

# Liver dysfunction in sepsis

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## Abstract

Despite continuous progress in medicine, sepsis remains the main cause of deaths in the intensive care unit. Liver failure complicating sepsis/septic shock has a significant impact on mortality in this group of patients. The pathophysiology of sepsis-associated liver dysfunction is very complicated and still not well understood. According to the Surviving Sepsis Campaign (SSC) Guidelines, the diagnosis of liver dysfunction during sepsis is based on the increase in bilirubin concentration  $>2$  mg/dL and the occurrence of coagulation disorders with INR  $> 1.5$ . The lack of specificity and ability to distinguish acute liver failure from previous liver dysfunction disqualifies bilirubin as a single parameter reflecting the complex liver function. Clinical manifestations of sepsis-associated liver dysfunction include hypoxic hepatitis, sepsis-induced cholestasis and dysfunction of protein synthesis manifesting with, e.g., coagulopathies. Detoxifying liver dysfunction, which is associated with an increase in serum ammonia concentration, manifesting with e.g., confusion, loss of consciousness and hepatic encephalopathy, may be disguised by analgesedation used in the intensive care unit. To determine a liver dysfunction in a critically ill patient, the concept of shock liver may be used. It is a complex syndrome of hemodynamic, cellular, molecular and immunologic changes leading to severe liver hypoxia. In clinical practice, there is no standardized diagnostic panel that would allow for an early, clear diagnosis of acute liver dysfunction, and there is no therapeutic panel enabling the full restoration of damaged liver function. The aim of the article is to present the pathophysiology and clinical manifestations of sepsis-associated liver dysfunction.

**Key words:** sepsis, MODS, liver dysfunction, shock liver

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## Introduction

Despite the continuous progress in medicine, sepsis remains the leading cause of deaths in the intensive care units (ICUs). American data estimate the incidence of sepsis to be about 300 cases/100,000 people, and the mortality rate ranges between 30% and 50%.<sup>1–3</sup> That is more than the number of deaths caused by prostate cancer, breast cancer and AIDS all together.<sup>4</sup>

The prevalence of sepsis in Poland according to recently published data is estimated to be about 25% of patients hospitalized in the ICUs. Among patients diagnosed with severe sepsis, almost half of them (44%) developed septic shock.<sup>5</sup>

The development of multiple organ dysfunction syndrome (MODS) is one of the complications of sepsis. A study conducted by Kubler et al, which analyzed the course and outcome of severe sepsis in Poland, revealed that patients admitted to ICUs were severely ill. Dysfunction of 1 or 2 organs was diagnosed in 9–12% of patients at the time of admission, whereas most of the patients (89%) developed dysfunction of 3 or more organs during their stay in ICUs.<sup>6</sup>

The level of organ dysfunction, including liver failure, may vary from a mild organ dysfunction to life-threatening fulminant organ failure.

During sepsis, not only infection itself, but also hyperactivity of the inflammatory response, microcirculatory failure, and side effects of the therapy are responsible for liver injury.

The liver plays a pivotal role in maintaining homeostasis. Its functions include: metabolism of carbohydrates, lipids, proteins and hormones; biosynthesis of blood components, enzymes and clotting factors; production of bile; detoxification; metabolism of nitrogen compounds – synthesis of urea; storage of glycogen, cholesterol, vitamins (A, D, B<sub>12</sub>), iron, and many more.

The incidence of sepsis-associated liver dysfunction (SALD) is hard to establish due to the lack of a homogeneous definition, and consequently lack of a thorough registry. What is more, the incidence of SALD varies, as currently there are no specific diagnostic tools available, especially ones that could detect liver injury in the early stages.

In a study performed by Birrer R. et al., the presence of hepatic injury was identified in 1.1% of admissions.<sup>7</sup> The causes of hepatic injury in the group of patients were: hypotension, congestive heart failure (secondary liver hypoperfusion), sepsis, respiratory failure resulting in hypoxia, and other causes resulting in hypoxemia. Sepsis was diagnosed in 16.1% of patients who developed hypoxic hepatitis.

Another study performed by Kobashi H. et al. observed SALD in 34.7% of the patients.<sup>8</sup> Among those who developed SALD, the authors distinguished 3 groups: “hepatocellular” (21.8%), “cholestatic” (48.1%) and “shock liver” (30.1%). In each group, jaundice as a complication was observed in 17.6%, 33% and 8.5% of cases, respectively.

The aim of this article is to explain the pathophysiology and review the clinical manifestations of sepsis-associated liver dysfunction.

## The liver in sepsis

The liver is a parenchymatous organ composed of 3 types of cells: hepatocytes (HCs), Kupffer cells (KCs), and liver sinusoidal endothelial cells (LSECs).

