Acquired Liver Injury in the Intensive Care Unit

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The liver plays a key role in the synthesis of proteins, metabolism of toxins and drugs, and in modulation of immunity. In critically ill patients, hypoxic, toxic, and inflammatory insults can affect hepatic excretory, synthetic, and/or purification functions, leading to systemic complications such as coagulopathy, increased risk of infection, hypoglycemia, and acute kidney injury. In severe cases, hepatic encephalopathy or brain dysfunction (acute liver failure) may occur. Because of the lack of specificity of standard laboratory investigations, identifying liver injury or dysfunction in critically ill patients remains a significant challenge. In addition, the great heterogeneity of criteria used to define the consequences of liver insults increases the difficulties for the clinician to properly interpret hepatic biochemical abnormalities. In this review, we choose to define liver injury as an elevation in serum concentrations of routinely measured hepatic enzymes, including aminotransferases (aspartate aminotransferase [AST]; alanine aminotransferase, [ALT]), alkaline phosphatase (ALP), and γ-glutamyl transpeptidase. Hepatic dysfunction refers to derangement of pathways related to synthetic or clearance function, including international normalized ratio (INR) and bilirubin. Hepatotoxicity refers to hepatic injury and dysfunction caused by a drug or another noninfectious agent. Acute liver failure designates liver injury that results in life-threatening hepatic synthetic dysfunction and brain dysfunction (encephalopathy) (fig. 1). Here we review the causes, mechanisms, and clinical implications of intensive care unit (ICU)-acquired liver injury and dysfunction in patients without previous known hepatobiliary disease on ICU admission. Consequently, this review will not cover liver injury caused by chronic liver disease; viral, metabolic, vascular, or autoimmune liver disease; pregnancy-related liver injury; or postoperative hepatic resection.

Acute Liver Injury

Despite the lack of a uniform definition, liver injury often is evaluated with routinely performed biochemistry tests, including AST, ALT, ALP, and γ-glutamyl transpeptidase. Hepatocellular injury is defined by elevation in serum aminotransferases, whereas cholestatic injury is associated with marked elevations in ALP and γ-glutamyl transpeptidase with moderate or normal elevation of serum aminotransferases. At ICU admission, these tests have been reported to be abnormal in as many as 61% of patients, correlating with short-term mortality.

Hepatocellular Injury

Hepatocellular injury is defined by injury to hepatocytes, which can be either a reversible disturbance or cell death. It is characterized by elevation of intracellular enzymes (aminotransferases) involved in α-amino group regulation. AST and ALT are cleared in the sinusoidal cells of the liver, and serum concentrations reflect hepatocyte turnover and clearance. During liver injury, hepatocellular permeability is increased, and consequently AST and ALT are released from the intracellular space into plasma. The duration of elevation depends upon the severity of hepatic insult and the half-life of the enzyme, which ranges from 17 h for AST to 50 h for ALT. The typical time course shows a rapid increase in serum aminotransferases followed by a slow decrease. In the ICU setting, the most common causes of hepatocellular injury are hypoxic hepatitis, congestive hepatopathy, septic shock, and drug-induced liver damage.
However, in critically ill patients, an accurate interpretation of serum aminotransferase evolution remains challenging. Indeed, AST is not specific to the liver but is also produced by various tissues, such as skeletal muscles, heart, lung, brain, kidney, pancreas, erythrocytes, and leukocytes, which may release AST, especially in ICU patients with altered tissue perfusion. Conversely, ALT is expressed mainly in the liver, and normal serum ALT would exclude primary liver injury. Nevertheless, an important exception is alcoholic liver disease, for which the concentration of ALT in serum is low. This is because patients with alcoholic liver disease have a deficiency in pyridoxal-5'-phosphate, which is necessary for ALT synthesis. Consequently, the ability of serum aminotransferase to detect liver injury remains very low because massively increased liver enzymes do not adequately correlate with liver dysfunction, and of equal importance, hepatic function may be impaired with minimally increased liver enzymes.

Cholestatic Injury

Cholestasis is defined by altered bile production, secretion, or excretion leading to a decrease or absence of bile in the duodenum. Consequently, laboratory abnormalities are related to the retention of substances in the blood that are normally excreted in bile (bile acids, conjugated bilirubin) and are associated with an increase in cholestatic enzymes such as ALP and γ-glutamyl transpeptidase. ALP is a very sensitive indicator of cholestasis. ALP is localized in hepatocytes and cholangiocytes, and usually is increased secondary to intrahepatic or extrahepatic biliary obstruction. Increased concentrations of bile acids caused by obstruction stimulate the synthesis of ALP that is released into the blood. In the icteric form of cholestatic injury (cholestatic jaundice), serum conjugated bilirubin is also increased.

