The Liver in Critical Illness

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KEYWORDS

- Acute liver failure (ALF) • Acute-on-chronic liver failure (ACLF) • Critical illness
- Multiple organ failure (MOF) • Intracranial hypertension (IH)
- Acute respiratory distress syndrome (ARDS)

KEY POINTS

- Kupffer cell dysfunction as a result of chronic liver disease or in the setting of acute hepatic insult results in inadequate endotoxin clearance and is a driver of multiple organ failure (MOF).
- Hepatic encephalopathy that progresses to cerebral edema with intracranial hypertension in acute liver failure warrants intracranial pressure monitoring in select patients.
- Treatment of acutely increased intracranial pressure includes administration of hypertonic saline or mannitol.
- Volume resuscitation is often warranted in the vasodilated hyperdynamic state that characterizes liver failure; an intervention that requires ongoing monitoring of objective endpoints including central venous pressure, stroke volume variation, and bedside echocardiography.

INTRODUCTION

The liver has long been known to play a central role in critical illness. Hippocrates appreciated that jaundice portends a poor prognosis and that this process can result from either direct hepatic injury or nonhepatic systemic illness **Boxes 1** and **2**.[1] Centuries later the role of the liver as a significant contributor in host defenses was further elucidated, this time with the additional hypothesis that liver dysfunction is a driver of multiple organ failure (MOF).[1,2] This article reviews pertinent anatomic and physiologic considerations of the liver in critical illness, followed by a selective review of associated organ dysfunction.

CAUSES OF LIVER DISEASE

Depending on the specific cause of acute liver failure (ALF), its presentation may vary from one without precedent signs or symptoms to one with an associated prodromal

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Box 1
Modified KCH Criteria (acetaminophen or paracetamol [APAP] intoxication)

Strongly consider listing for transplant if: Arterial lactate level greater than 3.5 mmol/L after early fluid resuscitation

List for transplant if: Arterial pH less than 7.3 or lactate level greater than 3.0 mmol/L after adequate fluid resuscitation

List for transplant if all 3 occur within 24-hour period: Serum creatinine level greater than 300 mol/L; INR greater than 6.5 (prothrombin time >100 seconds); Grade III/IV encephalopathy

From Bernal W, Donaldson N, Wyncoll D, et al. Blood lactate as an early predictor of outcome in paracetamol-induced acute liver failure: a cohort study. Lancet 2002;359(9306):562; with permission.

illness. Regardless of cause, liver failure and resultant hepatocyte dysfunction are directly linked to impaired host immune function, protein synthesis, and clearance of activated clotting factors.[3]

Kupffer cells (KC), or macrophages resident in liver sinusoids, comprise 80% to 90% of all tissue macrophages within the body and serve as the main site of clearance of particles from the bloodstream.[3,4] Anatomically, KC are positioned to serve as the first line of defense against bacteria, endotoxins, and microbial debris from the gastrointestinal (GI) tract, which are then delivered to the liver via the portal vein. The splanchnic circulation receives 25% of cardiac output; blood volume that subsequently circulates through an extensive network of hepatic sinusoidal microvasculature. The resultant blood-cell contact time results in consistent and effective hepatic clearance.[2]

In the setting of liver dysfunction, impaired KC endotoxin clearance results in increased blood-level presentation of microbial debris to other cells within the reticuloendothelial system, including splenic, pulmonary alveolar, and bony macrophages; a sequence referred to as spillover.[3] These extrahepatic reticuloendothelial sites are ill equipped to handle the full burden of endotoxin clearance. The result is a complex and interrelated sequence of inadequate endotoxin clearance and subsequent organ dysfunction, and this is summarized in **Fig. 1**.

Even in the setting of a previously healthy liver, the milieu of critical illness presents stress to previously functional hepatocytes as it exposes them to a mismatch between metabolic demand and hepatic blood flow. Critical illness, particularly illness that

Box 2
KCH criteria (non-APAP intoxication)

INR greater than 6.5 (PT >100)

Or at least of 3 of the following:

Age less than 11 years or greater than 40 years

Total bilirubin level greater than 17.6 mg/dL (300 μmol/L)

Interval between onset of jaundice and development of hepatic encephalopathy (HE) greater than 7 days

INR greater than 3.5 (PT >50)

Drug toxicity (non-APAP)

From O'Grady JG, Alexander GJ, Hayllar KM, et al. Early indicators of prognosis in fulminant hepatic failure. Gastroenterology 1989;97(2):443; with permission.