In the course of sepsis/septic shock, the metabolism of HCs is modified towards the inflammatory response. The main cytokine of the liver inflammatory response is interleukin-6 (IL-6), which is responsible for synthesizing acute phase proteins such as C-reactive protein (CRP),  $\alpha$ -1 antitrypsin, fibrinogen, prothrombin, and haptoglobin.<sup>9</sup> The increase in acute phase protein concentrations leads to inhibition of the protein C pathway, and thus it is responsible for the increase of coagulation factor activity. Secretion of IL-6 is induced by endotoxin (lipopolysaccharide – LPS) and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ).

Lipopolysaccharide also stimulates secretion of TNF- $\alpha$ , interleukin-1 $\beta$  (IL-1 $\beta$ ), interleukin-12 (IL-12) and interleukin-18 (IL-18) by KCs.<sup>10</sup> IL-18 is the main factor responsible for LPS-induced liver damage. IL-18 leads to interferon- $\gamma$  (IFN $\gamma$ ) secretion, which results in hepatocyte apoptosis, an increase in TNF- $\alpha$  concentration and upregulation of CD14 expression. CD14 is a monocyte/macrophage surface receptor responsible for binding the lipopolysaccharide binding protein (LPS/LBP) complex.

Kupffer cells are macrophages of the liver, which are responsible for scavenging portal vein blood from bacteria and endotoxins. As a response to LPS stimulation, KCs release TNF- $\alpha$ , IL-1 $\beta$ , IL-6, IL-12 and IL-18, reactive oxygen species (ROS), and nitric oxide (NO), which induce endothelial cell and hepatocyte injury. During the early stages of sepsis, as a response to KCs' release of TNF- $\alpha$  and leukotriene B<sub>4</sub>, neutrophils are recruited to the liver.<sup>11</sup> Cytokines produced by neutrophils are responsible for further damage of hepatocytes.

Endothelial cell (EC) dysfunction contributes to the development of MODS.<sup>12</sup> Liver sinusoidal endothelial cells are also involved in cytokine release in response to LPS stimulation, and they are the main hepatic source of endothelin-1 (ET-1), which is a strong vasoconstrictor.<sup>13,14</sup> During sepsis, ET-1 is secreted in response to NO release from inducible nitric oxide synthase (iNOS).<sup>15</sup>

Endothelin-1 has also been found to have a strong correlation with the inflammatory response. It involves the expression of cytokines such as TNF- $\alpha$ , IL-1 and IL-6, as well as the activation of transcription factors such as nuclear factor kappa B (NF- $\kappa$ B).<sup>16</sup> Endothelin-1 also increases synthesis of TNF- $\alpha$  in monocytes and macrophages.<sup>17</sup> In their study, Brauner et al. found ET-1 concentrations to be an early and sensitive predictor of mortality in patients with septic shock.<sup>18</sup>

In order to maintain a proper hepatic perfusion, a balance of vasoactive effects of ET-1 and NO is needed.

Nitric oxide is responsible for the relaxation of vascular smooth muscle cells, the regulation of hepatic blood flow and the inhibition of platelet aggregation and the adhesion of leukocytes to endothelium.<sup>19</sup> The impact of NO on liver depends on its source. The endogenous NO released from endothelial nitric oxide synthase (eNOS) helps protect the liver cells from damage caused by vasoconstriction induced by endothelin-1 (ET-1) release, whereas iNOS promotes microvascular dysfunction and thereby SALD.<sup>15</sup>

The other components that regulate the vasculature tone are carbon monoxide (CO) and hydrogen sulfide (H<sub>2</sub>S).

One of the products of cysteine metabolism is H<sub>2</sub>S, which is synthesized in the brain, in the liver, and in vessels.<sup>20</sup> H<sub>2</sub>S may also be synthesized by microflora of the gastrointestinal tract and transferred to the liver via the portal circulation.<sup>21</sup> Synthesis of H<sub>2</sub>S is increased during sepsis.<sup>22</sup> Hydrogen sulfide relaxes vascular smooth muscle cells and inhibits their proliferation and platelet aggregation.<sup>23</sup> Finally, H<sub>2</sub>S oxidation may contribute to exacerbation of sepsis-associated tissue hypoxia.<sup>24</sup>

Carbon monoxide (CO) is one of the products of heme degradation by heme oxygenases (HO) (Fig. 1). Carbon monoxide is responsible for maintaining the liver's regional perfusion, resulting in the activation of leucocytes.<sup>25,26</sup> Furthermore, HO-1/CO prevents EC apoptosis via suppressing inflammatory reactions contributing to EC apoptosis. CO generated through heme catabolism by HO has an anti-apoptotic effect on ECs through activation of mitogen-activated protein kinases (MAPK).<sup>27</sup> It is still not clear which of the above-mentioned properties of CO has a hepatoprotective influence in sepsis.

