REVIEW ARTICLE

Pathophysiology of sepsis-induced cholestasis: A review

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Abstract
Sepsis is a critical condition resulting from the excessive activation of the inflammatory/immune system in response to an infection, with high mortality if treatment is not administered promptly. One of the many possible complications of sepsis is liver dysfunction with consequent cholestasis. The aim of this paper is to review the main mechanisms involved in the development of cholestasis in sepsis. Cholestasis in a septic patient must raise the suspicion that it is the consequence of the septic condition and limit the laborious attempts of finding a hepatic or biliary disease. Prompt antibiotic administration when sepsis is suspected is essential and may improve liver enzymes. Cholestasis is a syndrome with a variety of etiologies, among which sepsis is frequently overlooked, despite a number of studies and case reports in the literature demonstrating not only the association between sepsis and cholestasis but also the role of cholestasis as a prognostic factor for sepsis-induced death.

Introduction
Sepsis is a severe, life-threatening complication of an infection. It occurs when the immune response becomes inadequate, triggering organ dysfunction. Sepsis involves a pro-inflammatory and anti-inflammatory response leading to organ failure. Sepsis may progress to septic shock, a condition associated with high mortality, defined as sepsis leading to metabolic and hemodynamic dysfunction severe enough to push lactacidemia above 2 mmol/L and to pull mean blood pressure below 65 mmHg, unresponsive to appropriate fluid resuscitation, and requiring vasopressor support. Cholestasis occurs in up to 40% of critical patients, sepsis being one of its multiple causes. According to Surviving Sepsis Campaign Guidelines, liver dysfunction associated with sepsis is defined by a rise in serum bilirubin above 2 mg/dL accompanied by defective coagulation reflected by an international normalized ratio (INR) above 1.5. Sepsis-associated liver dysfunction includes hypoxic hepatitis, sepsis-induced cholestasis, and faulty protein synthesis generating coagulopathy. Hypoxic hepatitis is defined by (i) clinical signs of cardio-circulatory and/or respiratory failure, (ii) a sudden and transient rise in serum transaminases (>20 times the upper limit of normal), and (iii) absence of other causes of hepatic necrosis. Hypoxic hepatitis may be associated with prolonged prothrombin time, acute kidney injury, and higher bilirubin. Notwithstanding preserved cardiac output, septic shock generates a craving for oxygen unmet by oxygen delivery and extraction, compounded by altered hepatic perfusion due to vasodilation–vasoconstriction imbalance. Endotoxins and inflammatory...
mediators too may promote hypoxic hepatitis. Sepsis-induced cholestasis results from: (i) impairment of bile acids and bilirubin uptake and transport due to hypoxia and hypoperfusion; (ii) deleterious effects of endotoxins and inflammatory cytokines on the genic expression of the proteins transporting bile acids and bilirubin, on the cytoskeleton architecture around the bile ducts, and on the tight junctions between hepatocytes.

The main hepatocellular transport proteins involved in sepsis-induced cholestasis are listed in Table 1 and their action mechanism is summarized in Figure 1. Sepsis-induced liver dysfunction is associated with high mortality; prompt infection control is a key step in improving the prognostic.

Methods

A PubMed (https://www.ncbi.nlm.nih.gov/pubmed) search for “cholestasis[Title/Abstract] AND sepsis[Title/Abstract]” provided the articles employed in this review. The authors endeavored to include (almost) all the relevant papers, giving priority to those attempting to define the pathophysiology of sepsis-associated liver dysfunction. The results of this search are summarized in Table 2.

Sepsis-induced cholestasis

Mechanisms interfering with membrane pumps activity. The decrease in bile acids uptake and excretion is the main mechanism engendering cholestasis. Although sepsis does not alter the synthesis and cytosolic transport of bile acids, it impairs bile acids uptake and secretion by upsetting membrane pumps. Conjugated bilirubin predominance suggests that bilirubin conjugation is not significantly impacted; indeed, depressed bile acids excretion in the bile ducts is one of the main mechanisms of the sepsis-associated cholestasis.

