between procoagulant and anticoagulant pathways in ALF is susceptible to dynamic disruptions, potentially leading to challenging thrombotic or bleeding complications (17).

The pathophysiology behind coagulopathy in ALF is due to a pronounced reduction in coagulation factor levels, evidenced by prolonged PT and International Normalized Ratio (INR) values. Hepatocytes, critical for synthesizing most coagulation factors, exhibit compromised functionality in the context of ALF. Historical studies from the 1970s and contemporary research on acute acetaminophen overdose reveal diminished levels of clotting factors II, V, VII, and X, coupled with heightened levels of factor VIII. The shortened half-life of coagulation factors further magnifies the impact of reduced production in ALF. There is also a simultaneous reduction in the synthesis of anticoagulant proteins by the liver including protein C and protein S (18).

In addition, it is essential to understand INR and its relation to ALF. INR was originally designed to assess interference in the Vitamin K-dependent clotting pathway, as seen in warfarin-induced coagulopathy, making it less relevant for ALF where both Vitamin K-dependent and -independent factors contribute. Secondly, INR only reflects changes in procoagulant factors, derived from prothrombin time (PT) and calculated as a ratio of the patient's PT to standardized PT. Conventional coagulation studies like PT and activated partial thromboplastin time (aPTT) capture only the reduction in procoagulant factors, neglecting deficiencies in anticoagulant factors like protein C, protein S, and antithrombin that are also reduced in ALF. INR is commonly utilized by clinicians to assess bleeding risk in ALF, but recent studies stress the importance of cautious interpretation within the context of hemostasis and bleeding.

Elevated INR is commonly observed in ALF, yet bleeding complications are infrequent. Munoz et al. studied over 1000 ALF patients, finding a mean INR of 3.8 with 81% having an INR between 1.5 and 5.0 at admission (19). Bernal et. Al. further studied 2095 ALF patients at Kings College Hospital. Amongst their study population, they demonstrated similar INR profiles to what Munoz et al. noted. Despite high INR values, spontaneous overt bleeding in ALF is rare typically manifesting as gastrointestinal mucosal bleeding. INR values in patients with bleeding did not significantly differ from those without bleeding in the ALF Study Group (20). In terms of trauma patients, bleeding complications from invasive procedures, such as intracranial pressure (ICP) monitor placement, were comparable to those without such procedures. A recent study reported a 10.6% overall bleeding incidence in

a cohort of 1770 ALF patients with INR not significantly differing between bleeders and non-bleeders (21). Bleeding complications accounted for 2.1% of patient deaths.

In the context of ALF, traditional thromboelastography (TEG) typically shows normal primary and secondary hemostasis parameters even when the INR is elevated. A study by Stravitz et al. found that despite an average elevated INR of 3.4, TEG parameters were normal in most cases with 63% of patients showing normal TEG studies and 8% having hypercoagulable TEG parameters (22). Interestingly, thrombotic complications were more prevalent than bleeding complications, with 11 patients experiencing thrombosis compared to six with bleeding. Overall, these findings challenge the conventional association between ALF and impaired hemostasis.

**Infection**

Patients experiencing ALF have an increased vulnerability to infection, sepsis, and septic shock culminating in increased morbidity and mortality. This susceptibility primarily emanates from immune system aberrations triggered by a systemic compensatory anti-inflammatory response. Bacterial infections are ubiquitous, affecting up to 80% of patients with pneumonia (50%), urinary tract infections (22%), and bloodstream infections (28%) constituting prevalent occurrences (23). The mortality linked to sepsis exhibits a wide-ranging spectrum spanning from 10% to 52%.

Diagnostic intricacies accompany these infections necessitating vigilant surveillance due to their consequential outcomes. A judicious approach involves routine cultures and judicious administration of broad-spectrum antibiotics particularly in the face of deteriorating clinical conditions. The recommended antibiotic regimen encompasses extended-spectrum β-lactam agents, such as piperacillin–tazobactam and ticarcillin–clavulanate, along with vancomycin. Consideration for *Candida* treatment is warranted in the presence of risk factors like diabetes, parenteral nutrition, prior exposure to broad-spectrum antibiotics, or abdominal surgery. Nevertheless, the precise antimicrobial strategy should be tailored to local microbiological data. Despite studied implications, the merits of antibiotic prophylaxis remain controversial, precluding widespread endorsement without consideration of local microbial profiles (11).

