Bacterial infections are very frequent complications of liver cirrhosis and now represent a major precipitating cause of death in patients with advanced disease. They are responsible for admission in approximately 10% of hospitalized cirrhotic patients, and up to 40% of those admitted because of an ongoing complication have an underlying infection. The most involved sites are ascites (spontaneous bacterial peritonitis (SBP)) and urinary tract, followed by respiratory tract, skin and blood. Nearly half of the infections acquired in the community are healthcare-related, while about one-third of patients develop nosocomial infections, a far higher incidence than that seen in the general hospital population. Patients with cirrhosis have an increased risk to develop sepsis, sepsis-induced organ failure and death, although classical diagnostic parameters are often inadequate to achieve a correct and timely diagnosis. The in-hospital mortality of cirrhotic patients with bacterial infection reaches up to 30% and exceeds 70% in the cases with septic shock, a much higher incidence compared to the non-cirrhotic counterpart. Prognosis is often dismal for respiratory infections, bacteremia and infections caused by *Clostridium difficile*. Finally, bacterial infections significantly prolong the hospital stay, increase costs, and lead patients awaiting liver transplantation to be de-listed.

We report a case of a 54-year old man with hepatitis C-related cirrhosis admitted to the hospital for worsening of his ascites and onset of hepatic encephalopathy, an excellent example for the management of sepsis in cirrhosis and the limits of current knowledge.

**Case Report**

A 54-year old man with hepatitis C-related cirrhosis was admitted to the hospital. During the last week,
his ascites had worsened with an increase in body weight of 6 kg and neuropsychiatric abnormalities had appeared (irritability, aggressiveness, sleep-wake cycle inversion, flapping tremor). His medical history showed he had developed ascites six months earlier with an episode of SBP and, after resolution he started antibiotic prophylaxis with norfloxacin. During the last three months his Model for End-Stage Liver Disease (MELD) score ranged between 14 and 15. Approximately two weeks before admission, during the assessment for liver transplantation, he spent two days in hospital for a coronary angiography that turned out to be negative. He had medium-risk esophageal varices and was receiving propranolol (40 mg/day) and spironolactone (200 mg/day) plus furosemide (50 mg/day) to treat his ascites.

On admission, there was no evidence of gastrointestinal bleeding, alcohol abuse or assumption of hepatotoxic drugs. The patient had an axillary temperature of 37.2°C, pulse was 78 beats per min, arterial blood pressure 115/70 mmHg (mean arterial pressure 85 mmHg), respiratory rate 22 breaths per min, and 95% peripheral oxygen saturation (SpO2). On physical examination, the patient appeared slowed down and slightly confused, and findings were grade II ascites and asterixis, while thoracic and abdominal findings were apparently normal. Laboratory investigation revealed thrombocytopenia (platelet count \(\times 10^9/L\)) and not leukocytosis (white-cell blood count 6.7 \(\times 10^9/L\)), with 78% neutrophil granulocytes. The serum parameters of renal function were within the normal range [creatinine 1.1 mg/dL, blood urea nitrogen (BUN) 48 mg/dL] with mild hyponatremia (132 mmol/L) and normal potassium level (4.3 mmol/L). Total bilirubin was 2.4 mg/dL, albumin 2.9 g/dL and international normalized ratio (INR) 1.47 (MELD score 15). C-reactive protein (CRP) was increased at 1.3 mg/dL (normal level <0.8 mg/dL). Urine tests turned out to be normal and, through a paracentesis, 3 L of ascitic fluid were evacuated and SBP was excluded since white cell count in the ascites showed a neutrophil concentration of 133/\(\mu\)L.

A chest X-ray was subsequently programmed for the next day and a specific therapy for hepatic encephalopathy with lactulose plus oral rifaximin and bowel enemas was started, achieving only a partial response in the following hours. Twenty-four hours after admission, the patient complained of dyspnea, and SpO2 dropped to 80%. On physical examination, moderate arterial hypotension (100/65 mmHg) and tachycardia (112 bpm) were recorded, respiratory rate was 27 per minute, axillary temperature was 38.6°C and hepatic encephalopathy had worsened with development of severe confusion and space-time disorientation. An arterial blood gas (ABG) was performed:

