Hypoxic liver injury and cholestasis in critically ill patients

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Purpose of review
Liver dysfunction frequently complicates the clinical picture of critical illness and leads to increased morbidity and mortality. The purpose of this review is to characterize the most frequent patterns of liver dysfunction at the intensive care unit, cholestasis and hypoxic liver injury (HLI), and to illustrate its clinical impact on outcome in critically ill patients.

Recent findings
Liver dysfunction at the intensive care unit can be divided into two main patterns: cholestatic and HLI, also known as ischemic hepatitis or shock liver. Both hepatic dysfunctions occur frequently and early in critical illness. Major issues are the early recognition and subsequent initiation of therapeutic measures.

Summary
Clinical awareness of the liver not only as a victim, but also as a trigger of multiorgan failure is of central clinical importance. Physicians have to identify the underlying factors that contribute to its development to initiate curative measures as early as possible.

Keywords
cholestasis, hypoxic liver injury, intensive care unit, jaundice

INTRODUCTION

Liver dysfunction is a frequent finding in critically ill patients. According to the clinical presentation, it can be divided into two major patterns: cholestatic dysfunction and jaundice on the one hand and hypoxic liver injury (HLI), which is also known as ischemic hepatitis or shock liver, on the other hand. About 20% of the patients develop cholestasis and 10% suffer from HLI during their stay at the intensive care unit (ICU) [1,2,3▪▪]. Both jaundice and HLI are associated with increased morbidity and mortality at the ICU. However, apart from the usage of bilirubin in several prognostic scores [4,5], clinical impact of liver dysfunction in critical illness has been underrepresented in critical care literature for years. Traditionally, hepatic dysfunction and jaundice are regarded as late features in critical illness. However, recent findings demonstrated that liver cell necrosis and cholestasis are usually early findings in life-threatening conditions and major risk factors for complications and increased mortality in patients at the ICU. The purpose of this review is to give an overview on the clinical aspects of liver dysfunction in critical illness.

EPIDEMIOLOGY

Sepsis and shock are one of the most common causes of jaundice in hospital. Cholestasis is the most common feature of liver dysfunction at the intensive care unit. Kramer *et al.* [1] reported the occurrence of early hepatic dysfunction – defined by bilirubin levels greater than 2 mg/dl – in up to 20% of a large cohort of critically ill patients within 48 h after ICU admission. Another large study found cholestasis in approximately 20% during the course of the ICU stay [2]. In the literature, prevalence of cholestasis ranges from 0.6 to 54% [6].

HLI is the most frequent cause of massively raised aminotransferase levels in hospital [7]. It occurs in up to 10% of critically ill patients at the

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KEY POINTS

- Hypoxic liver injury and cholestasis are frequent findings in critically ill patients.
- The liver is not only a victim in critical illness, but also contributes to the aggravation of multiorgan failure.
- Hypoxic liver injury and cholestasis contribute to increased morbidity and are independent predictors of mortality at the intensive care unit.

medical ICU [3▪▪]. The prevalence in selected patient populations like septic shock and low cardiac output is even higher ranging between 13 and 22% [8,9].

DIAGNOSIS

Proposed diagnostic criteria of HLI and cholestasis will be presented.

Hypoxic liver injury

HLI is usually defined by three clinical cornerstones: an acute setting of cardiac, circulatory or respiratory failure, a sharp but transient increase in serum aminotransferase levels to at least 20 times the upper limit of normal, and exclusion of other potential causes for increased aminotransferase levels like viral or drug induced hepatitis [8,10].

Centrilobular liver cell necrosis is the typical histopathological finding in patients with HLI. However, liver biopsy is usually not required for the diagnosis of hypoxic hepatitis because of its typical clinical pattern. The procedure may even cause severe complications in patients because of coagulation abnormalities and necessity of anticoagulant drugs because of their basic cardiac disease.