## THERAPEUTIC ADJUNCTS

N-Acetylcysteine

N-acetylcysteine (NAC) has long been known as the primary therapeutic agent for acetaminophen toxicity. Acetaminophen metabolism is related to glucuronidation and sulfation with a minor amount being oxidized to produce a toxic metabolite called N-acetyl-p-benzoquinone imine (NAPQI) which can cause cellular injury. Glutathione normally detoxifies these toxic metabolites to prevent tissue damage. NAC repletes glutathione reserves, binds to toxic metabolites, and scavenges free radicals. It further increases oxygen delivery to tissues, increases mitochondrial ATP production, and alters microvascular tone to increase blood flow and end organ oxygen delivery (24). Even in non-acetaminophen patients, there has been a demonstrated benefit to NAC.

In 2009, Mumtaz et al. prospectively studied 47 patients who received NAC for non-acetaminophen-induced ALF with 44 control patients (25). The two groups were comparable regarding ALF etiology and coagulation studies at the onset of the trial. They demonstrated that 47% of patients in the NAC group survived vs. 27% in the non-NAC group. Using a multivariable regression analysis, they showed that patients not given NAC (odds ratio 10.3), age > 40 years (odds ratio 10.3), and patients requiring mechanical ventilation (odds ratio 20.1) were all independent predictors of mortality.

In 2015, Hu et al. performed a meta-analysis combining four clinical trials for 616 patients (26). 331 patients had received NAC and 285 patients were in the control group. Compared with previous studies, they found no statistical difference between the NAC and control group regarding overall survival ($p=0.42$). However, they did find significant differences between the NAC and control group regarding survival with native liver ($p=0.01$) and post transplantation survival ($p=0.03$). They concluded that NAC is safe for non-acetaminophen related ALF and can prolong survival with native liver without transplantation and survival post transplantation but an impact on overall survival was not seen.

In 2021, Walayat et al. performed the most recent, comprehensive, updated meta-analysis studying the impact of NAC in non-acetaminophen related ALF (27). They included 7 studies with 883 patients. They found the odds of

overall survival were significantly higher in the NAC group vs. controls (odds = 1.77). They also showed statistical significance regarding post-transplant and transplant-free survival. Interestingly, they also demonstrated that patients in the control group had statistically significant longer lengths of inpatient hospital stay (mean difference of NAC vs. control 7.79 days). They concluded that NAC significantly improves overall survival, post-transplant survival, transplant free survival, and decreases overall length of hospital stay.

There are fewer studies that directly address the impact of NAC in patients with ischemic induced ALF. Shana et al. sought to address this via a retrospective single center analysis (28). They enrolled 30 patients with ischemia-induced ALF and divided this group in half. Half of the group received NAC and half did not. They found a statistically significant improvement in AST and creatinine levels in the NAC vs. non-NAC group. They also found fewer (albeit non-significant) median days on vasopressors. They concluded that NAC results in improved renal function at 72 hours.

The recommended dosing regimen for NAC in non-acetaminophen related liver toxicity is 150 mg/kg over the 1st hour, followed by 50 mg/kg over the following 4 hours, followed by 100 mg/kg over the following 16 hours. If patient demonstrates failure of improvement, recommend additional 150 mg/kg over 24 hours x 2 doses for total treatment course of 3 days.

Therapeutic plasma exchange

Therapeutic high volume plasma exchange (HVP) is defined as exchanging ~15% of a patient's ideal body weight with fresh frozen plasma. The mechanism of action in improving ALF symptomatology is secondary to removal of plasma cytokines and inflammatory markers and immune modulation. Larsen et al. performed a randomized, prospective, controlled multicenter study of 182 patients with ALF analyzing standard medical therapy (SMT) vs. HVP (29). Their endpoints were liver transplant-free survival and survival post liver transplantation. They demonstrated that patients in the HVP group had statistically significant increases in hospital survival (58.7% vs. 47.8%) with stratification for liver transplantation and increased transplant free survival at a time point of 3 months. They also demonstrated that SIRS (Systemic Inflammatory Syndrome) and SOFA scores fell in the HVP group compared to the control group ($p<0.001$).

In 2022, Maiwall et al. performed a randomized controlled trial of 40 consecutive patients with ALF (30). They randomized patients into either receiving standard medical treatment or standard medical treatment with the addition of standardized volume plasma exchange (SVPE). They found that on day five patients in the SVPE arm had increased clearance of lactate, improvements in SIRS response and SOFA scores, and reduction in ammonia levels. They also found a higher 21-day transplant free survival (75% vs. 45%) associated with SVPE. They concluded that SVPE is safe and effective in ALF patients in reducing ammonia levels, cerebral edema, and cytokine storm.

