Severe Sepsis in Cirrhosis

Thierry Gustot,1,3,4,5 François Durand,3,4,5 Didier Lebrec,3,4,5 Jean-Louis Vincent,2 and Richard Moreau3,4,5

Sepsis is physiologically viewed as a proinflammatory and procoagulant response to invading pathogens. There are three recognized stages in the inflammatory response with progressively increased risk of end-organ failure and death: sepsis, severe sepsis, and septic shock. Patients with cirrhosis are prone to develop sepsis, sepsis-induced organ failure, and death. There is evidence that in cirrhosis, sepsis is accompanied by a markedly imbalanced cytokine response (“cytokine storm”), which converts responses that are normally beneficial for fighting infections into excessive, damaging inflammation. Molecular mechanisms for this excessive proinflammatory response are poorly understood. In patients with cirrhosis and severe sepsis, high production of proinflammatory cytokines seems to play a role in the worsening of liver function and the development of organ/system failures such as shock, renal failure, acute lung injury or acute respiratory distress syndrome, coagulopathy, or hepatic encephalopathy. In addition, these patients may have sepsis-induced hyperglycemia, defective arginine-vasopressin secretion, adrenal insufficiency, or compartmental syndrome. In patients with cirrhosis and spontaneous bacterial peritonitis (SBP), early use of antibiotics and intravenous albumin administration decreases the risk for developing renal failure and improves survival. There are no randomized studies that have been specifically performed in patients with cirrhosis and severe sepsis to evaluate treatments that have been shown to improve outcome in patients without cirrhosis who have severe sepsis or septic shock. These treatments include recombinant human activated C protein and protective-ventilation strategy for respiratory failure. Other treatments should be evaluated in the cirrhotic population with severe sepsis including the early use of antibiotics in “non-SBP” infections, vasopressor therapy, hydrocortisone, renal-replacement therapy and liver support systems, and selective decontamination of the digestive tract or oropharynx. (HEPATOLOGY 2009;50:2022-2033.)

Sepsis, which is the host response to infection, is a complex pathophysiologic state characterized by the release of many proinflammatory and anti-inflammatory and procoagulant and anticoagulant substances in response to pathogens. One can identify three stages of severity, namely sepsis, severe sepsis (when acute organ failure is attributed to sepsis), and septic shock (when refractory hypotension requires the use of vasopressor agents (Table 1).

Patients with cirrhosis have increased risk to develop sepsis, sepsis-induced organ failure, and sepsis-related death.1 However, the incidences of sepsis, severe sepsis, and septic shock have not yet been extensively studied. In-hospital mortality of patients with cirrhosis who have
septic shock is higher than in other patients, and exceeds 70%. This review will focus on pathogenesis of sepsis in patients with cirrhosis and the management of sepsis in these patients.

Pathogenesis of Severe Sepsis in the General Population

Before commenting on sepsis in cirrhosis, it is important to have in mind some general information on how microbes trigger severe host inflammation. Microbes express macromolecular motifs, called microorganism-associated molecular patterns (MAMPs). MAMPs are spontaneously recognized by the immune system via receptors, named pathogen recognition receptors (PRRs), e.g., Toll-like receptors (TLRs) (Table 2). PRR engagement leads to immune cell activation characterized by initiation of microbe-killing systems, production and secretion of proinflammatory cytokines and chemokines, enhanced expression of costimulatory receptors essential for efficient T cell activation, production of arachidonic acid metabolites, and initiation of an extrinsic coagulation cascade (e.g., tissue factor). In favorable situations, the microbe-induced immune response results in infection resolution and had no harmful consequences for the host, because inflammation is tightly controlled by different mechanisms triggered by PRRs themselves, including inhibition of the TLR-related intracellular signaling (Fig. 1), production of soluble receptors and antagonists that neutralize proinflammatory cytokines, production of anti-inflammatory cytokines (e.g., interleukin-10 [IL-10]), and specific “silencing” of proinflammatory genes via epigenetic regulations (i.e., histone acetylation/methylation and nucleosome remodeling).

In some cases, the innate immune response to MAMPs is deregulated and accompanied by a markedly imbalanced cytokine response, which converts responses that are normally beneficial for fighting infections into excessive damaging inflammation. This may lead to multiple organ failure and death (Fig. 2).

