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Preface: Acute Liver Failure
Nikolaos T. Pyrsopoulos

Classification and Epidemiologic Aspects of Acute Liver Failure
Daniel Pievsky, Neil Rustgi, and Nikolaos T. Pyrsopoulos

Acute liver failure is a rare condition with high short-term morbidity and mortality. The most widely accepted definition is an abnormality in coagulation with any degree of encephalopathy in a patient without cirrhosis and an illness duration of less than 26 weeks. Multiple classification systems are currently in use to help categorize the condition. This article reviews the most commonly used systems. The epidemiologic aspects of the disease are also reviewed, including incidence, prevalence, demographics, geographic distribution, and racial and cultural factors, and are discussed for the various subtypes of acute liver failure.

Acute Liver Failure: Mechanisms of Disease and Multisystemic Involvement
Steven Krawitz, Vivek Lingiah, and Nikolaos T. Pyrsopoulos

Acute liver failure is accompanied by a pathologic syndrome common to numerous different causes of liver injury. This acute liver failure syndrome leads to potentially widespread devastating end-organ consequences. Systemic dysregulation and dysfunction is likely propagated via inflammation as well as the underlying hepatic failure itself. Decoding the mechanisms of the disease process and multisystemic involvement of acute liver failure offers potential for targeted treatment opportunities and improved clinical outcomes in this sick population.

The Pathology of Acute Liver Failure
Billie Fyfe, Francisco Zaldana, and Chen Liu

Varied injuries may manifest clinically as acute liver failure. The pathologic features include variable amounts of necrosis and regeneration. This article reviews pathologic classification of patterns of necrosis and associated inflammatory and regenerative responses in specimens from patients with acute liver failure. Detailed pathologic examination of these specimens with clinical pathologic correlation can give the multidisciplinary team vital information regarding the cause and timing, as well as the extent of injury and regenerative response. Pathologists are a vital component of the health care team for patients with acute liver failure.

Liver Regeneration in the Acute Liver Failure Patient
Keith M. Wirth, Scott Kizy, and Clifford J. Steer

Liver regeneration after simple resection represents a unique process in which the organ returns to its original size and histologic structure. Over the past 30 years, there has been significant progress in elucidating the
mechanisms associated with regeneration after loss of hepatic mass. Liver regeneration after acute liver failure shares several of these classical pathways. It differs, however, in key processes, including the role of both differentiated and stemlike cells. This article outlines these differences in addition to new molecular mechanisms, including immunomodulation, microRNAs, and the gut-liver axis. In addition, applications to the patient population, including prognostication and stem cell therapies, are explored.

**Viral Hepatitis and Acute Liver Failure: Still a Problem**

Daniel Sedhom, Melroy D’Souza, Elizabeth John, and Vinod Rustgi

Although the overall prevalence of viral hepatitis is on the decline, the condition still plays a major role in the development of acute liver failure (ALF) worldwide. Hepatitis A, B, D, and E contribute to most fulminant viral courses. These viruses have not gained much attention in recent years yet remain relevant from a clinical perspective, as the incidence in certain populations is on the increase. Other viral therapies and immunotherapies are currently being examined as treatments for hepatitis D and hepatitis E. Clinicians should still maintain a high index of suspicion for viral causes in approaching patients with ALF.

**Nonacetaminophen Drug-Induced Acute Liver Failure**

Arul M. Thomas and James H. Lewis

Acute liver failure of all causes is diagnosed in between 2000 and 2500 patients annually in the United States. Drug-induced acute liver failure is the leading cause of acute liver failure, accounting for more than 50% of cases. Nonacetaminophen drug injury represents 11% of all cases in the latest registry from the US Acute Liver Failure Study Group. Although acute liver failure is rare, it is clinically dramatic when it occurs and requires a multidisciplinary approach to management. In contrast with acetaminophen-induced acute liver failure, non–acetaminophen-induced acute liver failure has a more ominous prognosis with a lower liver transplant-free survival.

**Acetaminophen (APAP or N-Acetyl-p-Aminophenol) and Acute Liver Failure**

Chalermrat Bunchorntavakul and K. Rajender Reddy

Acetaminophen (APAP) is the leading cause of acute liver failure (ALF), although the worldwide frequency is variable. APAP hepatotoxicity develops either following intentional overdose or unintentional ingestion (therapeutic misadventure) in the background of several factors, such as concomitant use of alcohol and certain medications that facilitate the formation of reactive and toxic metabolites. Spontaneous survival is more common in APAP-induced ALF compared with non-APAP causes. N-acetylcysteine is recommended for all patients with APAP-induced ALF, and it reduces mortality. Liver transplant should be offered early to those who are unlikely to survive based on described prognostic criteria.