**Liver transplantation**

Liver transplantation has been long thought of as the 'last ditch' effort for management of ALF. Currently, ALF accounts for 8% of liver transplant activity within Europe and the USA. O'Grady et al. identified the most used prognostic factors in transplantation to be etiology, rate of disease progression, patient age, and lab markers for disease severity (31). Bernal et al. performed a retrospective single center study evaluating over 3300 patients in 30 years with ALF (32). They found that transplantation was associated with increased survival among ALF patients from 66 to 86%. Wigg et al. performed a retrospective analysis from a single center with over 100 patients and found that transplantation benefits were strongest among those with seronegative hepatitis and ALF of indeterminate etiology (33). O'Grady outlined basic criteria to consider when evaluating liver transplantation including an absence of co-morbidities independent of ALF that would impact survival or absence of complications of ALF associated with survival (31).

**REFERENCES**


1. Lee WM, Stravitz TR, Larson AM. Introduction to the revised American Association for the Study of Liver Diseases position paper on acute liver failure 2011. *Hepatology* 2012; 55(3):965–967.
2. Shingina A, Mukhtar NA, Wakim-Fleming J, Alqahtani SA, Wong RJ, Limketkai BN, Larson AM, Grant L. Acute Liver Failure Guidelines. *Am J Gastro* 2023; 118(7):1128–1153.
3. Bernal W, Hall C, Karvellas CJ, Auzinger G, Sizer E, Wendon J. Arterial ammonia and clinical risk factors for encephalopathy and intracranial hypertension in acute liver failure. *Hepatology* 2007; 46(6):1844–1852.
4. Slack AJ, Auzinger G, Willars C, Dew T, Musto R, Corsilli D, Sherwood R, Wendon JA, Bernal W. Ammonia clearance with haemofiltration in adults with liver disease. *Liver International* 2013; 34(1):42–48.
5. Cardoso FS, Gottfried M, Tujios S, Olson JC, Karvellas CJ. Continuous renal replacement therapy is associated with reduced serum ammonia levels and mortality in acute liver failure. *Hepatology* 2017; 67(2):711–720.
6. Rahimi R, Rockey DC. Novel Ammonia-Lowering Agents for Hepatic Encephalopathy. *Clinics in Liver Disease* 2015; 19(3): 539-549.
7. Stravitz RT, Gottfried M, Durkalski V, Fontana RJ, Hanje AJ, Koch D, Hameed B, Ganger D, Subramanian RM, Bukofzer S, Ravis WR, Clasen K, Sherker A, Little L, Lee WM. Safety, tolerability, and pharmacokinetics of l-ornithine phenylacetate in patients with acute liver injury/failure and hyperammonemia. *Hepatology* 2018; 67(3): 1003–1013.
8. Rahimi RS, Safadi R, Thabut D, Bhamidimarri KR, Pyrsopoulos N, Potthoff A, Bukofzer S, Bajaj JS. Efficacy and safety of ornithine phenylacetate for treating overt hepatic encephalopathy in a randomized trial. *Clinical Gastroenterology and Hepatology* 2021; 19(12): 2626-2635.e7.
9. Rajajee V, Fontana RJ, Courey AJ, Patil PG. Protocol based invasive intracranial pressure monitoring in acute liver failure: feasibility, safety and impact on management. *Critical Care* 2017; 21(1).
10. Canalese J, Gimson AES, Davis C, Mellon PJ, Davis M, Williams R. Controlled trial of dexamethasone and mannitol for the cerebral oedema of fulminant hepatic failure. *Gut* 1982; 23:625–629.
11. Acute liver Failure | Cleveland Clinic. https://my.clevelandclinic.org/departments/digestive/medical-professionals/hepatology/acute-liver-failure#management-tab (accessed August 6, 2024).
12. Kalal, C. R., Maiwall, R., Choudhary, A., Premkumar, M., Kumar, G., Vyas, A. K., & Sarin, S. K. (2021). Mannitol is comparable to hypertonic saline for raised intracranial pressure in acute liver failure (MAHAL study): a randomized controlled trial. *Digestive Diseases* 40(5):607–615.
13. Cutler NS, Sadowski BW, MacGregor DA. Use of lactulose to treat hyperammonemia in ICU patients without chronic liver disease or significant hepatocellular injury. *J Intens Care Med* 2021; 37(5):698–706.
14. Plauth M, Schuetz T. Hepatology - Guidelines on Parenteral Nutrition, Chapter 16. *Ger Med Sci* 2009; 7:Doc12
15. Vincent JL. Intensive care management of severe acute liver failure. *Annual Update in Intensive Care and Emergency Medicine* 2015:415–430.
16. Abenavoli L, Maurizi V, Boccuto L, Di Berardino A, Giostra N, Santori P, Scarcella ML, Procopio AC, Rasetti C, Scarpellini E. Nutritional support in acute liver failure. *Diseases* 2022; 10(4):108.
17. Kim A, Niu B, Woreta T, Chen P. Clinical considerations of coagulopathy in acute liver Failure. *J Clin Transl Hepatol* 2020; 8(4):1–7.
18. Lisman T, Leebeek FW. Hemostatic alterations in liver disease: A review on pathophysiology, clinical consequences, and treatment. *Dig Surg* 2007; 24(4):250–258.
19. Munoz SJ, Rajender Reddy K, Lee W. The coagulopathy of acute liver failure and implications for intracranial pressure monitoring. *Neurocrit Care* 2008; 9:103–107.
20. Bernal W, Hyyrylainen A, Gera A, Audimoolam VK, McPhail MJ, Auzinger G, Rela M, Heaton N, O'Grady JG, Wendon J, Williams R. Lessons from look-back in acute liver failure? A single centre experience of 3300 patients. *J Hepatol* 2013; 59(1):74-80.
21. Stravitz RT, Ellerbe C, Durkalski V, Schilsky M, Fontana RJ, Peterseim C, Lee WM. Bleeding complications in acute liver failure. *Hepatology* 2018; 67(5):1931–1942.
22. Stravitz RT, Lisman T, Luketic VA, Sterling RK, Puri P, Fuchs M, et al. Minimal effects of acute liver injury/acute liver failure on hemostasis as assessed by thromboelastography. *J Hepatol* 2012; 56:129–136.
23. Yan, J, Li S, Li S. The Role of the Liver in Sepsis. International Reviews of Immunology 2014; 33(6):498–510.
24. Ershad M, Naji A, Patel P, Vearrier D. N-Acetylcysteine. StatPearls - NCBI Bookshelf. https://www.ncbi.nlm.nih.gov/books/NBK537183/ (Accessed February 29, 2024)
25. Mumtaz K, Azam Z, Hamid S, Abid S, Memon S, Shah HA, Jafri W. Role of N-acetylcysteine in adults with non-acetaminophen-induced acute liver failure in a center without the facility of liver transplantation. *Hepatology International* 2009; 3(4):563–570.

