SEPSIS IN COMMON SERIOUS HEPATO-BILIARY DISORDERS: A REVIEW ARTICLE

Ahmed S. Alsheikhly, FRCSI, CABS, MISS-CIS; Wedad S. Alani, Msc, Mphil

ABSTRACT

Assessing hepatobiliary function among critically ill patients remains challenging, and neither static nor dynamic tests can be considered a gold standard. This issue could contribute to an underestimation of the frequency and importance of this system dysfunction during the course of sepsis. Because hepatic and biliary dysfunction is strongly associated with high morbidity and mortality in patients with sepsis, the ability to accurately assess these functions is of critical interest. During sepsis, the liver plays a key role in the pathophysiology of this disorder. It is implicated in the host response, participating in the clearance of the infectious agents and their products. Sepsis also can cause hepatobiliary damage through hemodynamic alterations or through direct or indirect assault on the hepatocytes or through both. Accordingly, hepatobiliary dysfunction induced by sepsis is recognized as one of the components that contribute to the severity of the disease. In this review article, we discuss the epidemiology, diagnostic tools, and some impact on outcome as well as the pathophysiological aspects, including the cellular events and clinical picture leading to hepatobiliary dysfunction. Finally, therapeutic considerations with regard to the weakness of the pertinent specific approach are examined.
INTRODUCTION

Sepsis and septic shock remains a prickly issue in public health care because of their high mortality rate, which has been reported to be between 30% and 50%.\(^1,2\) Sepsis can result in multiple organ dysfunction syndrome (MODS), whose severity accounts for a high morbidity and mortality rate. During sepsis, biliary system dysfunction is one of the MODS components and usually is associated with a poor prognosis but its precise incidence remains unclear. Whereas the liver plays a principle role in regulating a wide range of key metabolic, homeostatic, and host-defense activities, liver dysfunction is commonly viewed only as a consequence of shock and initial tissue hypoperfusion. In fact, the injured liver may be considered one of the main actors in the genesis and amplification of multiple organ failure. However, the lack of reliable diagnostic tools does not allow detection of early liver dysfunction.\(^2\)

This concise overview article aims to describe the role, epidemiology, pathophysiology and prognostic value of dysfunction during serious hepatobiliary disorders, then to review the aspects and clinical features of these dysfunctions, and finally propose a main therapeutic axis and perspectives on specific treatment.

1. Hepatobiliary sepsis and liver cirrhosis: Liver cirrhosis occurs in response to chronic liver injury and involves the development of regenerative nodules surrounded by fibrous bands in the liver parenchyma. This in turn causes distortion of the hepatic vasculature, leading to portal hypertension and end stage liver disease. Cirrhosis leads to shunting of portal and arterial blood into the hepatic central veins, thus compromising the exchange between hepatic sinusoids and hepatocytes.

Cirrhosis causes an impaired hepatocyte activity, portal hypertension and an increased risk of hepatocellular carcinoma. Hepatic vascular alterations and portal hypertension will in turn cause splanchnic vasodilatation, vasoconstriction and decreased renal perfusion, water and salt retention and an increased cardiac output.\(^3\)

The estimated prevalence of cirrhosis in the United States is 0.15%,\(^4\) though this may be an underestimate due to the high prevalence of undiagnosed cirrhosis in hepatitis C and Non-Alcoholic Steatohepatitis (NASH). Similar numbers have been reported from Europe, and numbers are even higher in most Asian and African countries where chronic viral hepatitis B or C are frequent. Since compensated cirrhosis is frequently not detected until routine investigations are performed, a reasonable estimate is that up to 1% of the world population may have histological cirrhosis. Alcoholic liver disease and hepatitis C are the commonest causes of cirrhosis in the Western world, while hepatitis B is the most common cause in most parts of Asia and sub-Saharan Africa. Cryptogenic cirrhosis (cirrhosis without a recognized cause) is nowadays rarely diagnosed, particularly after the identification of the hepatitis C virus in the late 1980s and with the identification of nonalcoholic steatohepatitis in obese and diabetic subjects.\(^3\)