Sepsis induces cholestasis by reducing the expression of: (i) NTCP, mediated by tumor necrosis factor-alpha (TNF-α) and interleukin 1beta (IL-1β), with consequent diminished bile salts transport from blood into the hepatocyte; (ii) BSEP and MRP 2 export pumps followed by a decrease in bile flow and in the excretion of bile acids; (iii) NTCP in conjunction with MRP 2, which depresses bile flow and biliary excretion of bile salts and glutathione. Consistent therewith, a study conducted in rats showed that Inchin-ko-to, a herbal medicine, partially prevents sepsis-associated cholestasis by increasing MRP 2 protein levels, which improves glutathione excretion and bile flow. In order to compensate for the sepsis-induced cholestasis, other mechanisms of ridding the hepatocyte of biliary acids are put into motion, mediated by basolateral exporters MRP 4 and MRP 3.

It was found that in rat hepatocytes, Na + K + -adenosine triphosphatase (Na + K + -ATPase) protein is located in the sinusoidal membrane, while ecto-adenosine triphosphatase (ecto-ATPase) protein, which is essential for liver cell function, resides in the canicular membrane. NTCP is a membrane pump whose function is dependent on the Na + K + -ATPase. Endotoxin, particularly IL-6, reduces the activity of Na + K + -ATPase, which is important for maintaining the electrochemical sodium gradient and implicitly for NTCP activity. Ecto-ATPase is a bile acid transporter whose level is decreased by lipopolysaccharides (LPS). Endotoxin and TNF-α impair the activity of NTCP and canicular ecto-ATPase, thereby diminishing taurocholate transport across sinusoidal and canicular membrane.

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**Table 1** The main hepatocellular transport proteins and their principal functions

| Hepatocellular transport proteins | Function | Reference |
|---------------------------------|----------|-----------|
| Sodium-taurocholate co-transporting polypeptide | Bile acids transport from plasma into the hepatocyte | 5 |
| Organic anion transporting polypeptides | Uptake of many compounds such as conjugated and unconjugated bile acids and unconjugated bilirubin into the hepatocytes | 6, 7 |
| Bile salt export pump | Bile salts excretion into the bile ducts | 8 |
| Multidrug resistance-associated protein 2 | Conjugated bile acids excretion from hepatocytes into bile | 9 |
| Multidrug resistance-associated proteins 3 and 4 | Expulsion of bile acids into the bloodstream | 9 |
| | | |

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**Figure 1** Sepsis-induced disruption of the: (i) Cytoskeletal architecture (black arrow) in the liver cells (four points star) lining the bile canaliculi (five points star), (ii) tight junctions (open arrow) between hepatocytes, and (iii) transporter proteins’ activity in liver cell membrane: sodium-taurocholate co-transporting polypeptide (NTCP) (which transports bile acids from plasma into hepatocytes), organic anions transporting polypeptides (OATP) (which transports conjugated and unconjugated bile acids and unconjugated bilirubin into hepatocytes), bile salt export pump (BSEP) (which transports bile salts into bile ducts), multidrug resistance protein (MRP) 2 (which transports conjugated bile acids and conjugated bilirubin from hepatocytes into bile ducts). MRP 3 and MRP 4 mediate the expulsion of bile acids from hepatocyte into the bloodstream, acting as a protective mechanism activated in cholestatic conditions. BAs, bile acids; BSEP, bile salt export pump; CB, conjugated bilirubin; UCB, unconjugated bilirubin.
Table 2 The main mechanisms involved in the development of sepsis-associated cholestasis and reports of sepsis-related cholestasis (H, human study; T, in vitro study; V, in vivo study)

