# Recent insights into pathophysiology of sepsis-associated liver dysfunction

M. Adler

Département Médico-Chirurgical de Gastro-entérologie et d'Hépatopancréatologie (J. Devière, M. Gelin), Hôpital Erasme – ULB, 808 Route de Lennik, 1070 Brussels, Belgium.

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As many of 54% of patients admitted to the Intensive Care Unit (ICU) have abnormal liver function tests (1) and jaundice has been documented in as many as 44% (2) of patients admitted to the ICU because of sepsis, trauma, major surgery, and/or extensive tissue damage. Of these, sepsis appears to be the most common precipitating factor. Severity of jaundice increases with the number of organs failing and correlates with mortality (2).

The aim of the present review is to reexamine recent pathophysiological data, and advances in molecular biology which have led to new insights in the understanding of the central role of gastrointestinal tract and the liver in the pathogenesis of sepsis and sepsis-associated liver dysfunction.

Sepsis, with or without bacteremia, is caused by the action of various bacterial cell wall components such as lipopolysaccharides (LPS), peptidoglycans and teichoic acid from gram- or gram+ organisms with the subsequent release of inflammatory cytokines.

The hepatic response is often accompanied by jaundice and conjugated hyperbilirubinemia leading to the picture of "septic jaundice", also called "jaundice of sepsis", "ICU jaundice", "sepsis associated cholestasis", "inflammation-induced cholestasis" (3,4,5). This type of cholestasis (which is endotoxin and cytokine mediated) must be differentiated from other causes of cholestasis in the critically ill patient such as drug induced injury, parenteral nutrition induced cholestasis, hemolysis, and obstructive cholestasis.

Critical situations such as major surgery, burns, polytraumatism, shock, hypovolemia, host immunity deficiencies, parenteral nutrition (3), cirrhosis (6,7,8), and portal hypertension (9) can potentially lead to systemic inflammatory response syndrome (SIRS) and multiple organ failure (MOF) with significant morbidity and mortality.

The gut is a reservoir of bacteria and endotoxin (10). Current hypothesis (10,11,12) implicates, as an important early step, gut barrier failure favoured by delayed intestinal transit time, intestinal bacterial overgrowth, deficient immune status, and reduced microcirculatory intestinal blood flow, observed in critically ill patients. This results in increased permeability, bacterial translocation, mesenteric lymph node overgrowth and macrophage (such as the Kupffer cell in the liver) cell signalling (Fig. 1).

The concept of the gut being the "motor" of MOF is based on experimental data showing gut mucosal hypoperfusion and increased intestinal permeability of test probes (11,13) in these patients although it has been disputed by other groups (14,15). Because of the gut barrier failure, bacteria can propagate to extra-intestinal sites, this leading potentially to infection and/or sepsis.

Endotoxins, which are LPS located on the outer membrane of gram- bacteria which translocated and/or are released from peripheral sites of infection (such as pyelonephritis) can activate Kupffer cells, with liberation (Fig. 2) of various cytokines and adhesion molecules. Toll-like receptors (16) for LPS activate nuclear factor kappa B (NFKB) which will translocate from the cytoplasm to the nucleus and will activate cytokine genes such as the TNF gene. Intestinal ischemia-reperfusion may also be a major trigger for cytokine gene expression in the absence of endotoxin (17).

NFK B from intestinal mucosa can also be activated during endotoxemia (18), adding support to the concept that intestinal mucosa is an important component of the inflammatory response.

These proinflammatory cytokines promote tissue injury and lead to apoptosis and/or necrosis of hepatocytes (19).

At a later phase, TNF induces activation of neutrophils (20) and secondarily neutrophil invasion through hepatocyte apoptosis (21) with liberation of reactive oxygen species which are further responsible for liver cell apoptosis and/or necrosis.

Increased liberation of LPS is also responsible (Fig. 2) for endothelial cell swelling which causes luminal obstruction and decreased intestinal blood flow.