Hepatic Dysfunction

Bilirubin

The plasma concentration of bilirubin is dependent on bilirubin formation (primarily related to erythrocytes senescence), albumin-bound plasma transport, uptake, conjugation, and excretion. Therefore, hyperbilirubinemia may be a consequence of increased production (hemolysis), hepatic dysfunction (decreased clearance), or posthepatic occlusion (decreased secretion or cholestasis). Bilirubin is conjugated with glucuronic acid in hepatocytes to increase its water solubility and allow its rapid transport into bile. Thus, increased serum conjugated bilirubin indicates that enzymatic function is intact but there is a failure of excretory function of the liver. In the ICU, major causes of hyperbilirubinemia include hypoxic insults leading to hepatocyte injury (ischemic cholestasis), sepsis-associated cholestasis, drug-induced liver injury, and parenteral nutrition. In recent studies, hyperbilirubinemia was found to complicate 11–32% of ICU admissions and was linked to ICU infection and prognosis. Trauma patients also may experience cholestatic injury with the risk increased with increasing age, injury severity, and incidence of shock and blood transfusion. In this population, hepatic dysfunction is associated directly with increased inhospital mortality. Serum bilirubin is the most facile test of
liver function because hemolysis is rare and biliary tract obstruction can be readily diagnosed. This explains partly why serum bilirubin has been incorporated in several organ dysfunction scoring systems, such as the Sequential Organ Failure Assessment (SOFA), and used in clinical trials assessing liver function. Unfortunately, it is a late marker of liver dysfunction, and serum bilirubin may remain low while results from other non-liver-specific tests, such as serum amino transferase, may become abnormal.

Serum Albumin
The liver is a major source of protein synthesis. Measurement of serum concentrations of proteins that are synthesized exclusively by the liver, such as albumin and coagulation factors, can be used to estimate synthetic function of the liver. Albumin is the most abundant circulating protein synthesized and is secreted solely by hepatocytes. Between 12 and 25 g of albumin is produced daily by the adult liver and accounts for as much as 50% of hepatic protein synthesis. Serum albumin concentration reflects the balance between the rate of appearance and disappearance in the intravascular space. This is influenced by albumin production, breakdown, and alterations in the intravascular and extravascular distribution of albumin. Thus, low serum albumin in ICU patients may reflect blood losses, altered vascular permeability with albumin loss, malnutrition, or hemodilution rather than hepatic dysfunction. In addition, albumin is a part of the acute phase response and concentrations often decrease rapidly with the onset of a major stress. For these reasons, serum albumin does not constitute a specific test of hepatic function in critically ill patients.

INR
The INR reflects activity of the intrinsic coagulation pathway, including factors II, V, VII, X, and fibrinogen. Because the half-lives of these factors are short, altered hepatic synthetic function and a decrease in production can result in a rapid increase in the INR. The INR has been developed to standardize the use of the prothrombin time for monitoring oral anticoagulant therapy by developing an international reference thromboplastin. With total bilirubin and creatinine, INR is one of the three components used to calculate the FibroScan instrument has been developed recently for the assessment of hepatic fibrosis in patients with chronic liver disease. When applied to critically ill patients, transient elastography appears to be a promising tool for detecting liver dysfunction, even in non-cirrhotic patients, and may have an expanded role in the future. Additional studies should be conducted to confirm the preliminary results.