| Mechanisms interfering with membrane pumps activity | Type of study | Findings | Reference |
|---------------------------------------------------|---------------|----------|-----------|
| NTCP + Na + K + -ATPase | (V) Sprague–Dawley rats or C57BL/6 mice | TNF-α and IL 1β → ↓ NTCP (mRNA, expression and uptake); ↑ Na + K + -ATPase → cholestasis and inflammation | 13 |
| NTCP + MRP | (V) Male Sprague–Dawley rats | LPS; ↓ bile flow, ↓ biliary bile salts and glutathione excretion, ↓NTCP and MRP 2 ICKT: less intense ↓ bile flow, normalization of glutathione excretion, ↑ MRP 2 → partially prevents LPS-induced cholestasis | 16 |
| NTCP + MRP + BSEP | (V) Domestic female pigs | ↓ NTCP and BSEP, ↑ MRP 4, ↓ MRP 2 | 15 |
| BSEP + MRP | (V) Male Sprague–Dawley rats | ↓ BSEP, ↓ MRP 2 → ↓ biliary excretion, ↓ bile flow | 14 |
| NTCP + ecto-ATPase | (V) Adult male Sprague–Dawley rats | ↓ NTCP and canaliculal ecto-ATPase → ↓taurocholate transport → sepsis-associated cholestasis | 20 |
| Rlst-1 + NTCP | (V) Male Sprague–Dawley rats | ↓ rlst-1 mRNA → ↓ taurocholate Transport (sodium-independent manner) | 21 |
| Bile acid secretion into bile and ↓ organic anion transport | (V) Rats | Sepsis: ↓ transport of bile acids and organic anions SIRS: no alteration of transport | 26 |
| Sepsis model: LPS i.p., SIRS model: sterile abscess formation (turpentine i.m.); bile acids (cholyltaurine and chenodeoxycholyltaurine) and organic anion (Sulfolithocholyltaurine) | (V) Male Sprague–Dawley rats | ↓ Basolateral and canaliculal bile acid ↓ organic anion transport, ↓ ATP-stimulated transport → cholestasis | 27 |
| LPS 0.3 mg/100 g body i.p.; bile acids (cholyltaurine and chenodeoxycholyltaurine) and organic anions (sulfobromophthalein and sulfolithocholyltaurine) | (V) Adult male Sprague–Dawley rats | ↑ Bile acid excretion | 28 |
| Bile acids secretion | (V, T) Male Sprague–Dawley rats, rat hepatocytes | ↑ Basal bile flow and salt excretion, ↓ bile salt stimulated bile flow; anti-TNF-α antibody blocked endotoxin-associated cholestasis | 29 |
| Endotoxin production by eight common bacterial pathogens | (T) Hepatocytes from male Sprague–Dawley rat livers | ↑ Bile salt uptake | 30 |
| Human stool suspension (1.2 μL/g body weight i.p.) and Candida albicans (2.5 × 10⁷ CFU/g body weight i.v. or 5 × 10⁶ CFU/animal i.p.) | (V) Male, 17–20-week-old C57BL/6 mice | C. albicans infection ↑ conjugated bile acids, ↓ hepatic uptake; PCI: ↑ unconjugated bile acids, defects in secretion | 31 |

Mechanisms interfering with nuclear receptors

| FXR | (V, T) Specific pathogen-free male C57BL/6 mice Human acute monocytic leukemia cell line THP-1 | Endotoxemia: ↑ OSTβ1, ↓ NTCP and BSEP → ↓ bile acids, ↓ FXR → ↑ NLRP3 inflammasome activation | 35 |
| Extensive surgery (“surgical critical illness”) or extensive surgery, cecal ligation and puncture (CLP) (“septic critical illness”) | (V, H) 24-week-old male C57BL/6J mice, human patients with | ↑ Bile acids, ↓ FXR and RXR, ↓ basolateral and canaliculal transporters, ↑ MRP 3 and MRP 4 | 17 |