Jaundice and cholestasis

Cholestatic liver dysfunction is basically characterized by impaired bile formation and transportation. A general distinction of cholestasis can be drawn between the extrahepatic form that is mainly a consequence of mechanical obstruction and consecutive decreased bile flow, and the intrahepatic form usually because of functional alterations at the hepatocellular level [11]. Although the terms jaundice and cholestasis are frequently used in clinical practice, there is no consensus definition of these disease patterns. Serum bilirubin or alternatively alkaline phosphatase and gamma-glutamyl transpeptidase is usually used with different cutoff levels as diagnostic criteria from a clinician's point of view. Jaundice is usually defined by increased levels of total serum bilirubin. Most commonly, total serum bilirubin levels greater than 3 mg/dl are used for the definition of jaundice and cholestasis, whereas others used total serum bilirubin levels greater than 2 mg/dl as threshold for hepatic dysfunction [1,2,12▪▪]. In particular, conjugated hyperbilirubinemia is a common finding during critical illness and sepsis [1,13]. Currently, the clinical awareness of bile acids is continuously increasing. They may indicate alterations of hepatic biotransformation and cholestatic dysfunction at an earlier stage during the course of the disease. Furthermore, they may offer new therapeutic options for targeted therapies [14▪▪,15▪▪].

PATHOPHYSIOLOGY

As the pathophysiology of cholestasis with special attention to sepsis is the cornerstone of another article in this review series (see M. Bauer), we will focus on the pathophysiology of HLI in this section.

Several pathophysiological alterations contribute to the development of HLI. Main factors are hepatic ischemia as a consequence of reduced hepatic blood flow. Additionally, passive venous congestion of the liver, reduced oxygen extraction on a hepatocellular level – as occurs in sepsis and septic shock – and increased oxygen consumption – as can be found in hyperthermia – and systemic hypoxemia represent other potential key components of development of HLI [8,16–20].

Alterations of the hepatic perfusion play a key role in the development of HLI. The liver has a dual blood supply consisting of the portal vein and the hepatic artery that provide 70–85 and 15–30% of the blood supply to the liver, respectively [21]. However, the bile ducts are supplied solely by the hepatic artery. The predominant regulatory mechanism of hepatic perfusion is the interplay of the hepatic artery's blood flow that varies inversely with the blood flow of the portal vein. However, the hepatic blood flow does not only follow the principle of supply and demand. For instance, decreased hepatic oxygen content is rather compensated via increased oxygen extraction than by enhancement of hepatic arterial blood flow [22]. Furthermore, the hepatic arterial buffer response (HABR), a widely accepted hypothesis, postulates that adenosine is a central regulator of hepatic arterial blood flow: a decrease of portal vein blood causes an accumulating of adenosine in the space of Mall that leads to dilatation of the hepatic artery and increased hepatic arterial blood flow. Vice versa, increasing portal venous blood flow decreases the adenosine concentration in the space of Mall via

washout and causes consecutively hepatic arterial vasoconstriction [23].

NATURAL HISTORY AND CLINICAL PRESENTATION

Underlying conditions and clinical presentation of HLI and cholestasis will be presented.

Hypoxic liver injury

Occurrence of HLI is usually the consequence of a multifactorial event. The main underlying conditions are low cardiac output and septic shock, which are found in approximately two-thirds and one-third as preceding condition, respectively [8,10]. In detail, cardiogenic shock, valvular and rhythmogenic heart disease, pericardial effusion, decompensated cardiomyopathy, pulmonary embolism and cardiac arrest are observed as underlying conditions contributing to the development of HLI [10]. Another study reported that HLI in patients with septic shock was associated with 84% in-hospital mortality rate [9]. Taken together, cardiac insufficiency is found in more than 80% of cases of HLI [10]. The coincidence of more than one of the contributing factors mentioned above is usually observed in patients with hypoxic hepatitis [10]. Recently, it was reported that – apart from severity of bleeding – the presence of portal vein thrombosis seems to be a major risk factor for hypoxic hepatitis in patients with liver cirrhosis after variceal bleeding [24▪].