Bacteraemic infections are more frequent in patients with hepatic cirrhosis. 9% of the overall number of bacteraemic episodes in newly-admitted patients occur in cirrhotic patients\(^5\) and 46% of cirrhotic patients have bacterial infections on admission.\(^6\) Advanced cirrhotics are more likely to have the systemic inflammatory response syndrome. This syndrome correlates with bacterial infection at admission and has been shown to be associated with a poor outcome.\(^7\) Animal studies have identified the gut as the principal source of infection in liver cirrhosis, mainly through bacterial overgrowth and translocation in the small bowel. However, cultures of small intestinal mucosal bacteria in cirrhotic patients have shown that these microbiodata are qualitatively and quantitatively normal. This has shifted attention towards factors that decrease gut integrity, or alter the removal of translocating bacteria as causative factors of bacteraemia in cirrhosis.\(^8\) It is hypothesized that the intestine is more permeable in cirrhosis, allowing bacteria easy access into the circulation through the gut mucosa with consequent macrophage activation. This permeability is further increased in patients with portal hypertension. Serum levels of interleukin-6 and soluble receptors of tumor necrosis factor were shown to be significantly higher in HIV-HCV co-infected and HCV mono-infected patients with decompensated cirrhosis when compared with those with compensated liver
disease.\textsuperscript{9} This susceptibility was also demonstrated in non-alcoholic steatohepatitis.\textsuperscript{10} In patients with cirrhosis and severe sepsis, high production of proinflammatory cytokines seems to cause a deterioration in liver function and predisposes to the development of shock, renal failure, acute lung injury or acute respiratory distress syndrome, coagulopathy, or hepatic encephalopathy. Variants of the NOD2 gene (100fs and G908R) appear to increase bacterial translocation in cirrhotics and have been associated with spontaneous bacterial peritonitis in a recent study.\textsuperscript{11} There is an increased risk for culture positive spontaneous bacterial peritonitis and infected ascites in cirrhotic patients with these variants.\textsuperscript{11}

The second theory is that patients with chronic liver disease tend to have impaired bacterial clearance. This was demonstrated when quantitative real-time polymerase chain reaction (PCR) using primers that amplify all known bacteria was used to measure bacteraemia following tooth-brushing. The investigators showed greater than 75% bacteraemia following tooth-brushing, but while control subjects were able to clear this bacteraemia, subjects with cirrhosis had prolonged bacteraemia, suggesting that cirrhotic patients may be more susceptible to sepsis because of ineffective bacterial clearance.\textsuperscript{12}

The mortality rate of patients with liver cirrhosis is significantly higher than that of patients with other diseases when they develop bacteraemia, and underlying cirrhosis is an independent risk factor for mortality in bacteraemia patients. In-hospital mortality rate in patients with liver cirrhosis and sepsis was shown to be up to 30%,\textsuperscript{13-16} with another 30% dying by 1 year.\textsuperscript{16} Factors which are significantly associated with in-hospital mortality are the presence of more than 1 site of infection, pneumonia, Child’s C status and a model for end-stage liver disease (MELD) score of 17 or more.\textsuperscript{13} In-hospital mortality rate increases as the number of factors increases (7% with one factor, 21% with two factors, 87% with three factors and 100% with four factors).\textsuperscript{13} The initial CRP level does not predict mortality secondary to sepsis in liver cirrhosis patients. However, serial CRP measurements during the first week of antimicrobial therapy may be a useful prognostic factor for mortality in cirrhotic patients.\textsuperscript{14} In a nationwide Korean surveillance study comparing bacteraemia in patients with liver cirrhosis with bacteraemia in patients with other liver diseases, patients with cirrhosis were shown to be more likely to have Klebsiella pneumonia bacteraemia (20.1% vs. 14.3%, \( p=0.018 \)) but less likely to have coagulase-negative staphylococcal bacteraemia (5.1% vs. 10.4%, \( p=0.028 \)).\textsuperscript{14}

One of the sequelae of cirrhosis is the development of ascites. Patients with ascites have an increased risk of developing spontaneous bacterial peritonitis (SBP) with a prevalence of 10-30%. Even with early diagnosis and management of spontaneous bacterial peritonitis, mortality is still 31% at 1 month and 66% at 12 months.\textsuperscript{16} SBP is a very common bacterial infection in patients with cirrhosis and ascites.\textsuperscript{17} Bacterial translocation is believed to be responsible for the first step in the pathogenesis of spontaneous bacterial peritonitis. Translocation is only possible because of the concurrent failure of the defensive mechanisms in cirrhosis. Research has confirmed an increased bacterial translocation in cirrhotic rats.