In a study on rodent model ischemia-reperfusion induced systemic inflammation, exogenous CO was shown to have a hepatoprotective effect via improving liver cell integrity and the redox state as well as protecting the liver microcirculation.<sup>28</sup>

## Clinical manifestations of SALD

In septic patients, the spectrum of liver dysfunction may vary from subclinical to symptomatic liver failure. In critically ill patients the concept of “shock liver” may be used. “Shock liver” is a syndrome of hemodynamic, cellular, immunologic and molecular disorders.<sup>29</sup> SALD can manifest in 2 clinical forms – jaundice/sepsis-induced cholestasis, and hypoxic hepatitis (HH).<sup>19</sup> Coagulopathy may be another symptom of SALD. These processes are still not well understood due to the complexity of their pathomechanisms.

### Jaundice/sepsis-induced cholestasis

The synthesis of bile is a complex process, requiring proper energy input and normal function of transmembrane

proteins.<sup>30</sup> Energy shortage caused by hypoxemia/liver hypoperfusion may impair most bile synthesis steps.<sup>31</sup>

Liver histological examinations in patients with jaundice occurring during bacterial infection revealed the presence of intrahepatic cholestasis. The impairment of bile transport is a result of alterations in genes activating transcription and modifying posttranslational treatment of bile acids transporting proteins caused by LPS and proinflammatory cytokines.<sup>32</sup>

Laboratory test abnormalities include an increase of total bilirubin (>2 mg/dL), alkaline phosphatase, ALT, and AST.<sup>33</sup>

### Hypoxic hepatitis

Hypoxic hepatitis (HH) may be the cause of fulminant hepatitis. In septic shock, an increase in blood flow and cardiac output is not enough to compensate increased hepatic oxygen demand.<sup>34</sup> Decreased hepatic blood flow in shock does not always cause HH; it may occur in patients with normal blood pressure.

Other risk factors causing HH are LPS and inflammatory cytokines. Hypoxic hepatitis may also be a result of the reoxygenation phase in the course of the ischemia/reperfusion phenomenon.

In the course of HH, except for a rapid (24 h from the onset of shock) substantial increase in aminotransferases and lactate dehydrogenase activity, an early decrease in serum prothrombin concentration is observed.<sup>35</sup>

### Coagulopathy

A wide range of coagulopathy may be observed in sepsis, starting with mild deviation in laboratory results (prolonged clotting time, decreased number of platelets) to severe coagulopathy and/or disseminated intravascular coagulation (DIC).

The main cause of coagulopathy in sepsis is microvascular endothelial injury resulting in an imbalance between fibrinolysis and coagulation.<sup>36</sup> The changes seen in endothelial injury include loss of vascular tone, capillary obstruction by platelet or fibrin clots, as well as the degradation of heparan sulfate leading to a pro-coagulant state.<sup>37</sup>

Coagulopathy may be another symptom of liver disease. Several factors may contribute to hemostatic changes in liver disease (Table 1).<sup>38</sup>

## Assessment of liver function

Diagnosis of liver dysfunction in sepsis, according to the Surviving Sepsis Campaign (SSC) Guidelines, is based on an increase in serum bilirubin concentration >2 mg/dL (34.2 μmol/L) and occurrence of coagulopathy (INR > 1.5).<sup>39</sup>

Currently, there are no specific biomarkers available that would allow for an early diagnosis of acute liver

damage in the course of sepsis/septic shock and distinguishing it from a pre-existing liver pathology. Liver function can be assessed using static and dynamic parameters.

Static parameters include:

- secretory capacity – bilirubin;
- parameters of cholestasis – alkaline phosphatase,  $\gamma$ -glutamyltransferase;
- intracellular enzymes activity – alanine aminotransferase, aspartate aminotransferase, glutamate dehydrogenase;
- synthesizing capacity – albumin, clotting factors V and VII.<sup>40</sup>

**Table 1.** Factors contributing to hemostatic changes in liver dysfunction

Hemostatic changes in liver dysfunction	
promoting hemostasis	impairing hemostasis
<ul style="list-style-type: none"> <li>• low plasminogen activity</li> <li>• decreased protein S, protein C and antithrombin activity</li> <li>• increased VWF activity</li> <li>• increased factor VIII serum concentration</li> </ul>	<ul style="list-style-type: none"> <li>• reduced hematocrit</li> <li>• thrombocytopenia</li> <li>• production of nitric oxide and prostacyclin</li> <li>• low serum concentration of coagulation factors II, V, VII, IX, X, and XI</li> <li>• dysfibrinogenemia</li> <li>• vitamin K deficiency</li> <li>• elevated activity of tPA</li> <li>• low serum concentrations of plasmin inhibitor, factor XII and TAFI</li> </ul>

VWF – von Willebrand factor; TAFI – thrombin activatable fibrinolysis inhibitor; tPA – tissue plasminogen activator.

