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**Objectives**

1. Define acute liver failure and differentiate it from acute liver injury.
2. Evaluate a patient with acute liver failure and identify the most common causes.
3. Develop a framework to guide initial management of acute liver failure.

**Teaching Instructions**

Plan to spend at least 30-60 minutes preparing for this talk by using the Interactive Board and clicking through the graphic animations to become familiar with the flow and content of the talk. Print out copies of the Learner’s Handout so learners can take notes as you review the definition, etiologies, and management of acute liver failure.

The anticipated time to deliver this talk is **20 minutes without cases and 30-35 minutes with cases.** The talk can be presented in two ways:

1. Project the “interactive Board for Presentation” OR
2. Reproduce your own drawing of the presentation on a whiteboard.

Begin with reviewing the objectives for the session. We recommend progressing in order, although this gives you the flexibility of doing more focused teaching on subtopics of interest. All clickable elements are indicated by a cursor icon A picture containing text

Description automatically generated.

**Objective 1:** ***Define ALF and differentiate it from acute live injury.* (Definition)**

Acute liver failure (ALF) is a rare but life-threatening illness with a high mortality rate (20-80% depending on underlying etiology). It requires prompt identification and management to improve survival. *Ask your learners what the three criteria for ALF are and click on each of the numbers to reveal additional information.* ALF is defined by the presence of ALL three of the following criteria: 1) acute liver injury, 2) coagulopathy, and 3) hepatic encephalopathy

1. **Acute liver injury** typically manifests as elevated transaminases (ALT/AST) and bilirubin, although elevations in alkaline phosphatase can also be seen to a lesser degree. By definition, onset of liver inflammation must have started within the past 26 weeks and occurs in the absence of underlying chronic liver disease. Notable exceptions include patients with autoimmune hepatitis, Wilson’s disease, or hepatitis B, where ALF can occur in the setting of preexisting liver disease.
2. **Coagulopathy** is defined by an INR > 1.5 (in the absence of warfarin or other anticoagulation). Coagulopathy is a marker of synthetic dysfunction of the liver as the inability to produce clotting factors results in derangements in clotting parameters (i.e., INR). Elevated INR is a key prognostic factor in ALF.
3. **Hepatic encephalopathy** (HE) is often the last component to present and helps to differentiate acute liver injury from acute liver failure. HE is graded on a scale of I-IV using the West Haven Criteria with more severe HE correlating with higher risk of ALF complications, particularly cerebral edema. HE can range from mild, with small changes in behavior or sleep-wake cycles, to severe with lack of responsiveness or coma.

**Objective 2:** ***Evaluate a patient with ALF and identify the most common causes.* (Etiologies)**

There are numerous potential etiologies of ALF. Four broad categories from the most to least common (in the United States) include: 1) drugs/toxins, 2) viral causes, 3) ischemic/vascular causes, and 4) other/miscellaneous. *Prompt your learners to provide a differential for each category of etiologies. Click once to reveal the differential diagnosis. Click again to reveal the work-up.*

* **Drugs/Toxins:** In the United States and Europe, drugs and toxins account for ~50% of ALF cases. Acetaminophen (APAP) toxicity is the most encountered cause although other notable drugs/toxins include herbal supplements and the *Amanita phalloides* mushroom.
* Initial evaluation should include acetaminophen level, toxicology screen, and thorough medication and supplement review. Medications and supplements should be cross referenced with LiverTox (livertox.nih.gov), a repository of medications with associated information on hepatotoxicity.
* It’s important to note that alcohol is NOT a cause of acute liver failure, although it may increase severity of another insult (e.g., APAP toxicity).
* **Viral**: In Asia and other parts of the world, viral hepatitis accounts for greater than 50% of cases. The most common viruses are hepatitis A, B, D, & E although HSV and VZV can also cause ALF in rare circumstances.
* Initial evaluation should include viral hepatitis serologies and PCRs (given that serologies may be negative in the acute setting). HIV serologies are typically checked given the risk of co-viral transmission, although HIV itself is not a cause of ALF.
* **Ischemic/vascular**: These include Budd-Chiari (hepatic vein clot), acute hepatic artery thrombosis, as well as ischemic hepatitis or shock liver, which usually occur secondary to a primary shock state (i.e., septic shock, cardiogenic shock).
* Evaluation for signs of shock and tissue hypoperfusion as well as a liver ultrasound with doppler can assess for vascular/ischemic etiologies.
* **Other:** Other causes of ALF include, but are not limited to, autoimmune hepatitis (AIH), HELLP or acute fatty liver of pregnancy and Wilson’s disease.
* Patients of childbearing age should receive a pregnancy test.
* Depending on the clinical history and presentation, autoimmune workup consisting of ANA, anti-smooth muscle Ab, anti-LKM-1, AMA, and immunoglobin levels can be considered.
* Additional evaluation should include consideration of acute Wilson’s disease, particularly in younger patients (age <55) and with an alkaline phosphatase/total bilirubin ratio of < 4. Ceruloplasmin can be normal in the acute setting so workup can be expanded to include 24hr urine copper and evaluation for Kaiser-Fleischer rings.
* If the initial workup is unrevealing, liver biopsy may be considered for histopathologic evaluation. Additional workup can be considered in the appropriate clinical setting and after consultation with a Hepatologist. Many cases of acute liver failure will not have a clear etiology and will be termed cryptogenic.