During sepsis, liver metabolism is usually increased (22) with an increase in protein synthesis (illustrated namely by elevation of acute phase reactants like C-reactive protein), lactate consumption or cytokine production. Although macrovascular liver flood blood is usually increased, microvascular liver blood flow is

M. Adler, Department of Gastroenterology, Hôpital Erasme, 808 route de Lennik, 1070 Bruxelles, Belgique.
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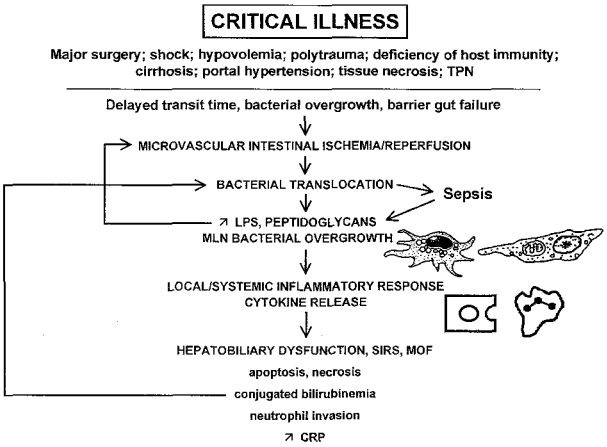


Fig. 1. — Pathogenesis of sepsis and other injuries-associated liver dysfunction. In case of critical illness such as major surgery, shock, hypovolemia, polytrauma, immune deficiency, tissue necrosis (such as burns) and in case of total parenteral nutrition (TPN) or portal hypertension, bacterial translocation can occur induced by factors such as delayed intestinal transit time, bacterial overgrowth, and microcirculatory intestinal ischemia.

Lipopolysaccharides (LPS) and peptidoglycans which translocate or are released from peripheral sites of infection generate local and systemic release of proinflammatory cytokines through activation of hepatic macrophages (Kupffer cells, Fig. 2).

NF-KB is activated in intestinal mucosa during endotoxemia, this contributing to the increase of several proinflammatory cytokines.

Endotoxins and some cytokines are potent cholestatic agents.

Other consequences include hepatic injury (apoptosis/necrosis) induced by TNF and the sequestrated polymorphonuclear neutrophils (PMN) which secrete destructive enzymes and $O_2$-derived radicals.

LPS is also responsible for endothelial cell swelling in the sinusoids, this leading to decreased macrocirculatory sinusoidal blood flow.

Abbreviations : NFKB = nuclear factor KB ; LPS = lipopolysaccharide ; MLN = mesenteric lymph nodes ; SIRS = systemic inflammatory response syndrome ; MOF = multiple organ failure ; CRP = C reactive protein.

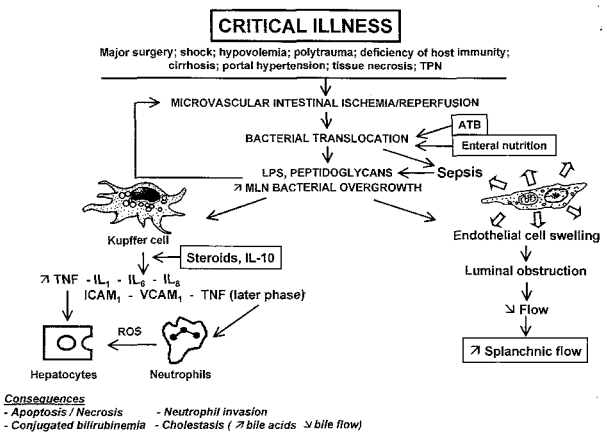


Fig. 2. — Pathogenesis of sepsis-associated liver dysfunction. Details of fig. 1.
Potential therapeutic options are inserted in a square.