Causes of Liver Injury in the ICU
Hypoxic Hepatitis
Hypoxic hepatitis (i.e., ischemic hepatitis, hypoxic hepatopathy, shock liver, or hypoxic liver injury) can be defined as liver injury as a consequence of a cardiovascular insult followed by a sudden transient elevation of aminotransferases greater than 10-fold above baseline with no other identified cause of liver damage. Hypoxic hepatitis often is characterized by the triad of acute elevation in serum aminotransferases, rapid elevation in INR, and altered renal function. Hypoxic hepatitis results from inadequate oxygen delivery to the liver. This can be caused by inadequate oxygen in blood (hypoxemic hypoxia), inadequate blood flow (ischemic hypoxia), or lack of carrying capacity (anemic hypoxia). Of note, ischemic hypoxia of the liver can be caused by increased venous pressures, as well as decreased arterial pressures. The
centrilobular hepatocytes are particularly vulnerable to hypoxia, so the primary injury is centrilobular necrosis (fig. 2A). Patients with unrecognized preexisting liver disease might be more susceptible to hypoxic injury. In this condition, elevation in liver enzymes may be difficult to interpret in cases of previous biochemistry abnormalities. In ICU patients, the prevalence of hypoxic hepatitis has been estimated to be between 1 and 12%. The conditions most frequently associated with the development of hypoxic hepatitis are hypovolemic or septic shock, cardiac failure (congestive and acute), and global hypoxia. In patients with septic shock, it has been associated with high in-hospital mortality (more than 80%).

**Sepsis**

The liver plays a key role in the development of the inflammatory response after bacterial infection. Kupffer cells remove bacteria from the circulation, ingest endotoxin, and modulate the immune response through the release of pro-inflammatory mediators. Several factors may contribute to the development of hepatic dysfunction during sepsis. The two most common causes of hepatic dysfunction in sepsis are hypoxic hepatitis and sepsis-associated cholestasis. During the initial phase of septic shock, the impairment of hepatic perfusion may result in hypoxic hepatitis, resulting in direct hepatocellular injury. Furthermore, clinical studies indicate that liver injury can develop despite an increase in splanchnic blood flow that increases proportionally to cardiac output. This is likely because there is increased splanchnic oxygen consumption so less oxygen reaches the liver through the portal system, or another flow-independent mechanism may explain hepatic dysfunction in patients with septic shock.

It is also possible that the initial injury of the centrilobular regions leads to swelling in this region and a specific loss of flow in the critical area.

In functional sepsis-associated cholestasis, increased intestinal permeability (loss of tight gap junctions) as a complication of sepsis can lead to endotoxin translocation from the intestinal lumen into the portal circulation. Endotoxin activates Kupffer cells, which in turn secrete pro-inflammatory cytokines such as tumor necrosis factor (TNF), interleukin-1

β (IL-1β), interleukin-6 (IL-6), and nitric oxide. This inflammatory process alters hepatocyte or cholangiocyte uptake of bile acids, intracellular architecture, transporter systems, and cellular junctions and reduces secretion of bile. In addition, hepatic microvascular impairment caused by microthrombi formation aggravates cellular dysfunction and in turn augments cholestasis (fig. 2B). Clinically, sepsis-induced hepatic dysfunction may be suspected in septic patients with biochemical cholestasis. However, the differential diagnosis of hyperbilirubinemia in this setting is broad and includes cold agglutinin-associated hemolytic anemia, drug-induced hemolysis, and transfusion reactions. This makes static laboratory blood tests unreliable in the assessment of hepatic function. The use of dynamic methods, such ICG-PDR monitoring, may in the future help to detect and monitor suspected hepatic dysfunction more reliably and earlier in septic patients.

**Drugs**

Because the liver is the main site of drug metabolism, it is susceptible to drug injury. Drug-related hepatotoxicity is relatively uncommon (1 in 10,000–100,000 patients). However, the risk of hepatotoxicity in critically ill patients is increased because of the number of pharmacologic agents used and significant potential interactions. In addition, drug pharmacokinetics are modified, and there is coexistence with other causes of liver injury, such as impaired liver perfusion, sepsis, and parenteral nutrition. Additional predisposing factors include advanced age, gender, medical comorbidity, and genetic factors.

Two primary mechanisms are responsible for drug-induced hepatotoxicity: direct drug toxicity (dose-dependent) and idiosyncratic drug reactions. Direct or indirect drug toxicity is dose dependent and reproducible, whereas idiosyncratic reactions, caused by hypersensitivity reactions from allergic or toxic factors, are dose independent, unpredictable, and not reproducible. Several mechanisms may initiate or contribute to drug-induced hepatotoxicity: phase one reactions (cytochrome p450) result in the production of highly reactive oxygen species that often are more cytotoxic to liver than is the premetabolized drug. In phase 2 reactions, deple-
The metabolism of glucuronide, sulfate, and glutathione can result in hepatocyte necrosis. Other cellular mechanisms of drug-induced hepatotoxicity include (1) disruption of cell membranes, (2) inhibition of cellular pathways of drug metabolism, (3) abnormal bile flow resulting from disruption of subcellular actin filaments or interruption of transport pumps leading to cholestasis or jaundice, and (4) inhibition of mitochondrial function with accumulation of reactive oxygen species and lipid peroxidation, fat accumulation, and cell death.

