CME

Acute liver failure

James Beck, PA-C; Jasleen K. Bolina, PharmD, BCPS, BCCCP; Lisa H. Boyd, MSN, ACNP

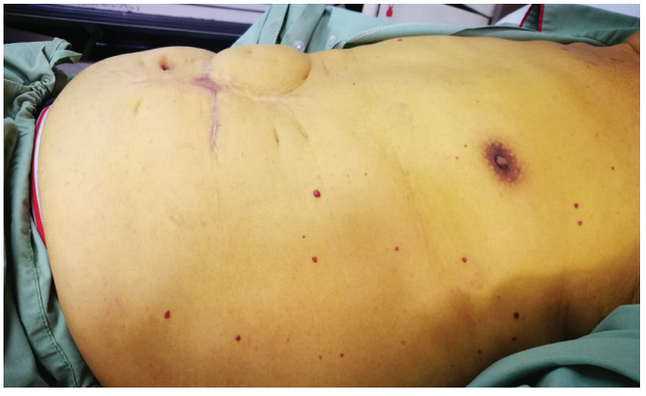
ABSTRACT

Acute liver failure, commonly caused by acetaminophen overdose, is associated with numerous systemic complications including cerebral edema, hypotension, acute kidney injury, and infection. Management is primarily supportive, with an emphasis on excellent neurocritical care. Although some antidotes and targeted treatments exist, the only definitive treatment remains orthotopic liver transplant.

Keywords: acute liver failure, hepatitis, acetaminophen, hyperammonemia, cerebral edema, transplant

Learning objectives

- Identify and differentiate ALF from more common conditions such as acute hepatitis, decompensated cirrhosis, and acute-on-chronic liver failure.
- Identify the most common causes of ALF.
- Understand the most common complications of ALF.
- Incorporate the best available evidence-based strategies into the resuscitation and initial management of patients with ALF.



Acute liver failure (ALF) is a life-threatening condition that occurs in patients with no preexisting liver disease, and is defined as liver injury as indicated by abnormal liver tests, coagulopathy (defined as an international normalized ratio [INR] greater than 1.5), and hepatic encephalopathy.[1] The presentation of ALF can be further classified based on the rapidity of onset of hepatic encephalopathy: hyperacute (less than 7 days), acute (7 to 21 days), and subacute (more than 21 days).[2,3] The degree of acuity can suggest certain causes and also can have prognostic value. For example, patients with ALF caused by acetaminophen overdose or ischemic hepatitis tend to have hyperacute presentations with a more favorable prognosis; patients whose ALF is caused by non-acetaminophen drug-induced liver injuries (DILI) or autoimmune hepatitis tend to have acute to subacute presentations with poorer prognosis.[1]

The most common cause of ALF in the United States is acetaminophen overdose, which may be intentional or unintentional.[4] In developing countries, most cases are related to viral hepatitis, most commonly hepatitis A, B, or E.[4] Other potential causes of ALF are outlined in **Table 1**.

In the United States, ALF is rare, with a prevalence of 2,000 to 3,000 cases annually.[5-8] Although relatively uncommon, ALF is associated with high morbidity and mortality. Before emergency orthotopic liver transplantation, survival rates for patients with ALF were estimated to be less than 15%.[6] Today, because of transplantation, improvements in critical care, and specialized care delivered at tertiary transplant centers, 1-year survival is now greater than 65%.[6] Although outcomes have improved, morbidity and mortality remain high, making it crucial for clinicians to rapidly identify these patients, begin initial diagnostic evaluation and management, establish early contact with a local transplant center, and consider early transfer as appropriate.[6]

PATHOPHYSIOLOGY

Through a variety of mechanisms, based on the specific underlying cause, ALF usually manifests with massive hepatic necrosis.[4] Notable exceptions are Reye syndrome and acute fatty liver of pregnancy, which are characterized by diffuse fatty infiltration of the liver.[9,10] The resulting severe hepatic dysfunction can cause patients to rapidly develop multiorgan dysfunction, manifesting with hepatic encephalopathy, cerebral edema, coagulopathy, hypotension, renal dysfunction, metabolic derangements, and hypoglycemia.