**Table 2.** Causes of hyperbilirubinemia in sepsis

1. Cholestasis
2. Hemolysis – drug-induced/infection-related
<ul style="list-style-type: none"> <li>• in normal RBCs</li> <li>• in RBCs with enzyme defects</li> </ul>
3. Hepatic dysfunction
<ul style="list-style-type: none"> <li>• ischemia: hypotension, hypoxia</li> <li>• hepatocellular damage</li> <li>• bilirubin transport dysfunction: decreased uptake, canalicular transport, clearance</li> </ul>

RBCs – red blood cells.

**Table 3.** Types of drug-induced liver injury. Examples of hepatotoxic drugs

Cellular ( $\uparrow$ alanine aminotransferase)	Cholestatic ( $\uparrow$ total bilirubin, $\uparrow$ alkaline phosphatase)	Mixed
<ul style="list-style-type: none"> <li>• Acetaminophen</li> <li>• Allopurinol</li> <li>• Amiodarone</li> <li>• Baclofen</li> <li>• Isoniazid</li> <li>• Ketoconazole</li> <li>• Lisinopril</li> <li>• Losartan</li> <li>• Methotrexate</li> <li>• NSAIDs</li> <li>• Omeprazole</li> <li>• Pyrazinamide</li> <li>• Rifampin</li> <li>• Statins</li> <li>• Tetracyclines</li> <li>• Valproate</li> </ul>	<ul style="list-style-type: none"> <li>• Amoxicillin/clavulanate</li> <li>• Anabolic steroids</li> <li>• Chlorpromazine</li> <li>• Clopidogrel</li> <li>• Oral contraceptives</li> <li>• Erythromycins</li> <li>• Irbesartan</li> <li>• Phenothiazines</li> <li>• Tricyclic antidepressants</li> </ul>	<ul style="list-style-type: none"> <li>• Amitriptyline</li> <li>• Azathioprine</li> <li>• Captopril</li> <li>• Carbamazepine</li> <li>• Clindamycin</li> <li>• Enalapril</li> <li>• Nitrofurantoin</li> <li>• Phenobarbital</li> <li>• Phenytoin</li> <li>• Sulfonamides</li> <li>• Trimethoprim/sulfamethoxazole</li> <li>• Verapamil</li> </ul>

However, these parameters cannot be used for continuous and rapid monitoring of liver function in patients treated in ICU, nor are they diagnostic or prognostic in this group of patients.<sup>40,41</sup> As mentioned above, according to the SSC Guidelines, serum bilirubin concentration ( $>2$  mg/dL or  $>34.2$   $\mu$ mol/L) is used as a single marker guideline to diagnose liver dysfunction.<sup>39</sup> Due to a number of drawbacks limiting its application, serum bilirubin is not an appropriate marker to reflect complex liver function. Increase in serum bilirubin concentration is neither specific nor does it allow acute liver dysfunction to be distinguished from a pre-existing liver pathology.<sup>41</sup> Table 2 shows causes of hyperbilirubinemia in sepsis.<sup>33</sup>

Dynamic parameters assessing liver function include:

- indocyanine green (ICG), caffeine and bromosulfophthalein clearance;
- liver detoxification capacity – measuring the concentration of  $^{14}\text{CO}_2$  in exhaled air (measuring the concentration of [ $^{14}\text{C}$ ]aminopyrine, [ $^{14}\text{C}$ ]methacetin, [ $^{14}\text{C}$ ]erythromycin metabolites) and measuring the concentration of lidocaine/midazolam serum metabolites;
- ability to eliminate galactose.<sup>40</sup>

## Maximal liver function capacity

Kaffarnik et al., in their study published in Critical Care in 2013, attempted to assess the maximal liver function capacity (LiMax) test as a useful tool for early diagnosis of sepsis-associated liver dysfunction.<sup>42</sup> LiMax is a non-invasive breath test using  $^{13}\text{C}$ -labeled methacetin, which is exclusively metabolized by cytochrome P450 (1A2) to  $^{13}\text{CO}_2$  and acetaminophen. The idea of the test is to measure the amount of exhaled  $^{13}\text{CO}_2$ . The result is given as the LiMax value in  $\mu\text{g}$  per kg of body weight per hour. It shows the speed of substrate metabolism, thus allowing one to evaluate the metabolic capacity of the liver.

