Acute Liver Injury and Failure

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KEYWORDS

• Liver jury • Liver failure • Hepatic encephalopathy • Coagulopathy

KEY POINTS

- Acute liver failure is the result of a rapid loss of functional hepatic mass, such that the synthetic functions of the liver are compromised.
- Treatment of acute liver injury/acute liver failure is largely supportive and directed at ameliorating the complications that arise as a result of severe liver dysfunction.
- Although some patients may make a clinical recovery with intensive care, the prognosis for acute liver failure is generally considered poor.

INTRODUCTION

Acute liver injury (ALI) and acute liver failure (ALF) are clinical syndromes that are frequently life threatening, characterized by a rapid loss of hepatocyte function in a patient without pre-existing liver disease.[1] Numerous definitions for ALF have been proposed in the published literature, most of which involve a combination of an acute onset of clinical signs, the presence of coagulopathy, icterus, and the development of hepatic encephalopathy (HE).[2] In people, ALF is further characterized as hyperacute, acute, or subacute based on the time interval between the development of icterus and the onset of HE, because this seems to have prognostic significance.[3] Similarly, in the veterinary literature, a variety of diagnostic criteria have been used to define ALF. A recently published retrospective case series involving canine patients defined ALF as the acute onset of clinical signs in conjunction with serum hyperbilirubinemia and a prothrombin time (PT) greater than 1.5 times the upper reference range, with or without evidence of HE.[4] In contrast to ALF, ALI is generally thought to involve an acute hepatic insult with sustained hepatic function. This article reviews the pathophysiology and clinical approach to the ALI/ALF patient, with a particular emphasis on the diagnostic evaluation and care in the acute setting.

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PATHOPHYSIOLOGY

In health, the liver is responsible for a multitude of homeostatic, synthetic, and excretory functions, including protein, carbohydrate, and lipid metabolism; detoxification of metabolites and chemical compounds; immune regulation; fat digestion; albumin production; and storage of vitamins, fats, and glycogen. Hepatic Kupffer cells are tissue macrophages that typically reside in hepatic sinusoids but can migrate into areas of hepatic tissue injury. These cells are highly efficient phagocytes; consequently, the liver is a major site of blood filtration and removal of circulating microbes and microbial antigens.[5]

Histologically, hepatocytes are arranged into 3 zones around the hepatic blood supply. Zone 1 contains hepatocytes that are closest to the arterial or portal inflow; cells in this region are exposed to blood with a higher concentration of oxygen, hormones like insulin and glucagon, and products of nutrient metabolism. Given their proximity to vascular inflow, hepatocytes in zone 1 are susceptible to injury from directly acting toxicants. Zone 2 contains transitional midzone hepatocytes, and zone 3 contains the periacinar hepatocytes, which are closest to the hepatic venule and thus receive a lower concentration of oxygen and nutrients, making them more susceptible to hypoxic injury. In addition, many of the hepatic biotransformation pathways are active in zone 3; thus, hepatocytes in this zone are more susceptible to injury caused by toxic metabolites of the cytochrome P450 systems.[5]

The liver has an extensive reserve system and clinical signs or biochemical manifestations of ALF often are not apparent until there has been loss of more than 70% of the functional hepatic mass.[6] However, in the setting of acute hepatocyte necrosis or hepatic cellular or lipid infiltrates, clinical signs may progress rapidly to those consistent with fulminant liver failure.

CAUSE

ALI/ALF may occur as a result of prolonged ischemia, toxin or toxicant exposure, idiosyncratic or dose-dependent drug reaction, neoplasia, metabolic disorders, and infectious and immune-mediated processes. In humans, ALF is considered relatively uncommon particularly in the developed world.[7] Drug-induced liver failure, most notably a result of accidental or intentional acetaminophen overdose, is a leading cause of human ALF in the United States, whereas there is a higher incidence of viral hepatitis in other parts of the world.[7–11] In a retrospective case series of 49 dogs with ALF, neoplasia was the most common underlying cause (13 of 49 dogs, 27%), followed by presumptive leptospirosis (4/49 dogs, 8%). In one dog, evidence of thrombi within a branch of the hepatic artery and hepatic veins was found on post-mortem examination, thus ischemia-induced ALF was suspected. No definitive cause was identified in 31 dogs, but 15 of these dogs had exposure to potential hepatotoxins.[4] In addition, ALI and ALF have been documented in several reports in the veterinary literature; **Table 1** summarizes the confirmed or suspected causes.[4,12–43] A comprehensive discussion of the various causes of ALI and ALF can be found elsewhere in the literature.[44]

CLINICAL APPROACH TO THE ACUTE LIVER INJURY/ACUTE LIVER FAILURE PATIENT

Quite often the presenting clinical signs in a patient with ALI or ALF can be vague and potentially attributable to numerous disease processes. Common chief complaints include anorexia, lethargy, vomiting, diarrhea with or without hematochezia or melena, weakness or other neurologic signs resulting from HE. Owners may note the presence