Abbreviations : NFKB = nuclear factor KB ; LPS = lipopolysaccharide ; MLN = mesenteric lymph nodes ; ATB = antibiotics ; IL = interkeulin ; ICAM = intercellular adhesion molecules ; VCAM = vascular cell adhesion molecules ; TNF = tumor necrosis factor ; ROS = reactive oxygen species.

generally decreased and, liver metabolism being increased, an imbalance between liver oxygen demand and supply develops (23).

Liver dysfunction is thus the consequence of the direct effect of endotoxin and/or cytokines but also of the hepatic perfusion, as emphasized by Pastor et al (24).

In such instances, it seems appropriate to avoid further ischemic event by prompt resuscitation. Avoidance of hypovolemia is the cornerstone of this therapy and fluid administration is recommended, together with some vasoactive agents (such as β adrenergic agents) which have been shown to increase splanchnic blood flow (25).

It is also important to provide drainage of septic collections, to give adequate antibiotics and to feed the patient adequately.

Enteral nutrition must be preferred to parenteral nutrition as this route has been shown to decrease the number of infections, to have fewer side effects, to increase immunological defenses and to decrease bacterial translocation (26,27).

Recent studies (28) emphasize the potential benefit of immuno-enriched formulas (such as glutamine) to decrease infectious morbidity because glutamine is the preferred fuel for both lymphocytes and enterocytes.

The potential benefit of intestinal decontamination in order to limit the passage of bacteria and their products through the gut barrier is still a matter of debate, although selective decontamination of the digestive tract has been shown to reduce morbidity (and perhaps mortality) and procedure has been shown to be cost-effective (29,30).

Modulation of the host response to bacterial endotoxin may also provide new treatment strategies. An example is a new class of 21-aminosteroids, devoided of gluco- or mineralocorticoid activity, which inhibit recruitment and activation of inflammatory cells and reduce endothelial cell damage (31). We have seen that critical situations increase the risk of sepsis because of bacterial translocation and propagation and that endotoxinemia derived from gut barrier failure and/or extra-intestinal bacterial infections stimulates cytokine production. Infection plays thus a key role in the development of inflammation-induced cholestasis and jaundice.

The most striking biochemical profile of septic jaundice is progressive rise in plasma conjugated bilirubin (32) with minimal elevation of liver enzymes (Fig. 3). Recent studies have shown that LPS/cytokine-induced cholestasis is caused by down-regulation of transporter proteins at the level of hepatocytes (33-38).

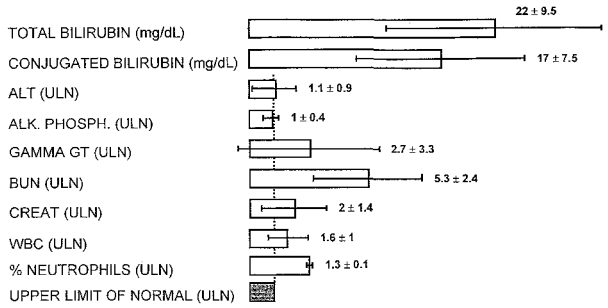


Fig. 3. — Biochemical profile, in a series of 31 patients who developed septic jaundice in our institution (27), with disproportionate elevation of conjugated bilirubinemia compared to liver enzymes.
Cause of infection included 21 gram negative bacteria (pseudomonas aeruginosa in 12, E. coli in 4), 8 gram positive bacteria (staphylococcus aureus in 8) and 2 candida albicans.

Abbreviation : ULN = upper limit of normal.