At Emory University Hospital in Atlanta, Ga., **James Beck** practices in critical care, **Jasleen K. Bolina** is a clinical pharmacy specialist in critical care, and **Lisa H. Boyd** is lead advanced practice provider in critical care. The authors have disclosed no potential conflicts of interest, financial or otherwise.

DOI:10.1097/01.JAA.0000000000000001

Key points

- ALF is defined as a severe liver injury with coagulopathy and hepatic encephalopathy developing within 26 weeks in the absence of preexisting liver disease.
- Acetaminophen toxicity is the most common cause of ALF in the United States.
- Patients with ALF are at increased risk for systemic complications, including cerebral edema, renal failure, infection, and severe metabolic abnormalities.
- The only definitive treatment for ALF is orthotopic liver transplant.

COMPLICATIONS

Neurologic Hepatic encephalopathy and hyperammonemia are closely related to cerebral edema and elevated intracranial pressure (ICP), arguably the most feared consequences of ALF. Incompletely understood, hepatic encephalopathy is a complex and multifactorial manifestation in which ammonia plays a key role. Under normal physiologic conditions, ammonia is detoxified by the liver and converted into urea. In patients with severe hepatic dysfunction, however, hepatic metabolism of ammonia is less efficient. Consequently, detoxification is left to the skeletal muscle and brain cells, specifically astrocytes.[4] As skeletal muscle becomes overwhelmed, astrocytes in the brain are left to detoxify excess ammonia to glutamine, causing cytotoxic edema and other deleterious central nervous system effects.[11]

Cardiovascular Hypotension and shock in patients with ALF can be multifactorial. Initially, patients may be hypovolemic because of decreased oral intake and gastrointestinal losses. Persistent hypotension following initial volume resuscitation often is vasodilatory and caused by a loss of systemic vascular resistance in patients with hepatic dysfunction.[6] Consider sepsis and severe acidemia and manage them accordingly.

Renal and metabolic Acute kidney injury (AKI) is common in patients with ALF, with one large retrospective study showing that up to 70% of patients had renal dysfunction and 30% required renal replacement therapy (RRT).[1] Typically, the underlying mechanism of renal injury differs from hepatorenal syndrome seen in patients with chronic liver disease. Instead, AKI may be caused by systemic inflammation, direct toxicity from acetaminophen metabolites, sepsis, hypovolemia, shock, or exposure to contrast medium or other nephrotoxins.[12]

Metabolic disorders are common in patients with ALF and may include various acid-base derangements, hypoglycemia, or electrolyte imbalances.[6] In particular, phosphorus is an important electrolyte to trend because it may correlate with liver recovery. As the liver regenerates, adenosine triphosphate synthesis increases rapidly, causing an influx of phosphorus into hepatocytes. Although this is a good prognosticator of liver recovery, it requires active management with aggressive repletion because patients can develop severe hypophosphatemia.[13]

Hematologic Coagulopathy is a result of synthetic liver failure. Individual laboratory values, notably prothrombin time (PT) and INR, may be markedly elevated and are important for monitoring synthetic liver function. However, similar to patients with chronic liver disease, patients with ALF have deficiencies in procoagulants and anticoagulants, leading to a rebalanced coagulation equilibrium; as a result, significant bleeding is uncommon.[12]

Infectious disease Patients with ALF have a high prevalence of bacterial and fungal infections secondary to increased gut permeability, endotoxemia, albumin and lipoprotein dysfunction, and toll-like receptor expression.[1,14]

CLINICAL PRESENTATION

ALF, by definition, is characterized by encephalopathy. This alteration in mentation can vary greatly, from impaired attention and dysregulated sleep to frank coma.[15] In addition to encephalopathy, patients may have a variety of other complaints including fatigue, anorexia, nausea, vomiting, abdominal discomfort, jaundice, and scleral icterus.[4,16-18]