- \(\text{PaO}_2\) was 56 mmHg, \(\text{PaCO}_2\) 31 mmHg, pH 7.35, \(\text{HCO}_3\) 17 mEq/L and lactate 3.1 mEq/L. Oxygen administration with a fraction of inspired oxygen (FiO\(_2\)) of 30% with a Venturi mask was started, thus succeeding in bringing SpO2 over 90%. The chest X-ray showed a right basal and left apical inflammatory infiltrates. New laboratory investigation revealed the onset of leukocytosis (white-cell blood count 12.1 \(\times 10^9/L\)) and mild renal impairment (serum creatinine 1.4 mg/dL and sodium 130 mmol/L). CRP rose to 3.4 mg/dL. Liver function also worsened: total bilirubin was 3.2 mg/dL, albumin 2.8 g/dL, INR 1.9 (MELD score reached 21). The physician made the diagnosis of bilateral pneumonia and expectorated sputum and blood samples were collected for culture. Finally, he prescribed intravenous (i.v.) levofloxacin (500 mg i.v. bid).

Forty-eight hours after admission, the patient continued to complain of dyspnea, while, with a FiO\(_2\) of 30%, the SpO2 was stable above 90%. Despite hemodynamic and respiratory stability, new laboratory tests showed the worsening of the renal function (creatinine rose to 1.7 mg/dL and BUN to 82 mg/dL) with hypokalemia (serum sodium 125 mmol/L). Twenty-four h urine output was approximately 400 mL. During the third day, because of the worsening of renal function, all diuretic drugs were stopped, a bladder catheter was placed, and volume expansion with albumin (1 g/kg/day) was started.

Furthermore, preliminary results of the culture of expectorated sputum showed the presence of \textit{Staphylococcus aureus} and a second chest X-ray revealed bilateral multiple infiltrates. A diagnosis of \textit{Staphylococcus pneumonia} was made and linezolid i.v. (600 mg bid) was added to treatment.

On the fourth day, the patient maintained a good hemodynamic compensation (arterial blood pressure 105/70), but renal failure worsened (24-h urine output dropped to 200 mL and serum creatinine rose to 2.2 mg/dL), while leukocytosis (white-cell count 13.6 \(\times 10^9/L\)) and elevated CRP (7.9 mg/dL) persisted. New urine tests excluded the presence of proteinuria and microhematuria. An abdominal ultrasound showed the presence of abundant ascites with the spleno-mesenteric portal venous axis patent; the kidneys appeared normal, in the absence of dilatation of the urinary tract and with preserved parenchyma.

Despite volume expansion, 24 h later, the physician witnessed a further deterioration of renal function, with a creatinine level of 2.9 mg/dL, sodium 121 mmol/L and potassium 5.8 mmol/L. Given the rapid increase in creatinine without apparent renal organic damage, a diagnosis of hepatorenal syndrome (HRS) type I was made and treatment with albumin (40 g/day) and terlipressin (3 mg/day) was started.

In the evening, SpO2 dropped to 86% and FiO\(_2\)
was elevated at 40% and then at 50%. Despite the elevation of the oxygen flow, SpO2 remained stable at around 86-88%. A new ABG showed respiratory deterioration with the addition of a component of metabolic acidosis (PaO2 58 mmHg, PaCO2 57 mmHg, pH 7.07, lactate 7.3 mEq/L and HCO3 15 mmol/L). The ratio of partial pressure arterial oxygen and fraction of inspired oxygen was 116, thus indicative of acute respiratory distress syndrome. The patient was, therefore, admitted to the Intensive Care Unit. Protective mechanical ventilation with low tidal volumes (6 mL/kg) and limited end-inspiratory plateau pressures (<30 cm H2O) was started. Unfortunately, the patient failed to improve with a progressive worsening of the respiratory, renal and hemodynamic parameters, and eventually died because of cardiorespiratory arrest on Day 6 of hospitalization.

Discussion

The present clinical case highlights the problems that can be encountered by a physician in the diagnosis and management of a patient with liver cirrhosis and bacterial infection.

Pitfalls of the diagnosis of bacterial infection in cirrhosis

On admission, the patient presented with ascitic decompensation and overt hepatic encephalopathy, but no clear clinical and laboratory evidence of infection. It is well known that acute deterioration of liver disease can be precipitated by SBP. According to the current guidelines, the physician in charge performed a diagnostic paracentesis that was negative for infection since polymorphonuclear count was below 250 cells/mm3. He also asked for a chest X-ray to be performed the next day. However, beside SBP, other microbial infections can have very serious adverse consequences, precipitating HRS and multiple organ failure, and their presence should always be rapidly ruled out whenever cirrhotic patients are admitted to the hospital with an acute clinical deterioration, even if the traditional signs and symptoms suggestive of infection are not detected.