(Continues)
| Sepsis model (where applicable)                                                                 | Type of study                                                                 | Findings                                                                                                                                                                                                 | Reference |
|------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------|
| Vivo: cecal ligation and puncture +/− medium containing dexamethasone                            | (V, T) Male Sprague–Dawley rats, hepatocytes derived from rats with sepsis    | ↓ RXR-α and FXR, ↓ RXR-α translocation from cytosol to nucleus, ↓ mRNA rBAT (↓ rBAT level); Dexamethasone: reversed sepsis-inhibited RXR-α, FXR/RXR binding to rBAT DNA and rBAT protein expression | 37        |
| LPS (10 mg/kg i.p) OCA (5 mg/kg gavage)                                                        | (V) Male C57BL/6 mice                                                       | OCA → ↑ FXR and BSEP, ↓ LPS-induced hepatocyte apoptosis and inflammatory infiltration, ↓ ALT, AST, TBA and TB, ↑ IL-1β, TNF-α, IL-6 → ↓ bile acid synthesis; stimulated ATF4-mediated autophagy activity | 38        |
| NTCP + HNF                                                                                     |                                                                               | ↓ HNF 1 and FpB BP → ↓ NTCP mRNA; ↓ NF-κB and AP-1                                                                                                                                             | 40        |
| LPS (1 mg/kg body i.p.)                                                                         | (V) Male Sprague–Dawley rats                                                 | Complete depletion Kupffer cells; ↓ IL-1β and TNF-α gene expression, ↓ TNF-α binding levels, ↑ NTCP RNA, ↓ plasma bile salt, preserved activity of RXR:RAR and HNF1α       | 39        |
| Activation of LPS/TLR4 signaling pathway                                                        |                                                                               | ↑ Oatp4 mRNA levels through TLR4                                                                                                                                                            | 43        |
| LPS (1 mg/kg i.p.), LPS (5 mg/kg i.p.)                                                          | (V) TLR4-normal C3H/OuJ mice, TLR4-mutant C3H/HeJ mice                      | LPS + TLR4 → ↓ ITPR3 via NF-κB → impairs ductular bicarbonate secretion                                                                                                                           | 23        |
| Activation of PI3K signaling pathway                                                             |                                                                               | ↓ PI3K/Akt signaling → ↓ MRP 2 → ↑ hepatic excretory dysfunction               | 44        |
| Peritoneal contamination and infection                                                           | (V) PI3K KO and PI3K KD mice lacking or expressing kinase-inactive PI3K     | ↓ Plasma bile acids, ↓ BSEP and MRP 2 ↑ PI3K → internalization of pseudovilli                                                             | 45        |
| Peritoneal contamination and infection with a stool suspension hepatoblastoma cells: a mix of TNF-α, IL-1β, IFN-γ, and LPS | (V, T, H) Male Wistar rats, PI3K−/− (12–16 weeks) mice, human hepatoblastoma cells, plasma from 48 patients fulfilling standard criteria for severe sepsis/septic shock |                                                                                                                                         |           |
| Generation of a pro-inflammatory state                                                          |                                                                               |                                                                                                                                           | 47        |
| NO donors sodium nitroprusside and S-nitrosocysteine                                            | (T) Human hepatoma cell line stably expressing NTCP (HuH-NTCP)              | NO → S-nitrosylation of NTCP → ↓ TC uptake ↓ NTCP in the membrane                                                                                                                              | 46        |
| LPS (4 mg/kg body i.p.)                                                                         | (V) Male Sprague–Dawley rats                                                 | ↓ Portal and systemic NO2− + NO3− plasma levels but LPS-induced NO does not modulate bile formation ↓ HCO3−, and glutathione output → ↓ bile flow | 22        |
| IL-6                                                                                           |                                                                               | ↓ NTCP and MRP 2 transcription → hyperbilirubinemia and cholestasis                                                               | 47        |
| Cecal ligation and puncture +/− IL-6                                                            | (V, T) Male Sprague–Dawley rats, IL-6-treated cultured hepatocytes from the livers of normal rats | ↑ Na + K + ATPase → ↓ sodium-dependent taurocholate uptake → cholestasis                                                                                                                          | 19        |
| Media containing IL-6                                                                           | (T) Cultured rat hepatocytes                                                 | Absence of IL-6 → ↑ hepatic dysfunction and mortality in sepsis ↑ IL-6 activity →                                               | 48        |

(Continues)
Table 2  (Continued)