When ALF is suspected, attempt to obtain a detailed history. This should include duration of symptoms and the patient's past medical history, which can help exclude similar, more common, clinical entities such as decompensated cirrhosis and acute-on-chronic liver failure; differentiation is critical because management of these conditions varies greatly. Additional history should assess for a cause such as a medication, intentional or accidental drug overdose or toxin ingestion, recent travel, recent medication changes, alcohol and substance use, pregnancy status, and family history. A complete physical examination should include a thorough neurologic

TABLE 1. Causes of ALF[4,38,39]

- **Drug-related (including dose-dependent toxins and idiosyncratic drug reactions):** acetaminophen, antituberculosis drugs, sulfonamides, phenytoin, disulfiram, propylthiouracil, various herbal and dietary supplements
- **Viral:** acute hepatitis (most often A, B, or E), herpes simplex virus, cytomegalovirus, adenovirus, Epstein-Barr virus, varicella-zoster virus, parvovirus B19
- **Pregnancy-associated:** fatty liver of pregnancy; hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome
- **Vascular:** veno-occlusive (including Budd-Chiari syndrome), ischemic (shock, cardiac)
- **Autoimmune hepatitis**
- **Toxins:** mushroom poisoning (*Amanita* species)
- **Other:** Wilson disease, sepsis, hemophagocytic lymphohistiocytosis, malignant infiltration, heat stroke

TABLE 2. Diagnostic evaluation for ALF[6,19,21]

- **Initial evaluation:** CBC count, CMP, PT/INR, partial thromboplastin time, fibrinogen, arterial blood gas analysis, lactic acid level, ammonia level, blood cultures, urinalysis, pregnancy screening
- **Toxicology:** acetaminophen level, ethanol level, urine toxicology screen
- **Viral serologies:** hepatitis A IgM; hepatitis B surface antigen, core antibody, and antibody; anti-hepatitis B virus IgM; hepatitis C antibody and RNA; anti-hepatitis E IgM; polymerase chain reaction tests for herpes simplex virus DNA, cytomegalovirus DNA, varicella-zoster virus DNA, Epstein-Barr virus, and adenovirus
- **Autoimmune markers:** antinuclear antibodies, anti-smooth muscle antibody, serum IgG level
- **Metabolic:** urine copper, serum ceruloplasmin
- **Imaging:** right upper quadrant ultrasound with Doppler, CT or MRI of the abdomen and pelvis and of the head

assessment evaluating the patient's degree of encephalopathy, and noting any focal neurologic deficits or signs of elevated ICP, which could include headache, nausea, vomiting, pupillary changes, or Cushing triad (hypertension, bradycardia, and irregular respirations).[19] Additionally, evaluate for signs of chronic liver disease, including ascites, caput medusae, palmar erythema, spider telangiectasias, and gynecomastia in males.

A thorough examination also may uncover features that are suggestive of specific causes, such as Kayser-Fleischer rings associated with Wilson disease, or a diffuse maculopapular eruption suggestive of drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome.

DIAGNOSTIC EVALUATION

An accurate diagnosis, including the underlying cause, is important for cause-specific management, which is promoted in clinical practice guidelines for ALF. Be suspicious for ALF in a patient with new-onset liver disease with increased PT. Evaluate liver enzymes to establish evidence of liver damage. Initial laboratory tests should include a complete blood cell (CBC) count, comprehensive metabolic panel (CMP), and PT/INR. Aspartate transaminase (AST) and alanine transaminase (ALT) typically are markedly elevated. Alkaline phosphatase also may be elevated, but typically to a lesser degree than AST and ALT, indicating a hepatocellular pattern.[20] By definition, INR will be elevated. If the patient's initial diagnostic evaluation is consistent with ALF, a thorough additional workup should include studies directed at identifying the underlying cause (**Table 2**).[1]