Thus, in the present case, an urgent chest X-ray would probably have allowed a prompt diagnosis of pneumonia to be made, avoiding the delay in starting antibiotic treatment. Although a correlation between delay in starting therapy and increased mortality has been demonstrated only in the general population, this is likely to be even more valid in cirrhotic patients who are more prone to develop sepsis, septic shock and multiple organ failure.

Pitfalls of the diagnosis of sepsis in cirrhotic patients

On admission, the patient presented only one out of four of the established criteria to define the systemic inflammatory response syndrome (SIRS): his respiratory rate was more than 20 breaths per minute, while his heart rate was lower than 90 beats per min, axillary temperature was below 38°C and leukocyte blood count was normal. As a result, the patient did not fulfil the established criteria for SIRS (Table 1). However, in patients with cirrhosis, recognition of SIRS and, therefore, sepsis can be difficult and sometimes misleading: tachycardia can be part of the hyperdynamic circulatory syndrome or can be prevented by beta-blockers, hyperventilation can be attributable to hepatic encephalopathy, hypersplenism and relative hypothermia may prevent full blown leukocytosis and fever.

Inflammatory serum markers are particularly helpful in recognizing sepsis. However, in cirrhotic patients, studies of diagnostic accuracy and threshold values of CRP and procalcitonin (PCT) did provide homogeneous results. In particular, since CRP is produced predominantly in the liver, its level should be interpreted with caution in patients with advanced liver disease. On the other hand, PCT is produced ubiquitously by thyroidal and extra-thyroidal tissues, including the liver, and some studies have shown its superiority compared to CRP. In the present case, the physician used CRP to follow the course of the infectious process and serum PCT was not measured.

Table 1. Diagnostic criteria of sepsis and pitfalls in cirrhotic patients.

| Infection (documented or suspected) plus two or more of the following | Pitfalls of the diagnosis of sepsis in cirrhotic patients |
|----------------------------------------------------------------------|--------------------------------------------------------|
| - Temperature >38°C or <36°C                                       | - Hypotemia                                            |
| - Heart rate >90 bpm                                               | - Hyperdynamic circulatory syndrome                     |
| - Use of β-blockers                                                | - Use of β-blockers                                    |
| - Respiratory rate >20 breaths/minute, or PaCO2 <32 mmHg           | - Hyperventilation in course of hepatic encephalopathy |
| - WBC count >12×10⁹/L; <4×10⁹/L or >10% immature (band) forms      | - Hypersplenism                                         |

WBC, white blood cell count. Modified from Cazzaniga et al., 2009 and Bone et al., 1992.
Therefore, at present, although CRP and PCT can provide useful information to guide diagnosis and therapy of bacterial infection and sepsis, their exact clinical value in the cirrhotic population needs further investigation.\(^1\)

**Was the first-line antimicrobial therapy appropriate?**

Empirical antimicrobial therapy must be selected according not only to the site and severity of infection, but also to the modality of acquisition and the local epidemiological pattern of antibiotic resistance. Furthermore, in patients with cirrhosis, even if effective, aminoglycosides and other nephrotoxic drugs should not be used because of the high risk of renal failure.\(^8\) In the present case, the initial empirical antibiotic therapy with levofloxacin was chosen according to the diagnosis of a community-acquired pneumonia. However, the physician missed the fact that the patient was at risk for healthcare-related pneumonia,\(^9\) since he had been hospitalized to perform a diagnostic coronary angiography two weeks earlier. It is now accepted that patients with community acquired-infections, but recent hospitalization or contact with the healthcare system, present rates of antibiotic resistance similar or close to those of nosocomial infections.\(^10\) As a result, currently recommended first-line antibiotic therapy for community-acquired pneumonia is followed by a reduced resolution rate in the cases of healthcare-related pneumonia and nosocomial infections. Furthermore, cirrhotic patients on long-term norfloxacin prophylaxis are at higher risk of developing infection caused by multiresistant Gram-negative bacteria as well as Gram-positive cocci.\(^11\)

An important fact that has also to be taken into consideration is represented by the major changes in the epidemiology of bacterial infections that have occurred in patients with cirrhosis in the last decade. The extensive administration of prophylaxis of SBP with norfloxacin has led to the emergence of bacterial strains resistant to quinolones, although such prophylaxis still maintains a good effectiveness. At the same time, the widespread use of invasive procedures, previous antibiotic therapy, including aminoglycosides and other nephrotoxic drugs should not be used because of the high risk of renal failure.\(^8\) Thus, an appropriate empirical first-line antibiotic therapy should have included meropenem or ceftazidime plus levofloxacin or ciprofloxacin, in association to a glycopeptide (vancomycin or linezolid) since risk factors for MRSA were also present (recent invasive procedures, previous antibiotic therapy, including norfloxacin, and nasal MRSA carriage).\(^3,13\)