Table 1. Definitions

<table>
<thead>
<tr>
<th>Condition</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic inflammatory response syndrome (SIRS)</td>
<td>When two or more of the following criteria are met: a. body temperature &gt; 38°C or &lt; 36°C b. tachycardia &gt; 90/minute c. hyperventilation: respiratory rate &gt; 20/minute or arterial hypocapnia &lt; 32 mmHg d. white blood cell count &gt; 12,000/µL or &lt; 4,000/µL or immature forms &gt; 10%</td>
</tr>
<tr>
<td>Sepsis</td>
<td>Documented or suspected infection (considered as pathologic process caused by invasion of normally sterile tissue, fluid or cavity by pathogenic or potentially pathogenic microorganisms) associated with SIRS</td>
</tr>
<tr>
<td>Severe Sepsis</td>
<td>Sepsis associated with organ failure for example based on the Sequential Organ Failure assessment (SOFA) score (See Supporting Information)</td>
</tr>
<tr>
<td>Septic shock</td>
<td>Sepsis associated with circulatory failure characterized by persistent arterial hypotension (decrease of systolic blood pressure below 90 mmHg or &gt; 40 mmHg from baseline, or mean arterial pressure &lt; 60 mmHg despite adequate fluid resuscitation) unexplained by other causes.</td>
</tr>
</tbody>
</table>

Table 2. Family of Pattern Recognition Receptors

<table>
<thead>
<tr>
<th>Receptors</th>
<th>Receptor localization</th>
<th>Ligands</th>
<th>Species</th>
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</thead>
<tbody>
<tr>
<td>TLRs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TLR1/TLR2</td>
<td>Plasma membrane</td>
<td>Triacyl lipopeptides</td>
<td>Bacteria and mycobacteria</td>
</tr>
<tr>
<td>TLR2</td>
<td>Plasma membrane</td>
<td>Peptidoglycans, Zymosan</td>
<td>GPB, Saccharomyces cerevisiae</td>
</tr>
<tr>
<td>TLR3</td>
<td>Endosomal membrane</td>
<td>dsRNA</td>
<td>viruses</td>
</tr>
<tr>
<td>TLR4</td>
<td>Plasma membrane</td>
<td>LPS, Mannan Envelope proteins</td>
<td>GNB, Candida albicans, RSV</td>
</tr>
<tr>
<td>TLR5</td>
<td>Plasma membrane</td>
<td>Flagellin</td>
<td>Flagellated bacteria</td>
</tr>
<tr>
<td>TLR6/TLR2</td>
<td>Plasma membrane</td>
<td>Diacyl lipopeptides</td>
<td>Mycoplasma, Group B Streptococcus</td>
</tr>
<tr>
<td>TLR7</td>
<td>Endosomal membrane</td>
<td>ssRNA</td>
<td>viruses</td>
</tr>
<tr>
<td>TLR8</td>
<td>Endosomal membrane</td>
<td>ssRNA</td>
<td>viruses</td>
</tr>
<tr>
<td>TLR9</td>
<td>Endosomal membrane</td>
<td>CpG DNA</td>
<td>Bacteria and mycobacteria</td>
</tr>
<tr>
<td>TLR11</td>
<td>Plasma membrane</td>
<td>Profilin-like protein</td>
<td>Toxoplasma gondii</td>
</tr>
<tr>
<td>NLRs</td>
<td>cytosol</td>
<td>Bacterial RNA</td>
<td>bacteria</td>
</tr>
<tr>
<td>NALP3</td>
<td>cytosol</td>
<td>iE-DAP</td>
<td>bacteria</td>
</tr>
<tr>
<td>NOD1</td>
<td>cytosol</td>
<td>MDP</td>
<td>bacteria</td>
</tr>
<tr>
<td>NOD2</td>
<td>cytosol</td>
<td>ND</td>
<td>Pseudomonas aeruginosa</td>
</tr>
<tr>
<td>IPAF</td>
<td>cytosol</td>
<td>Flagellin</td>
<td>Legionella pneumophilia</td>
</tr>
<tr>
<td>NAIP5</td>
<td>cytosol</td>
<td>dsRNA</td>
<td>viruses</td>
</tr>
<tr>
<td>RLHs</td>
<td>cytosol</td>
<td>dsRNA</td>
<td>viruses</td>
</tr>
</tbody>
</table>