Cholestasis

Cholestasis is frequently caused by a variety of hits to the liver. Apart from sepsis and septic shock, the most common causes are hemodynamic instability, renal insufficiency, hepatotoxic drugs, multiple blood transfusions, increased positive end-expiratory pressure levels and total parenteral nutrition (TPN). Moreover, clinical conditions such as liver cirrhosis, gastrointestinal surgery, liver or bone marrow transplantation, trauma and several drugs like ceftriaxone are factors contributing to cholestasis in the ICU setting [25–27,28▪▪,29]. The underlying mechanism includes hepatocellular injury leading to decreased bilirubin uptake, decreased intrahepatic processing, decreased canalicular transport and decreased clearance of conjugated bilirubin, consequences of medical therapy and finally to a lesser extent also increased bilirubin load because of hemolysis – in which unconjugated hyperbilirubinemia occurs [6]. Recently, it was reported that bile acid levels – especially conjugated bile acids – are strongly increased in agonal patients at the ICU [14▪▪]. Extrahepatic cholestasis is only rarely identified as a cause of cholestasis in critical illness, although biliary sludge is a very common condition especially during prolonged critical illness [2].

As cholestasis of critical illness is mainly the consequence of functional alterations at the hepatocellular level, it is usually reversible. Only a small subset of patients develops biliary fibrosis and liver cirrhosis because of progressive secondary sclerosing cholangitis (SSC) mainly as a consequence of septic shock, trauma and acute respiratory distress syndrome [30]. Presence of biliary casts and consecutive stricture formation and sclerosis within the biliary tree are typical patterns in endoscopic retrograde cholangiopancreaticography (ERCP), the diagnostic gold standard for SSC. SSC is a rapidly progressive disease frequently leading to the occurrence of cirrhosis within 1 year.

MORTALITY AND PROGNOSIS

HLI is an independent predictor of mortality. The intensive care unit mortality is more than 50% in these patients [10,20]. Recently, it was demonstrated that patients with hypoxic hepatitis and necessity of vasopressor treatment have a five-fold increased mortality rate independently of severity and cause of disease or other potential confounding factors in comparison to critically ill patients without HLI [3▪▪]. The main predictive factors of death are severity of disease, underlying septic shock and the degree of hepatic impairment (illustrated by International Normalized Ratio) [10]. Additionally, duration of HLI is also of prognostic importance: the longer the hepatic injury lasts, the worse the outcome. Patients with a prolonged duration of HLI (i.e. increasing aminotransferase levels >24 h) have an increased mortality risk [10].

Mortality is twice as high (23%) in critically ill patients with early hepatic dysfunction [1]. It exceeds the impact of all other organ dysfunctions in predicting mortality [1]. The risk for mortality increases with rising bilirubin levels. In-hospital mortality in patients with cholestatic liver failure (bilirubin >6 mg/dl) following cardiogenic shock ranges between 60 and 85% [31,32].

COMPLICATIONS AS A CONSEQUENCE OF HYPOXIC LIVER INJURY AND CHOLESTASIS

However, the liver is not only a victim of severe nonhepatic organ failure, but also may aggravate the course of the life-threatening condition *per se* mainly because of induction of an inflammatory

response syndrome [33]. HLI may cause deterioration of gas exchange abnormalities because of new onset of hepatopulmonary syndrome [19]. Recently, it could be demonstrated that new onset of jaundice occurs in approximately one-third of patients following HLI [12▪▪]. It is associated with increased rate of complications. In particular, an increased number of infections, gastrointestinal complications and renal failure were observed in this population. These complications seem to be a consequence of new onset of jaundice *per se* [12▪▪]. Furthermore, 1-year mortality rate in patients with HLI and consecutive jaundice was more than 90%. Finally, spontaneous hypoglycemia may be a consequence of HLI [10].