The American College of Gastroenterology (ACG) also recommends imaging studies for all patients as well as transplant candidates.[1] Imaging typically begins with a right upper quadrant ultrasound to assess the liver parenchyma and vessel patency.[21] Subsequent imaging including CT and/or MRI of the abdomen and pelvis also should be considered for further evaluation of the liver and vessels as well as for evidence of chronic liver disease. Finally, neuroimaging with a head CT is recommended for all patients with ALF. Although CT has low sensitivity for detecting early cerebral edema, it is useful for excluding other intracranial pathologies, such as intracranial hemorrhage.[19]

MANAGEMENT

Patients with ALF are best managed by a multidisciplinary care team with clinicians from hepatology and transplant hepatology, critical care, neurology, nephrology, and infectious diseases. All patients with ALF should be discussed with a transplant center and transfer should be strongly considered, because even patients with mild hepatic encephalopathy can rapidly deteriorate clinically.[6] Even patients without hepatic encephalopathy may reasonably be brought to the attention of a local transplant center for guidance and potential transfer.

Antidotes and targeted management Immediately contact poison control if a patient is suspected to have acetaminophen-induced ALF. N-acetylcysteine (NAC), the recommended antidote, is available in oral and IV formulations that typically are administered in standard 72-hour and 21-hour regimens, respectively. IV dosing of NAC usually divides 300 mg/kg over 21 hours via a two- or three-bag regimen, depending on the protocol followed. Prolonged NAC infusions and higher doses sometimes are used in patients with large ingestions or severely elevated serum acetaminophen concentrations.[22] Additionally, fomepizole, often used as an antidote for toxic alcohol ingestions, has been shown in case reports to be safe and possibly effective as an adjunct to NAC.[23]

NAC also can be used to manage non-acetaminophen-induced liver failure (NAI-ALF) because it acts as a free radical scavenger, providing oxidative benefits.[24] In a randomized, double-blind trial of patients presenting with DILI, autoimmune hepatitis, hepatitis B, or indeterminate ALF, NAC was found to improve transplant-free survival in those with early NAI-ALF (hepatic encephalopathy grade I or II).[24] Depending on the underlying cause, additional targeted interventions and treatments may be considered (**Table 3**). However, with the exception of NAC, management for many patients with ALF is primarily supportive.

Managing neurologic complications Management of elevated ICP associated with ALF includes prudent monitoring and both pharmacologic and nonpharmacologic interventions. Severe hyperammonemia (greater than 150 umol/L) correlates to encephalopathy and a higher risk of elevated ICP.[4] Neuroimaging with CT, although useful in evaluating for other intracranial pathologies, is not sensitive for early cerebral edema and

increased ICP. MRI is more sensitive, but often is more challenging to obtain.[25] Consultation with neurology generally is warranted, especially for patients with grades III or IV hepatic encephalopathy. Invasive ICP monitoring sometimes is considered, although it is not recommended by the Society of Critical Care Medicine.[6,26] Consider noninvasive neuromonitoring, which may include serial bedside neurologic assessments and continuous electroencephalogram.

Standard measures for managing ICP elevation include assessment and management of airway, breathing, and circulation; head-of-bed elevation; maintaining the neck midline; minimizing noxious stimuli; appropriate sedation and analgesia; and avoiding hyponatremia.[27] To further reduce the risk of elevated ICP, consider mild hypothermia and mild hypernatremia achieved via use of hypertonic sodium chloride solution.[6] The effect of therapeutic hypothermia is multifactorial because it can reduce overall metabolism of ammonia in addition to ammonia production and cerebral uptake.[4] For patients with refractory ICP elevation, consider more aggressive hyperosmolar therapy with additional hypertonic sodium chloride solution, hypothermia, deep sedation, and neuromuscular blockade.[25]

The ACG recommends consideration of early continuous RRT (CRRT) for the management of hyperammonemia even in the absence of traditional indications for RRT.[1]