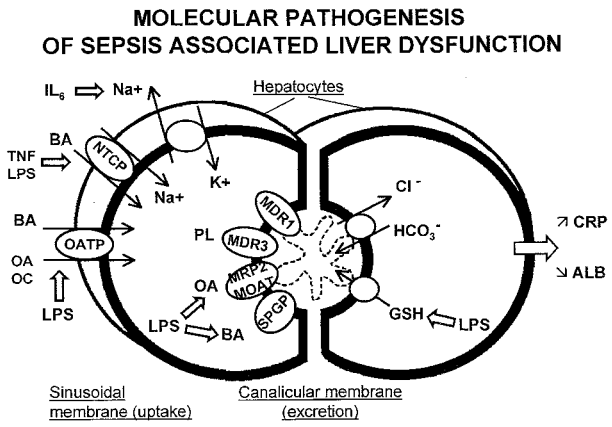


Fig. 4. — Molecular pathogenesis of sepsis-associated liver dysfunction.
LPS-induced cytokines, and LPS itself lead to liver dysfunction through down regulation (() of various critical transport systems both at the sinusoidal (uptake) and the canalicular (excretion) sites.

Abbreviations : IL = interleukin ; TNF = tumor necrosis factor ; BA = bile acids ; LPS = lipopolysaccharide ; OA = organic anions ; OC = organic cations ; PL = phospholipids ; NTCP = $Na^+$/taurocholate cotransporter ; OATP = organic anion transporting protein ; MDR1 = multidrug export pump ; MDR3 = phospholipid export pump ; MRD2-MOAT = conjugated export pump ; SPGP = bile salt export pump ; GSN = glutathione ; CRP = C reactive protein ; ALB = albumin.

Several lines of evidence suggest that LPS and/or venous cytokines (Fig. 4) interfere with transporters of bile acids and other constituents of the bile (such as bilirubin, phospholipids, glutathione, bicarbonate, leukotrienes and ions) both on the sinusoidal membrane of the hepatocytes (responsible for uptake) and the canalicular membrane (responsible for excretion).

Expression of sinusoidal membrane : $Na^+$/taurocholate cotransporter (NTCP) and organic anion transporting protein (OATP) and canalicular membrane : conjugated export pump ($MRP_2$) and bile salt export pump (SPGP) transport system is decreased or even absent.

A major target is the $MRP_2$ (36), an export pump also called the canalicular multispecific organic anion transporter (cMOAT), this explaining why sepsis-associated cholestasis is mainly due to bile acid independent bile flow and characterized, biochemically by disproportionate elevation of conjugated bilirubin (32) in the blood, in the absence of elevation of alkaline phosphatase, an enzyme influenced by the hepatocyte accumulation of bile acids.

Membrane transporters involved in bile secretion are downregulated by LPS and/or cytokines either via a reduction of nuclear transcription factors leading to decreased NTCP mRNA expression (39) or via a nitric oxide (NO)-mediated mitochondrial dysfunction which lead to hepatic depletion of ATP (40) and, consequently, affect the ATP-dependent canalicular membrane transporters such as multidrug export pump (MDR1), phospholipid export pump (MDR3), conjugated export pump (MRP2/MOAT) and SPGP (Fig. 4).

Excessive NO formation, in response to endotoxin and TNF( (41) has, on the other side, an effect on the microvilli cytoskeleton (42), altering canalicular contraction, and this may also contribute to the sepsis-associated cholestasis.

Histological cholestasis marked by bile stasis in the pericentral regions of hepatic acini, is also explained by down-regulation of specific transporters responsible for bile acid dependent (bile salts) and bile acid independent (bilirubin, glutathione) components of bile flow.

Hepatocyte apoptosis and/or necrosis (induced by cytokines and ROS) and neutrophil invasion (due to the later action of TNF) are also part of the morphological picture induced by the LPS/cytokine cascade (Figs. 1-2).

A vicious cycle ensues due to the fact that cholestasis causes more endotoxin absorption (43).

In the past few years, a great number of important breakthroughs have been made concerning the potential role of the digestive tract and the liver in the development of sepsis and its consequence on hepatobiliary dysfunction.

Recent discoveries in the basic biology of endotoxin provide a better understanding of old, well-recognized syndromes, such as septic jaundice, and open new potential treatment strategies in the management of sepsis and its consequences.

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