**Did the patient develop hepatorenal syndrome?**

When serum creatinine reached 1.7 mg/dL, thus exceeding the threshold for the possible diagnosis of HRS, diuretics were stopped and volume expansion with human albumin was started with good reason. In our patient, serum creatinine rose from 1.1 to 2.9 mg/dL in five days, thus fulfilling, in the absence of signs of organic kidney disease and improvement after volume expansion with albumin, the diagnostic criteria of the International Club of Ascites (ICA) for HRS type 1 (Figure 1). According to the actual international guidelines, the physician started a treatment with terlipressin plus albumin. However, this approach is able to reverse HRS only in 40-50% of the cases and unfortunately this did not occur in our patient.\(^14\)

It has been shown that the higher the levels of serum creatinine at the beginning of treatment the lower is the possibility of HRS reversal.\(^15\) Thus, it can be hypothesized that initiating terlipressin and albumin earlier, when the serum creatinine was lower, would have given this patient a greater chance of response. For the moment, this question remains unanswered but the current criteria for the diagnosis of HRS as defined by the ICA are under revision and we are waiting for up-dated guidelines for HRS treatment.\(^16\)

**Was the administration of albumin indicated at the time of pneumonia diagnosis?**

Bacterial infections can alter the hemodynamic status of cirrhotic patients inducing a marked effective hypovolemia and eventually precipitating renal failure. One-third of patients with SBP do so, and at least half of SBP-induced renal failure is progressive. It has already been demonstrated that intravenous albumin administration reduces both the incidence of renal failure...
and mortality (1.5 g/kg at diagnosis plus 1 g/kg on Day 3) in patients with SBP. Very recently, a prospective study shows some benefit on survival also in non-SBP infections. However, further larger confirmatory studies are needed to support the administration of albumin with bacterial infections other than SBP.

Did the patient present acute-on-chronic liver failure?

The term acute-on-chronic liver failure (ACLF) is used to define an acute deterioration of liver function in patients with cirrhosis and results in one or more organ failures and high short-term mortality. Since it is crucial to identify early the patients at high risk of death requiring specific treatments and/or intensive management, a major point was to rule out the possibility that our patient had an ACLF on admission. Although MELD, rather than Child-Pugh score, retains prognostic power in this setting (at admission Child-Pugh score was B9 and MELD score 14), it has to be outlined that in cases of acute deterioration of cirrhosis, short-term mortality is related to extra-hepatic organ failure rather than to the severity of the liver disease. However, some elements of the scores currently in use do not take into account special features present in patients with cirrhosis. To overcome this limitation, the European Chronic Liver Failure Consortium (CLIF) has recently proposed a modification of the Sequential Organ Failure Assessment (SOFA) score, called the CLIF-SOFA, that has yet to be fully published.

Based on organ failure assessment by CLIF-SOFA, the CLIF consortium has recently defined ACLF and its grading: ACLF Grade 1 is defined by the presence of renal failure, as single organ failure, or a non-kidney organ failure associated with renal dysfunction (identified by serum creatinine between 1.5 and 2.0 mg/dL) and/or hepatic encephalopathy grade I or II. Two organ failures define grade 2 and three or more define grade 3. There is a 28- and 90-day mortality gradient across

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**Figure 1.** Diagnostic workup and criteria for diagnosis of hepatorenal syndrome in cirrhosis (modified from European Association for the Study of the Liver, 2010). Cr, creatinine; HRS, hepatorenal syndrome; US, ultrasound; SBP, spontaneous bacterial peritonitis.
the grades, with a sharp watershed between grade 1 and the absence of ACLF. According to this definition, our patient developed an ACLF grade 3 with three organs failing: lung, kidney and brain, that implies a 28-day mortality rate of over 75%.20

Conclusions

Even when recognized early, the outcome of bacterial infections in cirrhosis remains poor. In our case, the delay in recognizing pneumonia and sepsis and the inappropriate choice of the empirical antibiotic therapy have presumably contributed to such a dismal outcome. However, many other aspects are still controversial and a great effort must be made to improve a timely diagnosis of the complications precipitated by bacterial infections and the related most appropriate management.

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