Pharmacologic interventions to reduce ammonia concentrations, such as lactulose and rifaximin, which commonly are used to treat hepatic encephalopathy in patients with chronic liver disease, generally are not recommended for patients with ALF.[11]

Additional management and supportive care The goal of initial resuscitation is to maintain adequate renal and cerebral perfusion. Administer crystalloids initially to attain a mean arterial pressure goal of 65 to 75 mm Hg, and escalate to vasopressor support as appropriate.[6,12,28] Avoid hypotonic fluids because of their potential for causing hyponatremia and increased cerebral edema.[4]

Patients with ALF are at increased risk for bacterial and fungal infections. Although prophylactic antibiotics are not routinely recommended, surveillance blood cultures are recommended with a low threshold to initiate antimicrobials in patients with evidence of infection or clinical deterioration.[6]

Consider early intubation in patients presenting with respiratory failure, those unable to protect their airway, and those presenting with grade III or IV hepatic encephalopathy.[4,21]

Enteral nutrition is preferred over parenteral nutrition because of its lower risk of infection, ileus, and bowel ischemia.[29] Consider using a nasogastric tube to reduce aspiration risk.[29] Enteral nutrition should be initiated as feasible but avoid excess protein, which can worsen hyperammonemia.[21,29]

To assess coagulopathies, viscoelastic testing, such as thromboelastography (TEG) and rotational thromboelastometry (ROTEM), are more reliable than laboratory markers such as INR, platelet count, or fibrinogen level.[28] Because of the rebalanced hemostasis seen in patients with ALF, elevated INR or low platelet count alone should not preclude routine use of deep vein thrombosis prophylaxis with low-molecular-weight heparin or unfractionated heparin in appropriate patients.[6,28] If a patient requires correction, platelet transfusions typically are recommended at normal thresholds: patients with no signs of bleeding and fewer than 10,000 to 20,000 cells/mm^3, or patients with bleeding and fewer than 50,000 cells/mm^3.[6] Generally, avoid correcting coagulopathy in patients without bleeding.[28] Vitamin K can be considered to empirically treat concurrent nutritional deficiency.[6]

Extracorporeal management Consider RRT for typical indications such as severe metabolic and electrolyte disturbances, volume overload, and uremia. RRT has the added benefit of reducing ammonia concentrations, and the ACG recommends considering early initiation of CRRT specifically for this reason.[1,30] A retrospective cohort study by Cardoso and colleagues showed that CRRT was associated with reduced ammonia levels and an improved 21-day transplant-free survival rate, although this was following adjustment for confounding variables.[31] CRRT is preferred over intermittent hemodialysis because it provides greater hemodynamic stability and often is introduced early.[4,12]

TABLE 3. Targeted management of NAI-ALF[40-50]

Cause	Management
Viral	
Hepatitis B	Entecavir or tenofovir
Herpes simplex virus	Acyclovir
Cytomegalovirus	Valganciclovir
Adenovirus	No approved treatments. Cidofovir may be considered.
Varicella-zoster virus (VZV)	Acyclovir with or without VZV immune globulin
Other	
DILI	Discontinue the offending agent. If valproic acid-induced, administer levocarnitine
Vascular	• Veno-occlusive (Budd-Chiari): anticoagulation, thrombolysis, angioplasty, transjugular intrahepatic portosystemic shunt • Ischemic: supportive care
Autoimmune hepatitis	Corticosteroids
Hypersensitivity reaction	Corticosteroids
Wilson disease	Copper removal: chelating agent (zinc), RRT, plasma exchange, MARS

The molecular adsorbent recirculating system (MARS) is a type of extracorporeal liver support in which albumin-bound and water-soluble toxins such as bilirubin and ammonia can be removed. MARS use has been associated with improved systemic vascular resistance, which theoretically can contribute to reduced vasopressor requirements, improved perfusion, and an improvement in hepatic encephalopathy and ICP.[32] Several studies, largely observational or nonrandomized, have not shown significant survival benefit with the initiation of MARS in critically ill patients, and benefits should be weighed against the potential risks.[32,33] Use in the ICU for patients with ALF depends on availability in and experience of the institution.[26]