In critically ill patients, hepatotoxicity often is detected on routine hepatic biochemistry. Patterns of injury may be hepatocellular, cholestatic, or mixed. Although strict definitions do not exist, criteria proposed by the United States Drug-induced Liver Injury Network require an elevation in aminotransferases more than five times the upper limit of normal or an elevation in ALP more than two times the upper limit of normal or an elevation in serum total bilirubin more than 2.5 times the upper limit of normal with any elevation of ALT, AST, or ALP. Tests reflecting hepatotoxicity alone do not necessarily predict or are indicative of serious hepatic dysfunction. In this case (dysfunction), hepatotoxicity is coupled with synthetic functional impairment, decreased serum albumin, increased serum lactate, and increased INR. Rarely, acute liver failure (synthetic dysfunction and encephalopathy) can occur and represents a life-threatening complication. Acute liver failure may improve after drug discontinuation and treatment (e.g., acetaminophen with N-acetyl cysteine) or may result in the need for assessment for liver transplantation. In the general population, the four main classes of drugs responsible for acute liver failure necessitating transplantation are acetaminophen and antituberculosis, antiepileptic, and antibiotic drugs. Although no data exist concerning the critically ill, commonly prescribed medications used in the ICU that may cause significant hepatotoxicity are listed in Table 1.

### Table 1. Medications Frequently Prescribed in the Intensive Care Unit that Potentially May Cause Liver Injury*

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Pattern</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiinfectious agents</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ketoconazole</td>
<td>Hepatocellular</td>
<td>Idiosyncratic reaction</td>
</tr>
<tr>
<td>Tetracyclines</td>
<td>Hepatocellular</td>
<td>Microvesicular steatosis</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>Hepatocellular</td>
<td>Idiosyncratic reaction (CYP3A4?)</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>Hepatocellular</td>
<td>Idiosyncratic reaction (CYP3A4?)</td>
</tr>
<tr>
<td>Amoxicillin or clavulanate</td>
<td>Cholestatic</td>
<td>Toxic-allergic reaction</td>
</tr>
<tr>
<td>Macrolides (e.g., erythromycin)</td>
<td>Cholestatic</td>
<td>Idiosyncratic reaction, role of CYP450?</td>
</tr>
<tr>
<td>Trimethoprim-sulfamethoxazole</td>
<td>Mixed</td>
<td>Idiosyncratic reaction</td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td>Mixed</td>
<td>Idiosyncratic reaction</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>Mixed</td>
<td>Idiosyncratic reaction</td>
</tr>
<tr>
<td>Antiepileptics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Mixed</td>
<td>Idiosyncratic reaction</td>
</tr>
<tr>
<td>Valproic acid</td>
<td>Hepatocellular</td>
<td>Anticonvulsant hypersensitivity syndrome</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Mixed</td>
<td>Idiosyncratic reaction</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>Mixed</td>
<td>Anticonvulsant hypersensitivity syndrome</td>
</tr>
<tr>
<td>Acetaminophen</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acetaminophen</td>
<td>Hepatocellular</td>
<td>Direct toxicity</td>
</tr>
<tr>
<td>Others</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amiodarone</td>
<td>Hepatocellular</td>
<td>Alcohol hepatitis-like reactions</td>
</tr>
<tr>
<td>Statins</td>
<td>Hepatocellular</td>
<td>Unknown</td>
</tr>
<tr>
<td>Propofol</td>
<td>Hepatocellular</td>
<td></td>
</tr>
</tbody>
</table>

* Adapted from Lat et al., Navarro and Senior, and Mindikoglu et al.

CYP3A4 = cytochrome P450 3A4; CYP450 = cytochrome P450.