| Sepsis model (where applicable) | Type of study       | Findings                                                                 | Reference |
|--------------------------------|---------------------|--------------------------------------------------------------------------|-----------|
| IL 8 + CCL2 + CXCL2            | (V) Domestic female pigs | ↑ IL8, CCL2, and CXCL2 → inflammatory reaction and recruitment of monocytes and neutrophils | 49        |
| P-selectin                     | (V) Adult male C57/BL/6 mice | Immunoneutralization of P-selectin; ↓ leukocyte infiltration, ↓ hepatocellular apoptosis and necrosis, maintains intact bile flow, expression of hepatocyte transporters, and excretory function | 50        |
| Mechanisms interfering with aquaporins | (V) Adult male Wistar rats | LPS → ↑TNF-α → ↑ AQP8 (cytokine-induced AQP8 proteolysis) → ↓ canalicular membrane water permeability → LPS-induced cholestasis | 51        |
| Impairment of liver enzymes with hepatic histopathological changes | (H, V) Observational study: patients with S. aureus endocarditis and hyperbilirubinemia; New Zealand white rabbits | Hyperbilirubinemia in S. aureus sepsis → high risk of dying lipoteichoic acid → defective hepatic excretory function → hyperbilirubinemia | 52        |
| E. coli-derived LPS (0.2 mg i.v.), Staphylococcus aureus (10⁵ to 10⁶ CFU/mL i.v.), lipoteichoic acid 5 mg i.v. | (H) Inpatients who had elevations of ALP above 1000 U/l, observational study | Extremely high elevations of ALP: in sepsis, malignant obstruction, and AIDS | 53        |
| Gram-negative or Gram-positive infection | (H) Retrospective study, 4 cases with Gram-negative or Gram-positive infection | Disproportionately high levels of BT compared to GOT, GPT, LDH, ALP and GGT levels, histological: cholestasis, Kupffer cell hyperplasia and cell infiltration in the sinusoid and portal areas | 54        |
| Intrapерitoneal sepsis (IS) group by cecal ligation and total parenteral nutrition (TPN) group | (V) Female adult Wistar rats | IS group: degeneration of hepatolobules, enlargement of bile canalici with altered microvilli | 55        |
| 1.75 mL/kg stool suspension i.p. | (V) Male Wistar rats; the organic anionic dyes: indocyanine green and benzopyrylium-based hemocyanine | Sepsis → liver injury, cholestasis, sinusoidal perfusion impairment → ↓ excretion and accumulation organic anions in the liver parenchyma | 56        |
| (Case report) A 46-year-old man with mediastinal abscess that contained acid-fast bacilli | (Case report) A 58-year-old woman septic shock from | Conjugated bilirubin, near-normal ALT, ALP, and PT; after treatment: bilirubin normalization | 57        |
| (Case report) A 58-year-old woman septic shock from | (Case report) A 58-year-old woman septic shock from | Bilirubin, GGT and ALP, → sepsis-related cholestasis | 58        |

(Continues)
An organic anion transporter in the rat liver, rlst-1, is involved in bile acids and organic anions transport in a sodium-independent manner. Its downregulation in sepsis reduces bile acids secretion, thus contributing to sepsis-associated cholestasis.\textsuperscript{21}

LPS may induce cholestasis by hindering bile acid-independent bile flow; it inhibits biliary excretion of glutathione\textsuperscript{16,22} and bicarbonate.\textsuperscript{22,23} Glutathione acts as an osmotic agent important for bile formation.\textsuperscript{24} Altered bicarbonate secretion into the bile may reflect liver impairment.\textsuperscript{25}

Sepsis-associated cholestasis involves: (i) reduced bile acids and organic anion transport\textsuperscript{26} in conjunction with impairment of ATP-stimulated transport\textsuperscript{27}; (ii) decreased bile acids excretion\textsuperscript{28} or decreased basal bile flow and basal bile salt excretion induced by TNF-\textalpha;\textsuperscript{29} (iii) reduced bile salts uptake by hepatocytes with defective bile acids secretion into bile.\textsuperscript{30}

**Mechanisms interfering with nuclear receptors involved in inflammatory responses.** The farnesoid X receptor (FXR) is a nuclear receptor expressed in many tissues, but especially in liver, where it is activated by bile acids as a monomer or as a heterodimer in association with retinoid X receptor (RXR).\textsuperscript{31} FXR is involved in bile acid homeostasis, its activation closing a negative feedback loop that limits bile acids synthesis.\textsuperscript{32} FXR induces BSEP expression involved in bile salts excretion from hepatocytes into the bile ducts.\textsuperscript{33} FXR blocks mitochondrial

| Table 2 | (Continued) |
| --- | --- |
| **Sepsis model (where applicable)** | **Type of study** | **Findings** | **Reference** |
| Sepsis model (where applicable) | **Findings** | **Reference** |
| Cholestatic syndrome with jaundice | Intrahepatic cholestasis: inspissated bile | |
| Patients with different type of sepsis | Cholestatic and hepatocyte necrosis, hepatosplenomegaly, liver biopsy: intrahepatic cholestasis; after treatment: cholestasis and hepatosplenomegaly disappearance | |
| (Case report) A 57-year-old woman with bronchopneumonia (S. aureus) | Intrahepatic cholestasis: inspissated bile within dilated and proliferated portal and periportal bile ductules | |
| (Case reports) (1) A 55-year-old white female with ulcerative colitis and subphrenic pelvic and lesser sac abscesses. (2) A 66-year-old black male with fulminant hepatitis (3) A 58-year-old black female with Torulopsis glabrata pneumonia | Cholestatic syndrome with jaundice → inflammation-induced cholestasis | |
| (Case report) A 47-year-old female with spondylodiscitis and paravertebral abscess | Sepsis-associated cholestasis was strongly associated with older age, biomarkers of organ dysfunction, and clinical composite scores (APACHE II and SOFA); higher mortality in patients with sepsis-associated cholestasis | |