Plasma exchange is recommended to treat hyperammonemia in critically ill patients.[26] Often used in conjunction with CRRT, it can remove water-soluble and albumin-bound toxins and has been shown to improve transplant-free survival.[34] Complications associated with plasma exchange include hypocalcemia from citrate, hypofibrinogenemia, transfusion reactions, and potential hemodynamic instability.[34]

TRANSPLANT

Patients with ALF, unlike patients with chronic liver disease, can be listed for transplant with 1A status (urgent), giving them the highest priority on the transplant list.[6] The King's College Criteria for Acetaminophen Toxicity is the preferred model for use in predicting outcomes with transplantation, and it differentiates acetaminophen from non-acetaminophen-induced causes of ALF.[6] It can be helpful in identifying patients who may benefit from consideration of a transplant and/or transfer to a transplant center because it has 82% to 92% specificity; however, it has a 68% to 69% sensitivity, so it may overlook patients who are more likely to have poor outcomes.[35]

Although many factors influence transplant-free survival, the most significant factor is the cause of liver injury. Patients with acetaminophen overdose, hepatitis A, or ischemic liver injury have relatively favorable prognoses, with transplant-free survival rates of 56% to 75%.[36] Patients with autoimmune hepatitis have a much poorer transplant-free survival rate of only 25%.[36]

In an ALF study of 1,147 patients, 44% were listed for transplant, 25% were transplanted, 45% recovered spontaneously, and 30% died.[37] Posttransplant survival at 1 year was about 70%.[37]

Ultimately, the decision to pursue transplantation is beyond the scope of this article but remains an important consideration as the only definitive treatment for ALF.

CONCLUSION

ALF is a life-threatening medical condition that requires prompt identification. After patients with ALF are identified, clinicians must provide early and aggressive resuscitation and stabilization, initiate an appropriate diagnostic work-up, and establish early contact with a local transplant center. **JAAPA**

Earn AAPA Category 1 CME credit by reading both CME articles in this issue, reviewing the post-test, then taking the online test at http://cme.aapa.org. Successful completion is defined as a cumulative score of at least 70% correct. This material has been reviewed and is approved for 1 AAPA Category 1 CME credit. The term of approval is for 1 year from the publication date of May 2024.