Acquired Liver Injury in the Intensive Care Unit

Parenteral Nutrition

Mild liver injury occurs frequently in infants and adults treated with parenteral nutrition (PN). After an initial mild elevation of the aminotransferases, a mixed pattern is seen. Although incompletely identified, the etiology of PN-induced hepatotoxicity may be related to hepatic bile acid transporter alterations, modifications of gene expression involved in apoptotic pathways, and/or alterations in detoxification processes. In a prospective study that included more than 3,000 critically ill patients, Grau et al. found that acute hepatotoxicity (defined as cholestasis, hepatocellular injury, or a mixed pattern) occurred more frequently in patients receiving PN than in those receiving enteral nutrition (30 and 18%, respectively). Daily caloric intake greater than 25 kcal/kg appears to be one of the most important factors predictive of PN-associated hepatotoxicity, along with total quantity of PN and sepsis.

Clinical Implications

The mainstay of clinical management of liver injury in the ICU is related to early diagnosis and correct identification of etiology. In patients with acute liver injury presenting with systemic inflammatory response criteria, the first measures are as follows. Define the type of liver injury: hepatocellular...
injury, cholestasis (differentiate unconjugated [search for hemolysis in this case] from conjugated hyperbilirubinemia), and mixed pattern. Perform microbiologic analysis and hepatic ultrasound. Maintain adequate arterial perfusion and fluid and electrolyte balances. Start early antibiotic therapy in case of ongoing infection. Stop administering hepatotoxic medications.

Preventive measures have been evaluated. For example, based on data from a large trial that assessed the usefulness of intensive insulin therapy (glycemia 80–110 mg/dl) in medical ICU patients, Mesotten et al proposed that intensive insulin therapy can reduce cholestasis and biliary sludge in prolonged critical illness. Strategies have been proposed to reduce the incidence of PN-induced cholestasis in critically ill patients. Because it has been shown that nutrient deficiency may cause liver injury, strictly adapted nutrient prescriptions (including micronutrients and macronutrients) should be used. In addition, ω-3–enriched lipid emulsion, by inhibiting inflammation induced by ω-6 fatty acids, may represent a promising strategy that needs further evaluation. The timing of PN initiation is also of importance. In a recent randomized study in which early and late initiations of PN in critically ill patients were compared, the late initiation group more frequently had increased serum bilirubin concentrations, but the group had faster recovery and fewer complications compared with the early initiation group. In most cases of drug-induced hepatotoxicity, there are no effective treatments apart from discontinuing use of the offending drug and providing general supportive care. Exceptions include the rapid use of N-acetylcysteine for acetonaminophen hepatotoxicity and intravenous L-carnitine treatment for valproate-induced hepatotoxicity.

In patients who experience acute liver failure, N-acetylcysteine now has an expanded role. In a recently published study, intravenous N-acetylcysteine was associated with improved transplant-free survival in patients with early encephalopathy caused by nonacetaminophen acute liver failure. The etiologies of acute liver failure in patients included drug-induced liver injury, autoimmune hepatitis, hepatitis B, and indeterminate. Except for patients requiring invasive procedure and those with active bleeding, platelets or fresh frozen plasma systemic administration should be avoided. In patients with acute failure, increased INR and/or low platelet count are not necessarily associated with excess risk of bleeding, in part because of compensatory mechanisms. INR is a marker of the synthetic function of the liver and constitutes an important prognosis marker used in several scoring systems. In addition, fresh frozen plasma alone does not allow adequate correction of coagulopathy and exposes patients to the risk of volume overload and transfusion related-acute lung injury.

Future research should focus on ways to prevent liver injury in critically ill patients. Recent promising results have been reported in animals studies with nitric oxide production regulation. Opioid preconditioning via inducible nitric oxide synthase expression and early neuronal and delayed inducible nitric oxide synthase blockade have been shown to attenuate liver injury in vivo. However, clinical studies are required to support these findings.

Conclusion

Acquired liver injury and hepatotoxicity occur frequently in critically ill patients and affect prognosis. The main causes of acquired liver injury include shock, sepsis, drugs, and parental nutrition. Synthetic dysfunction may complicate liver injury and lead to systemic complications and rarely acute liver failure. Despite poor specificity, routine laboratory biochemistry, such as aminotransferases, bilirubin, INR, and factor V, may help to detect liver injury but remains of limited value in evaluating hepatic function. The development of novel techniques to assess hepatic function at the bedside potentially may help to standardize the definition of acute liver injury or dysfunction. Currently, supportive therapy for most patients remains the mainstay of therapy.

The authors thank Dominique Wendum, M.D., Ph.D. (Service d’Anatomie et de Cytologie Pathologiques, Hôpital Saint-Antoine, Paris, France), for providing liver biopsy descriptions and figure.

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