In the study, a pathologic deterioration of LiMax values in patients with septic shock was observed within 2 days after the onset of sepsis. Among patients with LiMax,  $<100 \mu\text{g}/\text{kg}/\text{h}$  the mortality rate was 55%, and with LiMax  $>100 \mu\text{g}/\text{kg}/\text{h}$  the mortality rate was 0%. The authors' conclusion was that LiMax values  $<100 \mu\text{g}/\text{kg}/\text{h}$  could be a good predictor of morbidity and mortality.

## Indocyanine green clearance

Indocyanine green (ICG) is a non-toxic, water-soluble fluorescent dye. Its spectrophotometric evaluation does not depend on oxygen saturation and serum bilirubin concentration. Indocyanine green clearance (ICG PDR) can be used to reflect the liver function. Because it is not metabolized, it is secreted almost exclusively by the liver and it is not subject to enterohepatic circulation.<sup>43</sup>

A significant limitation in using ICG PDR is the hemodynamic condition of the patient, as ICG PDR depends on hepatic blood flow.<sup>44</sup> Additional parameters limiting the use of this test are the serum bilirubin concentration, serum albumin concentration, body weight, and patient's age.<sup>45</sup> Studies have shown that ICG PDR may be a diagnostic and prognostic tool in monitoring acute liver failure in critically ill patients in the ICU, but there are still no randomized control trials clearly confirming the utility of ICG PDR in daily clinical practice.<sup>43</sup>

It is worth underlining that in clinical practice there are no standardized diagnostic panels allowing for an early, clear diagnosis of acute liver dysfunction. Until now only a few studies have been published, and their results remain equivocal.

## Therapeutic considerations

Currently, there is no specific therapeutic treatment available for the full restoration of damaged liver function. The therapy, according to the SSC Guidelines, should focus on eradicating infection and treating sepsis and its complications.<sup>39</sup> Furthermore, there are tools available that could reduce the risk of further damage to this organ.

These include:

1. avoiding potentially hepatotoxic drugs;
2. early enteral feeding of hemodynamically stable patients;
3. glucose concentration monitoring and adequate glucose supply if necessary;
4. extracorporeal liver support – Molecular Adsorbent Recirculating System (MARS) albumin dialysis, single-pass albumin dialysis (SPAD).<sup>19,46,47</sup>

Drugs are an important cause of liver injury. Examples of potentially hepatotoxic drugs are given in Table 3.<sup>48</sup>

La Mura proposed simvastatin administration for the prevention of LPS-induced intrahepatic endothelial dysfunction. He found that prophylactic simvastatin prevents endotoxemia-induced liver injury, reduces liver inflammation, and prevents microvascular dysfunction in rodents.<sup>49</sup> In other studies, prophylactic simvastatin has also been reported as being able to correct endothelial dysfunction.<sup>50</sup>

## Summary

The incidence of sepsis-associated liver failure is hard to estimate, but it is incontestable that liver failure as a complication of sepsis dramatically worsens the outcome of the patients. It is important to remember that during sepsis not only the infection itself is responsible for liver dysfunction, but also hyperreactivity of the inflammatory response, microcirculatory failure, and side effects of the therapy. Only an early diagnosis of sepsis and its complications as well as quick implementation of therapeutic bundles allow reducing the incidence of severe organ complications, to shorten the hospitalization time and improve patients' quality of life.

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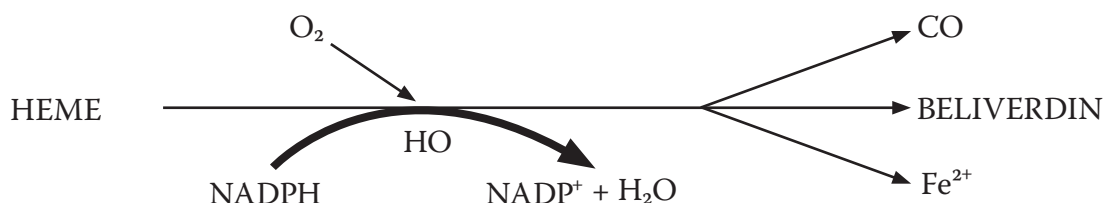


Fig. 1. Heme degradation products

HO – heme oxygenase; CO – carbon monoxide; NADPH – reduced form of nicotinamide adenine dinucleotide phosphate; NADP<sup>+</sup> – nicotinamide adenine dinucleotide phosphate.

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