REFERENCES

1. Shingina A, Mukhtar N, Wakim-Fleming J, et al. Acute liver failure guidelines. *Am J Gastroenterol*. 2023;118(7):1128-1153.
2. O'Grady JG, Schalm SW, Williams R. Acute liver failure: redefining the syndromes. *Lancet*. 1993;342(8866):273-275.
3. Bernuau J, Benhamou JP. Classifying acute liver failure. *Lancet*. 1993;342(8866):252-253.
4. Bernal W, Wendon J. Acute liver failure. *N Engl J Med*. 2013;369(26):2525-2534.
5. Stravitz RT, Lee WM. Acute liver failure. *Lancet*. 2019;394(10201):869-881.
6. Lee WM, Stravitz RT, 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.
7. Vento S, Cainelli F. Acute liver failure. *Lancet*. 2020;395(10240):1833.
8. Thanapirom K, Treeprasertsuk S, Soonthornworasiri N, et al. The incidence, etiologies, outcomes, and predictors of mortality of acute liver failure in Thailand: a population-base study. *BMC Gastroenterol*. 2019;19(1).
9. Chapman J, Arnold JK. Reye syndrome. Treasure Island, FL: StatPearls Publishing; 2023. https://pubmed.ncbi.nlm.nih.gov/30252357. Accessed January 25, 2024.
10. Ko H, Yoshida EM. Acute fatty liver of pregnancy. *Can J Gastroenterol*. 2006;20(1):25-30.
11. Nanchal R, Subramanian R. Brain and the liver: cerebral edema, hepatic encephalopathy and beyond. *Hepatic Crit Care*. 2017:83-103.
12. Moore JK, Love E, Craig DG, et al. Acute kidney injury in acute liver failure: a review. *Exp Rev Gastroenterol Hepatol*. 2013;7(8):701-712.
13. Baquerizo A, Anselmo D, Shackleton C, et al. Phosphorus as an early predictive factor in patients with acute liver failure. *Transplantation*. 2003;75(12):2007-2014.
14. Leber B, Spindelboeck W, Stadlbauer V. Infectious complications of acute and chronic liver disease. *Semin Respir Crit Care Med*. 2012;33(1):80-95.
15. Weissenborn K. Hepatic encephalopathy: definition, clinical grading and diagnostic principles. *Drugs*. 2019;79(suppl 1):5-9.
16. Bunchorntavakul C, Reddy KR. Acute liver failure. *Clin Liver Dis*. 2017;21(4):769-792.
17. Khan R, Koppe S. Modern management of acute liver failure. *Gastroenterol Clin North Am*. 2018;47(2):313-326.
18. Anand AC, Singh P. Neurological recovery after recovery from acute liver failure: is it complete? *J Clin Exp Hepatol*. 2019;9(1):99-108.
19. Stevens RD, Shoykhet M, Cadena R. Emergency neurological life support: intracranial hypertension and herniation. *Neurocrit Care*. 2015;23(suppl 2):S76-S82.
20. LiverTox: Clinical and Research Information on Drug-Induced Liver Injury. Bethesda, MD: National Institute of Diabetes and Digestive and Kidney Diseases. Acute liver failure. www.ncbi.nlm.nih.gov/books/NBK548171. Accessed January 25, 2024.