There is also pronounced impairment of gastrointestinal tract motility in cirrhosis. A disturbance of the gut microflora thus occurs and this, in association with changes in the permeability of the gastrointestinal tract, causes the passage of microorganisms and endotoxins to the mesenteric lymph nodes.\textsuperscript{18} The diagnosis of SBP is based on diagnostic paracentesis. Half the episodes of SBP are present on hospital admission while the rest are acquired during hospitalization.\textsuperscript{19} SBP may present with peritonitic signs pain, tenderness, vomiting, ileus, fever, elevated white cell count, tachycardia, hypotension, worsening of liver function, hepatic encephalopathy, renal failure and gastrointestinal bleeding. However, cirrhotic patients with SBP may be completely asymptomatic. Empirical antibiotics should be started immediately following the diagnosis of SBP. The first line antibiotic treatment in SBP as the third generation cephalosporins, as the commonest causative organisms are Gram-negative aerobic bacteria.\textsuperscript{20} Other options include co-amoxiclav, ciprofloxacin and ofloxacin (though quinolones should not be used in patients who are using these antibiotics for SBP prophylaxis, in areas where there is a high prevalence of quinolone resistance.
or in nosocomial SBP). Antibiotics are effective in the management of SBP in approximately 90% of patients. Failure of antibiotic therapy usually occurs due to bacterial resistance or because of missed secondary bacterial peritonitis. If secondary bacterial peritonitis has been excluded, the antibiotic needs to be changed according to the culture and sensitivity results of the isolated organisms, or else modified to an alternative empiric broad spectrum agent.\textsuperscript{21}

Hepato-renal syndrome (HRS) refers to the rapid deterioration of renal function in patients with liver cirrhosis. It occurs in approximately 30% of patients with SBP treated with antibiotics alone and is associated with a very poor survival. Albumin administration (1.5 g/kg at diagnosis and 1 g/kg on day 3) decreases the frequency and mortality of HRS in cirrhotic patients with SBP. For this reason, the European Association for the Study of the Liver (EASL) guidelines recommend that all cirrhotic patients who develop SBP should be treated with intravenous albumin and empirical antibiotics.\textsuperscript{21} In patients at high risk of developing SBP, antibiotic prophylaxis is recommended.\textsuperscript{21} Since it is hypothesized that SBP occurs following the translocation of enteric Gram negative bacteria from the gut to the circulation, the ideal prophylactic antibiotic needs to be effective at decreasing the amounts of these organisms in the gut without altering the protective anaerobic flora. The use of prophylactic antibiotics should be strictly restricted to patients at high risk of SBP to decrease the risk of developing resistance. These high-risk patient populations include cirrhotics with acute gastrointestinal hemorrhage, those with low total protein content in ascitic fluid and no prior history of SBP (primary prophylaxis) and patients with a previous history of SBP (secondary prophylaxis). In such high-risk patients, antibiotics should be started immediately (i.e. following upper gastrointestinal bleed, after a first episode of SBP or upon finding low total protein) and are recommended life-long, or until liver transplant is performed.