CpG DNA, unmethylated DNA CpG motif; dsRNA, double-stranded RNA; GNB, Gram-negative bacteria; GPB, Gram-positive bacteria; iE-DAP, γ-D-glutamyl-meso-diaminopimelic acid; IPAF, ICE protease-activating factor; LPS, lipopolysaccharide; MDA5, melanoma-differentiation-associated gene 5; MDP, muramyl dipeptide; ND, not defined; NAIP, neuronal apoptosis inhibitor; NOD, nucleotide-binding and oligomerization domain; RIG-1, retinoic acid-inducible gene-1; ssRNA, single-stranded RNA;
Fig. 1. Prototype of Toll-like receptor (TLR) signaling: TLR4 engagement by the Gram-negative bacteria byproduct lipopolysaccharide (LPS). After LPS recognition, TLR4 dimerizes and undergoes conformational changes, inducing activation of intracellular cascades. TLR4 activation induces phosphorylation of inhibitor of nuclear factor-κB (IκB) by IKK (IκB kinase), its polyubiquitination and degradation, releases NF-κB to the nucleus and induces proinflammatory genes such as tumor necrosis factor (TNF), interleukin-1β (IL-1B), IL-6, IL-8, and IL-12B, encoding TNF-α, IL-1β, IL-6, IL-8, and IL-12p40, respectively. The TLR4-induced activation of mitogen-activated protein kinase (MAPK) signaling pathway via transcription factor activator protein–1 (AP–1) contributes to cytokine gene induction. In addition, the constitutively active glycosogen synthase kinase 3 (GSK3) favors NF-κB–elicited induction of proinflammatory genes. It is important to note that activation of TLR4 also induces negative regulator pathways (pink color) to control the inflammatory process. For example, LPS stimulation induces IL-1 receptor–associated kinase M (IRAK-M) expression blocking NF-κB and MAPK activation by TLR4. TLR4 activation results in phosphoinositol-3 kinase (PI3K)–mediated Akt (protein kinase B) phosphorylation, inducing inactivation of GSK3 and inhibition of proinflammatory cytokine gene transcription. In addition, Akt activation induces NF-κB inhibition via the activation of mammalian target of rapamycin (mTOR). Moreover, TLR4 activation mediates transcription of anti-inflammatory cytokines (e.g., IL-10), reducing the effects of proinflammatory cytokines.

Pathogenesis of Severe Sepsis in Patients with Cirrhosis

I. Prevalence of Infection in Patients with Cirrhosis

Bacterial infections are much more common in patients with cirrhosis than in the general population. Infection is more frequent in patients with decompensated cirrhosis than in those with compensated cirrhosis. The mechanisms of increased susceptibility to infections in cirrhosis are unclear. It has been suggested there is a role for deficiencies in C3 and C4, down-regulation of monocyte human leukocyte antigen–DR expression (and subsequent impaired antigen presentation ability), and impairment of macrophage Fcy receptor–mediated clearance of antibody-coated bacteria. Patients with alcoholic cirrhosis have depressed neutrophil phagocytic and intracellular killing (of Staphylococcus aureus or Escherichia coli).

II. Sites of Infection and Types of Microorganisms

In patients with cirrhosis, the most common infection is spontaneous bacterial peritonitis (SBP), followed by urinary tract infection, pneumonia, bacteremia following a therapeutic procedure, cellulitis, and spontaneous bacteremia. Infections are culture-positive in 50%-70% of cases. The causative organisms of community-acquired infection are Gram-negative bacilli (GNB), especially E. coli, in about 60%, Gram-positive cocci (GPC) in about 30%-35%, and mixed in the last 5%-10%. This pattern is different in nosocomial infections with 60% for GPC and 30%-35% for GNB, as a result of the use of therapeutic procedures and previous antibiotic therapies. Beside E. coli, the most frequently isolated bacteria are S. aureus, Enterococcus faecalis, and Streptococcus pneumoniae. At least in the case of SBP, less-virulent strains of E. coli are responsible of infection when liver function worsens, suggesting that in advanced cirrhosis, bacteria do not need to develop strategies to circumvent host defenses and invade the host. Fungal infections (Candida spp.) are involved in up to 15% of severe sepsis in cirrhosis.

III. Initiation of Sepsis

In patients with cirrhosis and bacterial infection, the initiation of the proinflammatory host response is abnormally enhanced. Indeed, in the early phase of bacterial sepsis, circulating levels of the proinflammatory cytokines tumor necrosis factor–α (TNF–α) and IL-6 are significantly higher in infected patients with cirrhosis than in those without. In vivo TLR4 activation by lipopolysaccharide (LPS, a GNB byproduct) induces higher circulating TNF–α and IL-6 levels in cirrhotic rats than in normal rats. This excessive response to LPS is recapitulated ex vivo with the stimulation of isolated peripheral blood mononuclear cells or monocytes from patients with cirrhosis. The LPS-induced monocyte production of TNF–α is higher in Child C than in Child B cirrhosis, suggesting a role for the severity of liver disease in the excessive innate immune response. The absence of induction of the inhibitor IL-1 receptor–associated kinase M in LPS-stimulated cirrhotic monocytes may at least in part explain TNF–α hyperproduction. Cirrhotic monocytes are also defective in LPS-induced production of anti-inflammatory IL-10. The influence of the cause of cirrhosis on the immune response to LPS is unclear, because this response has been investigated mainly in the context of alcoholic cirrhosis. However, monocytes from patients with primary biliary cirrhosis also exhibit an excessive ex vivo response to LPS.