21. Warrillow S, Bellomo R. Intensive care management of severe acute liver failure. *Annu Update Intensive Care Emerg Med*. 2015;2015:415-430.
22. Chiew AL, Buckley NA. Acetaminophen poisoning. *Crit Care Clin*. 2021;37(3):543-561.
23. Link SL, Rampon G, Osmon S, et al. Fomepizole as an adjunct in acetylcysteine treated acetaminophen overdose patients: a case series. *Clin Toxicol*. 2021;60(4):472-477.
24. Lee WM, Hynan LS, Rossaro L, et al. Intravenous N-acetylcysteine improves transplant-free survival in early stage non-acetaminophen acute liver failure. *Gastroenterology*. 2009;137(3):856-864.
25. Siwicka-Gieroba D, Robba C, Gołacki J, et al. Cerebral oxygen delivery and consumption in brain-injured patients. *J Pers Med*. 2022;12(11).
26. Nanchal R, Karvellas C, Subramanian R. Guidelines for the management of adult acute and acute-on-chronic liver failure in the ICU (Part II). *Crit Care Med*. 2023:51657-51676.
27. Ratcliff JJ, Morrison C, Tran DS, Ruzas CM. Emergency neurological life support. Intracranial hypertension and herniation protocol version 4.0. https://higherlogicdownload.s3.amazonaws.com/NEUROCRITICALCARE/fdc4bb32-6722-417b-8839-f68ac1ef3794/UploadedImages/ENLS_Documents/ENLS_V4.0%20slide%20decks/ENLS_V4_0_ICP_Slides_12_10_19.pptx. Accessed January 25, 2024.
28. Nanchal R, Subramanian R, Karvellas CJ, et al. Guidelines for the management of adult acute and acute-on-chronic liver failure in the ICU. *Crit Care Med*. 2020;48(3):415-419.
29. Abenavoli L, Maurizi V, Boccuto L, et al. Nutritional support in acute liver failure. *Diseases*. 2022;10(4):108.
30. Gupta S, Fenves AZ, Hootkins R. The role of RRT in hyperammonemic patients. *Clin J Am Soc Nephrol*. 2016;11(10):1872-1878.
31. Cardoso FS, Gottfried M, Tujios S, et al. Continuous renal replacement therapy is associated with reduced serum ammonia levels and mortality in acute liver failure. *Hepatology*. 2017;67(2):711-720.
32. Cheungpasitporn W, Thongprayoon C, Zoghby ZM, Kashani K. MARS: should I use it? *Adv Chronic Kidney Dis*. 2021;28(1):47-58.
33. Saliba F, Camus C, Durand F, et al. Albumin dialysis with a noncell artificial liver support device in patients with acute liver failure: a randomized, controlled trial. *Ann Intern Med*. 2013;159(8):522-531.
34. Chris-Olaiya A, Kapoor A, Ricci KS, Lindenmeyer CC. Therapeutic plasma exchange in liver failure. *World J Hepatol*. 2021;13(8):904-915.
35. Gotthardt D, Riediger C, Weiss KH, et al. Fulminant hepatic failure: etiology and indications for liver transplantation. *Nephrol Dial Transplant*. 2007;22(suppl 8):viii5-viii8.
36. Kumar R, Anand U, Priyadarshi RN. Liver transplantation in acute liver failure: dilemmas and challenges. *World J Transplant*. 2021;11(6):187-202.
37. Lee WM, Squires RH Jr, Nyberg SL, et al. Acute liver failure: summary of a workshop. *Hepatology*. 2008;47(4):1401-1415.
38. Lin S, Li Y, Long J, et al. Acute liver failure caused by hemophagocytic lymphohistiocytosis in adults. *Medicine*. 2016;95(47).
39. Bower WA, Johns M, Margolis HS, et al. Population-based surveillance for acute liver failure. *Am J Gastroenterol*. 2007;102(11):2459-2463.
40. Li M, Luo Q, Tao Y, et al. Pharmacotherapies for drug-induced liver injury: a current literature review. *Front Pharmacol*. 2022;12.
41. Parekh J, Matei VM, Canas-Coto A, et al. Budd-Chiari syndrome causing acute liver failure: a multicenter case series. *Liver Transpl*. 2017;23(2):135-142.
42. Sedano R, Castro L, Venegas M, et al. Liver transplantation in acute liver failure due to hepatitis B. Two clinical cases. *Ann Hepatol*. 2021;21.
43. Chávez SM, Poniachik JM, Urzua ÁM, et al. Acute liver failure due to herpes simplex virus: diagnostic clues and potential role of plasmapheresis. *Medicine*. 2021;100(35).
44. Zahid M, Ali N, Saad M, et al. Acute cytomegalovirus (CMV) hepatitis in an immunocompetent adult. *Am J Case Rep*. 2020;21.
45. Verma A, Vimalesvaran S, Lampejo T, et al. Use of cidofovir in recent outbreak of adenovirus-associated acute liver failure in children. *Lancet Gastroenterol Hepatol*. 2022;7(8):700-702.
46. Brewer EC, Hunter L. Acute liver failure due to disseminated varicella zoster infection. *Case Rep Hepatol*. 2018;2018.
47. Rahim MN, Miquel R, Heneghan MA. Approach to the patient with acute severe autoimmune hepatitis. *JHEP Rep*. 2020;2(6).
48. Pandey CK, Karna ST, Pandey VK, Tandon M. Acute liver failure in pregnancy: challenges and management. *Indian J Anaesth*. 2015;59(3):144-149.
49. Santi L, Maggioli C, Mastroroberto M, et al. Acute liver failure caused by *Amanita phalloides* poisoning. *Int J Hepatol*. 2012;2012.
50. Bakhsh S, Teoh CW, Harvey EA, Noone DG. Single pass albumin dialysis and plasma exchange for copper toxicity in acute Wilson disease. *Case Rep Nephrol Dial*. 2019;9(2):55-63.