Bacterial infection is a major problem in cirrhotic patients with acute gastrointestinal hemorrhage, occurring in 25-65% of these patients.\textsuperscript{22} Bacteraemia in patients with variceal hemorrhage is associated with a decreased ability to control bleeding,\textsuperscript{23} an increased rebleeding rate, and increased hospital mortality.\textsuperscript{24} Antibiotic prophylaxis has been shown to prevent infection in patients with gastrointestinal bleeding and decrease the rate of rebleeding. A meta-analysis of five studies performed in patients with gastrointestinal bleeding\textsuperscript{25-29} has shown that antibiotic prophylaxis significantly decreased both the incidence of severe infections (SBP and/or sepsis) and mortality. The preferred antibiotic for SBP prophylaxis is norfloxacin (400 mg/12 h orally for 7 days) which sepsis, the liver and the gut provides selective intestinal decontamination. Norfloxacin is a quinolone antibiotic with antibacterial activity against Gram-negative bacteria but not against Gram-positive cocci or anaerobic bacteria. However, in view of the increasing incidence of quinolone-resistant bacteraemia\textsuperscript{30,32} and because a substantial number of infections in patients with gastrointestinal hemorrhage are caused by Gram-positive bacteria, ceftriaxone has been studied as a prophylactic agent in cirrhotics with gastrointestinal bleeding. A study comparing oral norfloxacin with intravenous ceftriaxone for the prophylaxis of bacterial infection in cirrhotic patients with gastrointestinal bleeding showed that ceftriaxone was more effective than norfloxacin in the prevention of infections.\textsuperscript{33} The main disadvantage with ceftriaxone is that it must be given intravenously and is therefore limited to hospital use. Cirrhotic patients with low protein concentrations (<10 g/L) in their ascitic fluid and/or high serum bilirubin levels are at an increased risk of developing SBP.\textsuperscript{34} Studies have shown that norfloxacin (400 mg/day) is effective as a prophylactic agent against SBP and improves survival in patients with low total protein in their ascitic fluid.\textsuperscript{35-37} Following an episode of SBP, the cumulative recurrence rate at 1 year is approximately 70%,\textsuperscript{38} with a 1-year survival probability of 30-50% and a 2-year survival probability of 25-30%. Prophylactic norfloxacin (400 mg/day, orally) reduces the risk of recurrent SBP. Other antibiotics which may be used in SBP prophylaxis after the first episode of SBP include ciprofloxacin (750 mg once daily, orally) or co-trimoxazole (800 mg sulfamethoxazole and 160 mg trimethoprim daily orally), but the evidence with these antibiotics is not as strong as with norfloxacin. The EASL guidelines also recommend that patients recovering from SBP should be considered for liver transplantation.\textsuperscript{21}
The American Association for the Study of the Liver and the British Society of Gastroenterology guidelines\textsuperscript{39,40} have similar recommendations for the management of spontaneous bacterial peritonitis and its prophylaxis. Terlipressin is a vasoactive agent used in patients with septic shock and which has a selective affinity to vascular V1 receptors. It is an effective pressor agent in patients with catecholamine-unresponsive septic shock. Additional studies are needed to identify the best time to start terlipressin, the efficacy and dosages of continuous infusion versus bolus administration as well as the safety and efficacy of this compound in comparison with other vasoactive drugs.\textsuperscript{41,42}

2. Hepatobiliary sepsis and acute cholangitis:

Acute cholangitis and biliary sepsis are severe infectious diseases, frequently observed in patients with obstructive jaundice. The presence of bacteria in the biliary tract increases in the presence of biliary obstruction, particularly in the presence of foreign bodies like stones, but also in the presence of malignant obstruction secondary to pancreatic head carcinoma or cholangiocarcinoma. Reflux of bacteria from the biliary tract to the systemic circulation is believed to be the primary etiologic factor in bacteraemia and the development of sepsis in cholangitis. Biliary tract obstruction is the initiating factor in the pathogenesis of acute cholangitis causing elevated intraluminal pressures, and subsequent infection of the normally sterile bile. Bacteria may infect bile retrogradely from the gut through the haematogenous route or via lymphatics. The presence of bacteria in the biliary tract (bactibilia) increases rapidly with the development of biliary obstruction, in particular in the presence of foreign bodies like stones. Biliary obstruction causes local and systemic changes in the host defenses. There is decreased bile passage into the small bowel and decreased secretory IgA from the gastrointestinal tract. This promotes changes in the gut bacterial flora which in turn cause loss of mucosal integrity, decreased endotoxin inactivation and bacterial overgrowth. These changes cause portal bacteremia, endotoxemia and increased translocation of endotoxins to the liver, resulting in sepsis and also decreasing the hepatic Kupffer cell function in these patients. In view of these pathophysiological changes, early biliary decompression is necessary to restore normal function of the Kupffer cells in the liver and thus prevent functional alterations in the liver because of chronic, long-standing obstruction and cholestasis. Early biliary decompression also decreases postoperative morbidity and mortality.\textsuperscript{43} The increased expression of triggering receptor expressed on myeloid cells (TREM-1) in the peripheral blood mononuclear cells of sepsis patients with acute cholangitis suggests an important role of TREM-1 in the development of acute cholangitis.\textsuperscript{44,45}