\[ \text{References:} \textsuperscript{1, 0.029} \text{activating, elevation, increase, upregulated; } \rightarrow, \text{ results, cause, induce; } \downarrow, \text{ reduce, negative regulator, suppress, decrease, downregulated, inhibit; AdhAQP1, adenovirus encoding human aquaporin-1; AIDS, acquired immune deficiency syndrome; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AP-1, activating protein 1; AQPB, aquaporin-B; AST, aspartate aminotransferase; BA, bile acids; BSEP, bile salt export pump; ecto-ATPase, ecto-adenosinetriphosphatase; CCL2, C-C motif chemokine ligand 2; CD3, cluster of differentiation 3; CDCA, chenodeoxycholic acid; CFU, colony forming units; CXCL2, C-X-C Motif Chemokine Ligand 2; DCA, deoxycholic acid; DNA, deoxyribonucleic acid; FpB BP, footprint B binding protein; FXR, Farnesoid X Receptor; GGT, gamma-glutamyl transferase; GOT, glutamic oxaloacetic transaminase; HCO3, bicarbonate; HNF, hepatocyte nuclear factor; i.p., intraperitoneal; i.v., intravenous; ICKT, Inchin-ko-to; IL, interleukin; INR, international normalized ratio; IPV, portal vein; ITPR3, type 3 inositol 1,4,5-trisphosphate receptor; IPV, portal vein; ITRX, type 3 inositol 1,4,5-trisphosphate receptor; KCa, potassium channel; KATP, ATP-sensitive potassium channel; LTB4, leukotriene B4; LPS, lipopolysaccharide; mRNA, messenger ribonucleic acid; MRP, multidrug resistance protein; Na\text{+}, sodium ion; NADPH oxidase; NLRP3, nucleotide-Binding Domain; Leucine-Rich Repeat Family; Pyrin Domain-Containing 3; NO, nitric oxide; NTCP, sodium taurocholate co-transporting polypeptide; OATP, organic anions transporting polypeptides; OCA, obeticholic acid; OST, organic solute transporter; P2X7, purinergic receptor P2X7; PDE4B, phosphodiesterase type 4B; PI3K, phosphatidylinositol 3-kinase; PT, prothrombin time; rAd, recombinant adenovirus; rlst-1, complementary DNA encoding human liver-specific organic anion transporter; RFX, Retinoid X Receptor; RXR:RAR, retinoid X receptor-retinoid acid receptor; SEB, Staphylococcal enterotoxin B; SIRS, systemic inflammatory response syndrome; TBA, total bile acid; TBLR, toll-like receptor 4; TNF-\textalpha, tumor necrosis factor-\textalpha; UDCA, ursodeoxycholic acid. \]
NLRP3 inflammasome assembly by interfering with NLRP3 and caspase 1 (Fig. 2). NLRP3 3 inflammasome consists of intracellular proteins: nucleotide-binding domain, leucine-rich repeat family, pyrin domain-containing 3 (NLRP3), an apoptosis-associated speck-like protein containing a CARD (ASC), and pro-caspase 1. FXR, a nuclear receptor, blocks mitochondrial NLRP3 inflammasome assembly by interfering with NLRP3 and pro-caspase 1. (b) High bile acids levels in the bloodstream lead to: (i) Toll-like receptor (TLR) -nuclear factor-kappa B (NFκB) pathway activation followed by NLRP3 and pro-IL-1β synthesis; (ii) FXR downregulation, which promotes NLRP3 inflammasome assembly with consequent caspase-1 activation engendering IL-1β from pro-IL-1β. FXR activation by bile acids depresses bile acids synthesis and induces bile salt export pump (BSEP) expression. DAMPs, danger-associated molecular patterns; II, Interleukin, leucine-rich-containing family, pyrin domain-containing-3PAMPs, pathogen-associated molecular patterns.

It has been shown that depletion of Kupffer cells, which are responsible for cytokine release, leads to the preservation of NTCP expression by maintaining RXR:RAR and HNF 1 activity.