26. Hu J, Zhang Q, Ren X, Sun Z, Quan Q. Efficacy and safety of acetylcysteine in “non-acetaminophen” acute liver failure: A meta-analysis of prospective clinical trials. *Clinics and Research in Hepatology and Gastroenterology* 2015; 39(5):594–599.
27. Walayat S. Role of N-acetylcysteine in non-acetaminophen-related acute liver failure: an updated meta-analysis and systematic review. *Ann Gastroenterol* 2021; 34(1):1-6.
28. Kothari S, Kalinowski M, Brindise E, Kobeszko M, Silva R. 1082 N-Acetylcysteine: a novel agent for patients with ischemic hepatopathy. *Am J Gastro* 2019; 114(1):S612–S613.
29. Larsen FS, Schmidt LE, Bernsmeie, C, Rasmussen A, Isoniemi H, Patel VC, Triantafyllou E, Bernal W, Auzinger G, Shawcross D, Eefsen M, Bjerring PN, Clemmesen JO, Hockerstedt K, Frederiksen H, Hansen BA, Antoniade CG, Wendon,J. High-volume plasma exchange in patients with acute liver failure: An open randomised controlled trial. *J Hepatology* 2016; 64(1):69–78.
30. Maiwall R, Bajpai M, Singh A, Agarwal T, Kumar G, Bharadwaj A, Nautiyal N, Tevethia H, Jagdish RK, Vijayaraghavan R, Choudhury A, Mathur RP, Hidam A, Pati NT, Sharma MK, Kumar A, Sarin SK. Standard-Volume plasma exchange improves outcomes in patients with acute liver failure: a randomized controlled trial. *Clinical Gastroenterology and Hepatology* 2022; 20(4): e831–e854.
31. O’Grady J. Timing and benefit of liver transplantation in acute liver failure. *J Hepatology* 2014; 60(3):663–670.
32. Bernal W, Hyyrylainen A, Gera A, Audimoolam VK, McPhail MJ, Auzinger G, Rela M, Heaton N, O’Grady JG, Wendon J, Williams R. Lessons from look-back in acute liver failure? A single centre experience of 3300 patients. *J Hepatology* 2013; 59(1):74–80.
33. Wigg AJ, Gunson BK, Mutimer DJ. Outcomes following liver transplantation for seronegative acute liver failure: Experience during a 12-year period with more than 100 patients. *Liver Transplantation* 2004; 11(1):27–34.