**Objective 3:** ***Develop a framework to guide initial management of acute liver failure.* (Management)**

There are several over-arching concepts when it comes to caring for a patient with ALF. Given the high risk of complications, patients with ALF should be managed in the ICU. *Click on each step to reveal additional information.*

1. **Address Complications**: The first, and largest, is recognizing and addressing the many multisystem complications of ALF. While not an exhaustive list, conditions associated with ALF include the following. *Ask your learners what common complications are seen in ALF before clicking to reveal the complications. Click on each complication to reveal additional information.*

* **Cerebral Edema**: Encephalopathy and intracranial hypertension from cerebral edema warrants medical ICU admission for frequent neurologic exams (q1-2 hrs) and prompt intervention when present. Intubation may be indicated for patients with grade III or IV HE. Maintain high vigilance for worsening intracranial hypertension, which can manifest as progressive encephalopathy. While head CT can show ventricular dilation and loss of gray-white matter differentiation, this is not sensitive for detection of elevated intracranial pressure (ICP). Direct ICP monitoring is possible, although this is rarely pursued given associated bleeding risks. If there is high concern for elevated ICP, administer hypertonic saline or mannitol to help lower ICP. If the patient is intubated, hyperventilation can be used to drive down PaCO2 and reduce ICP. Additionally, IVF should be minimized/avoided as much as possible, even in the setting of progressive renal failure, since it can precipitate or worsen cerebral edema.
* **Hypoglycemia**:This common complication occurs as a result of impaired gluconeogenesis. Patients should have blood glucose monitored frequently (q1-2 hours) and may require continuous dextrose infusions.
* **Multiorgan failure:** Close cardiorespiratory monitoring in the ICU is vital as patients may need endotracheal intubation and mechanical ventilator or inotropic/vasopressor support. A TTE can be helpful to evaluate for signs of biventricular failure and exclude cardiogenic shock or cardiac dysfunction as contributing to critical illness.
  + Severe electrolyte derangements and acidemia can occur from lactic acidosis, hypoperfusion, and renal failure. Frequent laboratory draws are routine (every 4-6 hours). Kidney dysfunction warrants close monitoring and early consideration of renal replacement therapy.
* **Coagulopathy** from liver synthetic dysfunction (inability to generate clotting factors) is common and should be a consideration when procedures are performed. Administration of vitamin K to correct any nutritional deficiency is appropriate and does not limit prognostic value of INR (given this is driven by synthetic dysfunction and not nutritional deficiency). However, administration of FFP or concentrated factors should be avoided unless there is active bleeding as this will limit the prognostic value of INR. Liver function tests and coagulation factors should be monitored every 4-6 hours.
* **Infection**: ALF causes a systemic inflammatory response that can mimic sepsis, although these patients are also at high risk for infection due to impaired function of the immunological system. Some centers/providers choose to prophylactically start antibiotics given this risk.

1. **Give NAC**: Empirically start N-acetylcysteine (NAC) for patients presenting with ALF. NAC serves two roles. First, in the setting of acetaminophen overdose NAC helps replenish glutathione, which is the rate-limiting enzyme in the breakdown of acetaminophen byproducts. Second, NAC has been shown to be beneficial in ALF even when not caused by acetaminophen toxicity, potentially through replenishing glutathione and by preventing oxidation of other molecules, although the pathophysiology is yet to be fully elucidated.4 For these reasons, NAC is recommended by AASLD guidelines to be given to all patients with ALF. Other empiric therapies, such as acyclovir, should also have a low threshold for initiation in the appropriate clinical setting (e.g., fever).
2. **Prognostication:** In consultation with a hepatologist, use evidence-based risk calculators (King’s College Criteria or MELD score) to assist in determining which patients are unlikely to spontaneously recover. Patients who are unlikely to recover should be considered for a liver transplant.

* *Bonus: Click on "Learn more about KCC" for additional learning on King's College Criteria and prognostication in ALF. These are unlikely criteria that internists will be applying alone without the aid of a hepatologist.*

1. **Transfer**: Lastly, and possibly most importantly, patients with ALF (particularly those who meet KCC criteria and/or are high risk of requiring a liver transplant) should be transferred to a liver transplant capable center if they are a potential transplant candidate. Regardless of care and interventions received, some patients with ALF will not recover with supportive care and will need a liver transplant. Patients should be transported as early as possible given further progression of disease may preclude them from safe transfer when transplant is needed.

**Cases:** After completion of the above objectives, review the practice cases to consolidate and apply the information that was learned.

**Take Home Points**

* ALF is defined by evidence of liver injury (<26 weeks duration) in the presence of hepatic encephalopathy and synthetic dysfunction (INR > 1.5).
* Viral hepatitis and drug toxicity (particularly acetaminophen) account for >50% of all cases of ALF, although other important categories to be aware of include autoimmune hepatitis, ischemic and vascular causes, and pregnancy related causes of liver injury.
* NAC should be started as soon as possible in patients with ALF as this has shown to be beneficial even in cases unrelated to acetaminophen toxicity.
* Any patient with ALF should be immediately considered for transfer to a liver transplant center, especially if they meet King’s College Criteria.

**References**

1. 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. doi:10.1002/hep.25551
2. Bernal W, Wendon J. Acute Liver Failure. NEJM. 2013; 369(26):2525-2534.
3. R Todd Stravitz, William M Lee, et al. Acute liver failure. *The Lancet,* Volume 394, Issue 10201, 2019; Pages 869-881.
4. Lee WM, Hynan LS, Rossaro L, et al. Intravenous N-acetylcysteine improves transplant-free survival in early stage non-acetaminophen acute liver failure [published correction appears in Gastroenterology. 2013 Sep;145(3):695. Dosage error in article text]. Gastroenterology. 2009;137(3):856-864.e1. doi:10.1053/j.gastro.2009.06.006.