Activation of LPS/TLR4 and PI3K signaling pathways. LPS are components of the membrane of gram-negative bacteria that bind to the cluster of differentiation 14 (CD14) and initiate the systemic inflammatory response. CD 14 is a glycoprotein receptor attached to the membrane of monocytes, macrophages, and neutrophils, named membrane-bound CD14 (mCD14). Through mCD14, LPS activate toll-like receptor 4 (TLR 4), followed by stimulation of various kinase proteins that spur cytokine production. Furthermore, TLR 4 activation is followed by a decrease in OATP4 mRNA levels. Moreover, nuclear factorκB (NF-κB), activated by TLR 4, reduces type 3 inositol trisphosphate receptor (ITPR3) (an intracellular Ca2+ release channel found in cholangiocytes), which impairs bile formation, contributing to cholestasis. The soluble form of CD 14 (sCD14) found in plasma originates from monocytes, macrophages, and granulocytes either by secretion or by being cleaved from their membrane; sCD14 may bind to LPS and form a complex that activates various cells, thereby driving the immune response; sCD14 may be cleaved by various proteases, thus yielding presepsin, a 13 kDa fragment closely correlated with bacterial infections (Fig. 3).

Phosphatidylinositol-3-kinase (PI3K) signaling is involved in liver dysfunction by reducing MRP 2 plasma membrane levels in conjunction with decreasing BSEP and by disturbing the cytoskeleton, which results in microvilli effacement and consequent impairment of bile acid and organic anion transport.

Generation of pro-inflammatory state. In sepsis, Kupffer cells release pro-inflammatory cytokines, reactive oxygen...
Nitric oxide promotes sepsis-associated IL-6 contributes to gamma-glutamyl transferase (GGT), aspartate aminotransferase (AST), alanine aminotransferase (ALT). On pathological specimens, bile acids have been noticed both in the bile ducts and in the liver cells cytoplasm. Bile acids can be found in the perisinusoidal spaces and are taken up by the Kupffer cells, leading to their hyperplasia. Other findings in sepsis-associated cholestasis include mononuclear cells infiltrating portal space, steatosis, dilated portal, and periportal bile ducts.

Liver histological changes include Kupffer cell hyperplasia, cell infiltration, and dilated biliary ductules lined by cells topped by distorted microvilli. Sepsis may damage sinusoidal perfusion, leading to cholestasis with consequent accumulation of organic anions. Various combinations of changes in liver enzymes and histology are reported to occur in sepsis-induced cholestasis: (i) high conjugated bilirubin and almost normal ALT, ALP, and prothrombin time; (ii) increase in total bilirubin, GGT, and ALP, with normal ALT and INR; (iii) high total bilirubin and ALP with near-normal ALT and AST; (iv) liver histological changes and reactive intrahepatic cholestasis.

Sepsis-induced cholestasis may result from the direct action of the bacterial components or from the immune response to infection. The advent of cholestasis is associated with higher mortality in patients with sepsis. Sepsis-induced cholestasis seems to correlate with old age, organ dysfunction markers, and APACHE II and SOFA scores.

Conclusions

Cholestasis and sepsis occurring simultaneously may lie not only in a synchronous relation by originating from a common etiology (such in the case of cholangitis), but also in a diachronic relation, one (sepsis) being the cause of the other (cholestasis); the diachronic relationship is actually more common than the synchronous one and should therefore be the first suspicion when the serum level of biliary enzymes is increased, sometimes accompanied by conjugated hyperbilirubinemia, in a septic patient.

Numerous studies have shown that LPS-induced sepsis may lead to cholestasis by: (i) interfering with: (a) membrane pumps’ activity, (b) aquaporins, and (c) nuclear receptors involved in inflammatory responses; (ii) activating LPS/TLR4 and PI3K signaling pathways; (iii) generating a pro-inflammatory state. The reality of sepsis-associated cholestasis is supported by the conclusions of both experimental and human observational studies, and is corroborated by case reports.

Mechanisms interfering with aquaporins. Another mechanism by which LPS provokes cholestasis relies on aquaporins. By downregulating aquaporin-8, TNF-α decreases canalicular membrane water permeability, thus contributing to sepsis-associated cholestasis. Furthermore, adenovirus-mediated transfer of human aquaporin-1 gene into the liver cells may reduce LPS-induced cholestasis by improving BSEP activity.

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