**Nonviral or Drug-Induced Etiologies of Acute Liver Failure**

Russell Rosenblatt and Robert S. Brown Jr

Acute liver failure (ALF) is a rare but highly fatal condition. The most common causes include drug-induced and viral hepatitis, but other less
common causes, especially autoimmune hepatitis, Budd-Chiari syndrome, and Wilson disease, need to be considered. Because diagnosis is frequently tied to potential for reversibility of ALF and prognosis, early identification in a timely manner is crucial. Other causes of ALF are more easily recognizable based on specific circumstances, such as ALF in pregnancy or ischemic hepatitis. Ultimately, maintaining a wide differential diagnosis in patients with ALF is essential to identifying the proper treatment and prognosis.

The Clinical Spectrum and Manifestations of Acute Liver Failure
Sarah Zahra Maher and Ian Roy Schreibman

Acute liver failure (ALF) is a rare life-threatening condition characterized by rapid progression and death. Causes vary according to geographic region, with acetaminophen and drug-induced ALF being the most common causes in the United States. Determining the cause aids in predicting the prognosis and the presentation of manifestations and guides providers to perform cause-specific management. At initial presentation, nonspecific symptoms are present but may progress to complications, including cerebral edema, infection, coagulopathy, renal failure, cardiopulmonary failure, and acid-base and/or metabolic disturbances. Although some cases of ALF resolve with conservative measures, liver transplant is the ultimate treatment in many cases.

Prognostic Models in Acute Liver Failure
Avantika Mishra and Vinod Rustgi

There is a strong imperative to develop valid and accurate prognostic modeling for acute liver failure (ALF). Despite the numerous clinical models that have been proposed thus far and the use of some such models, that is, King’s College Criteria and Model for End-Stage Liver Disease, in clinical practice to aid decision making, there is a significant need for improvement for determining patients’ clinical course, survival, and requirement for liver transplant. Future prognostic models shall need a stronger statistical foundation and accountability for time and variability in the clinical course of ALF and be applied for pretransplant and posttransplant outcomes.

Non–Intensive Care Unit Management of Acute Liver Failure
Andres F. Carrion and Paul Martin

Acute liver failure (ALF) is an uncommon syndrome with a highly variable and unpredictable clinical course. The initial diagnostic evaluation is typically performed in a non–intensive care unit (ICU) setting, such as the emergency department or general hospital ward. Prompt restoration of intravascular volume with intravenous fluids and correction of electrolyte, metabolic, and acid-base disturbances are important initial interventions in the management of ALF and can be safely accomplished in non-ICU settings in many patients. Similarly, therapies such as administration of N-acetylcysteine for acetaminophen-induced ALF and other cause-specific interventions can also be administered in non-ICU settings, thus minimizing delay.
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Management of Acute Liver Failure in the Intensive Care Unit Setting 403
Priyanka Rajaram and Ram Subramanian

This article discusses the intensive care unit management of patients with acute liver failure. It focuses on the clinical presentation, identification, and management of the myriad of complications seen in patients with acute liver failure.

Liver Transplantation for Acute Liver Failure 409
Raquel Olivo, James V. Guarrera, and Nikolaos T. Pyrsopoulos

With the advent of liver transplant for acute liver failure (ALF), survival rate has improved drastically. Liver transplant for ALF accounts for 8% of all transplant cases. The 1-year survival rates are 79% in Europe and 84% in the United States. Some patients with ALF may recover spontaneously, and approximately half will undergo liver transplant. It is imperative to identify patients with ALF as soon as possible to transfer them to a liver transplant center for a thorough evaluation. Emergent liver transplant in a patient with ALF may place the patient at risk for severe complications in the postoperative period.

Future Approaches and Therapeutic Modalities for Acute Liver Failure 419
Pavan Patel, Nneoma Okoronkwo, and Nikolaos T. Pyrsopoulos

The current gold standard for the management of acute liver failure is liver transplant. However, because of organ shortages, other modalities of therapy are necessary as a possible bridge. This article discusses the current modalities as well as the future management of acute liver failure. Liver assist devices, hepatocyte transplant, stem cell transplant, organogenesis, and repopulation of decellularized organs are discussed.