The predominant pathogens cultured from bile specimens in patients with obstructive jaundice (samples obtained at endoscopic retrograde cholangio-pancreatography ERCP) or percutaneous transhepatic biliary drainage) were gram-negative bacteria (68%) followed by gram-positive bacteria (26%), anaerobes (3%) and Candida (3%).\textsuperscript{46} The predominant gram-negative pathogens were Escherichia coli, Acinetobacter baumannii complex, Klebsiella pneumonia and Enterobacter cloacae. The most effective antibiotics against the gram-negative bacteria were shown to be imipenem (susceptibility: 97.9%), cefoperazone/sulbactam (89.4%), piperacillin/tazobactam (85.1%) and cefepime (85.1%).\textsuperscript{46} Another study on patients with acute cholangitis\textsuperscript{47} confirmed that gram-negative organisms are responsible for most bacteraemias (95%), with the commonest ones being Escherichia coli (62%), and Klebsiella pneumonia (26%). This study found that bacteraemias caused by biliary tract infection represented 5.5% of all causes of bacteraemias. Thirty-day mortality among these patients was 14% with 57% of these patients dying secondary to septic shock.\textsuperscript{47} The management of ascending cholangitis involves the use of appropriate antibiotics and drainage of the biliary tract. Treatment should target Enterobacteriaceae with a cephalosporin, and if the patient becomes hypotensive, an aminoglycoside effective against ESBL producing E. coli or Klebsiella pneumonia should also be administered. Biliary drainage, by ERCP or percutaneous transhepatic cholangiography, is frequently needed for adequate biliary decompression.\textsuperscript{47}

Patients undergoing ERCP tend to be at high risk of sepsis because of the underlying biliary obstruction which predisposes to cholangitis and because of the
invasive nature of the procedure. The use of prophylactic antibiotics before ERCP is therefore recommended by all major international gastroenterological societies, especially in the presence of an obstructed biliary system.\textsuperscript{48-50} The use of prophylactic antibiotics attempts to decrease or eliminate the incidence of cholangitis, sepsis and pancreatitis after the procedure.\textsuperscript{48} During ERCP, bacteraemia is believed to occur because of the injection of contrast and the iatrogenic introduction of foreign substances in the bile of patients who already have underlying pathologies such as biliary obstruction or pancreatic pseudocysts. Bacteraemia during ERCP is relatively uncommon in patients who do not have evidence of biliary or pancreatic ductal obstruction.\textsuperscript{49} Bacteraemia is however well recognised during ERCP for biliary obstruction with pancreatic or biliary infection occurring following 0.4-0.8\% of endoscopic biliary procedures. These episodes must always be taken seriously because of the associated 8-20\% mortality risk.\textsuperscript{50} Biliary dilatation, the insertion of biliary stents, prolonged procedure time and hilar cholangiocarcinoma have been shown to give an increased risk of post-ERCP cholangitis.\textsuperscript{51}

The British Society of Gastroenterology and the American Society of Gastrointestinal Endoscopy have similar recommendations on the prophylactic use of antibiotics for ERCP.\textsuperscript{52,53} Patients with ongoing cholangitis who will be needing therapeutic endoscopic intervention should always be on appropriate antimicrobial therapy upon admission to hospital. Additional pre-ERCP antimicrobial prophylaxis is not normally recommended for those who are already taking antibiotics therapeutically for cholangitis. Routine prophylaxis for ERCP is not usually necessary, unless it is not possible to adequately decompress the biliary system during the procedure, in which case a full antibiotic course is indicated until adequate drainage can be achieved. Indications for routine antibiotic prophylaxis during ERCP include specific biliary disorders, such as primary sclerosing cholangitis or hilar cholangiocarcinoma (where complete biliary drainage will be difficult or impossible to achieve during one procedure), patients with a history of liver transplantation, patients with pancreatic pseudocysts, patients with severe neutropenia and/or advanced haematological malignancy. When antibiotic prophylaxis for ERCP is given, oral ciprofloxacin or intravenous gentamicin is usually recommended.

**CONCLUSIONS**

Sepsis in hepatobiliary dysfunction is a frequent event and is strongly associated with high morbidity and mortality. During the past few decades, its pathophysiology, including hypoxic and cholestasis aspects, has been better understood. However, the tools to diagnose liver dysfunction earlier and more accurately remain limited. At this time, the treatment of these dysfunctions is included only in the general therapeutic steps on sepsis syndrome management. An earlier and better identification of patients with mentioned dysfunctions is warranted and may be the way to evaluate new therapeutic strategies and further improve prognostic goals.

**REFERENCES**