Apart from the issues mentioned above, cholestasis contributes to an unbalanced immune response and may aggravate bacterial infections [34], fortifies hypotension because of the vasodilatory properties of bile acids [35], alters glucose and lipid metabolism and increases energy expenditure [36]. Furthermore, cholestasis impairs renal function that may even lead to acute tubular necrosis despite adequate fluid balance [12▪▪,37].

THERAPEUTIC OPTIONS

Currently, there is a lack of studies investigating therapeutic options in critically ill patients with cholestasis or HLI.

Natural course and outcome seems to depend on several factors. First, an early elimination of the underlying condition that caused the hepatic dysfunction seems to be of central prognostic importance. The increased mortality rate in patients with prolonged duration of HLI seems to be at least in part the consequence of the inability to stabilize the underlying condition contributing to HLI or cholestasis [10]. Second, protracted duration of liver dysfunction may also aggravate organ dysfunction *per se* as mentioned above [12▪▪,38,39]. Third, hepatic recovery and clinical outcome are significantly worse in patients with HLI requiring vasopressor therapy [3▪▪]. However, 50–90% of patients with HLI suffer from different kinds of shock and require vasopressor treatment.

Patients with low cardiac output and HLI may benefit from the administration of positive inotropic substances like dobutamine. In a recent, randomized controlled clinical study, administration of dobutamine lowered the degree of hepatic injury and improved hepatic perfusion and oxygenation in cirrhotic patients following liver resection [40]. In cardiogenic shock following acute myocardial infarction, urgent therapy in the cardiac catheterization laboratory should be performed. Fluid supply and vasopressor therapy should be initiated to re-establish adequate hepatic perfusion and oxygen supply as early as possible in hypotensive patients. Administration of oxygen and mechanical ventilation should be applied in case of hypoxia. Patients suffering from severe sepsis and septic shock should be treated according to the corresponding guidelines.

Intensive insulin therapy significantly reduces the rate of cholestatic liver dysfunction but does not have any effect on the course of HLI [2]. On the other hand, tight glycemic control is necessary to recognize and treat hypoglycemia in particular in HLI as early as possible.

In case of extrahepatic biliary obstruction or SSC, ERCP may help to restore the biliary flow. Future promising therapeutic approaches may be targeted bile acid signaling in critical illness. However, up to date, there is no clear evidence that supports these therapeutics in critical illness.

Most cases of drug-induced cholestasis improve by detection and stopping admission of the toxic metabolite [28▪▪].

Hyperammonemia is a frequent finding in patients with HLI and is associated with increased mortality [16]. However, there are no data indicating that ammonia-lowering therapies improve the neurological situation and outcome in this population. Additionally, a randomized controlled study demonstrated no efficacy of L-ornithine L-aspartate in patients with acute liver failure [41]. Until now, there is no indication for targeted ammonia-lowering therapies in patients with cholestasis or HLI at the intensive care unit in the absence of cirrhosis.

Ischemic hepatitis is considered as a potential cause of acute liver failure by the American Association for the Study of Liver Diseases [42]. However, HLI is a clear contraindication for liver transplantation. In contrast, liver transplantation should be considered in patients with SSC. Ursodeoxycholic acid and ERCP are only of limited efficacy in these patients [43].

Extracorporeal artificial liver support systems are able to remove albumin-bound toxins. The most commonly used systems are the molecular adsorbents recirculatory system (MARS), fractionated plasma separation and adsorption (FPSA or Prometheus) and single-pass albumin dialysis (SPAD). MARS is reported to improve hemodynamics in patients with acute-on-chronic liver failure [44–46]. In a small randomized controlled study in patients with cholestatic HLI, El Banayosy *et al.* [31] found no significant survival benefit in patients undergoing MARS treatment. However, as study results on extracorporeal liver support systems remain conflicting, further studies are needed.

CONCLUSION

New onset of liver dysfunction is a frequent finding in critical illness and significantly contributes to increased morbidity and mortality. Early recognition and subsequent therapy of the underlying conditions are still the therapeutic cornerstones.

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Conflicts of interest

The authors declare that there is no conflict of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 164).

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