Little is known about the response against GPC and TLR2 signaling in patients with cirrhosis. TLR2 is over-expressed in peripheral blood mononuclear cells from noninfected patients with cirrhosis. Monocytes from patients with primary biliary cirrhosis produce more IL-8 in response to the GPC byproduct lipoteichoic acid and...
peptidoglycans (Table 2) than do monocytes from control individuals.

IV. Sepsis-Induced Organ Failure in Cirrhosis

Multiple organ failure is common in patients with cirrhosis and severe sepsis. Although the mechanisms leading to this multiorgan failure are poorly understood, an excessive production of proinflammatory cytokines seems to play an important role.

Liver Failure. Sepsis is known to rapidly worsen liver function in patients with cirrhosis. This acute deterioration, called acute-on-chronic liver failure, is associated with poor short-term prognosis.

In addition to the classic theory of “altered liver reserve” in cirrhosis, other alterations as experimental data may explain the higher frequency of acute liver failure during sepsis in patients with cirrhosis. In vivo LPS challenge induces the production of TNF-α which encodes a proapoptotic signal. However, TNF-α does not trigger apoptosis of normal hepatocytes, which are protected by activation of nuclear factor-κB (NF-κB)-dependent antiapoptotic pathways. Such pathways are deficient in cirrhotic animals, due to inhibition of translation of NF-κB–dependent antiapoptotic messenger RNAs into proteins as a result of hepatocyte endoplasmic reticulum (ER) stress. Moreover, livers from LPS-challenged cirrhotic rats exhibit an endothelin-1–mediated neutrophil infiltration and hepatocyte necrosis (which is not observed in LPS-challenged control rats). Taken together, these findings suggest that acute-on-chronic liver failure, at least in the setting of experimental cirrhosis, is a result of hepatocyte death caused by TNF-α–induced apoptosis and/or endothelin-1–elicited necrosis. It should be noted that ER stress also blocks overall protein synthesis (in particular, that of secretory proteins). In LPS-challenged cirrhotic animals, general “shutdown” of hepatocyte protein synthesis may be involved in liver dysfunction. Studies are needed on ER function in patients with cirrhosis and severe sepsis.

Circulatory Failure. Even in the absence of an infection, patients with cirrhosis have a hyperdynamic circulation, characterized by high cardiac output, relatively low arterial pressure, and low systemic vascular resistance. When infection develops in patients with cirrhosis, systemic circulation becomes even more hyperdynamic and hyporeactive to pharmacological doses of α-adrenoreceptor agonists.
In patients without cirrhosis, sepsis may induce profound left ventricular dysfunction with cardiac dilatation contributing to shock. There are no specific data on myocardial function in patients with cirrhosis and septic shock.

Acute Renal Failure. Renal failure occurs in 33% of patients with cirrhosis who have SBP and in 27% of those with sepsis unrelated to SBP. In SBP, there is a good relation between high circulating and ascitic TNF-α, IL-6, and nitric oxide (NO) metabolite levels, arterial underfilling, and development of renal impairment.

Little is known about the mechanisms implicated in sepsis-induced renal failure in cirrhosis. Patients with cirrhosis and severe sepsis (without shock) may have pre-renal failure which may or may not be responsive to fluid therapy. Prerenal failure that does not respond to fluids is called type 1 hepatorenal syndrome (HRS). Patients with cirrhosis and septic shock rapidly develop renal failure due to ischemic acute tubular necrosis.

Respiratory Failure. Pulmonary complications are common in patients with decompensated cirrhosis. Tense ascites reduces the basal lung expansion. Pulmonary cellular baseline functions are also altered in cirrhosis, with reduced alveolar macrophage antibacterial activity, alteration of T lymphocyte subsets, and altered capillary permeability. The alterations of consciousness due to hepatic encephalopathy increase the risk of aspiration pneumonitis. Experimental data show that cirrhosis increases the number of pulmonary intravascular phagocytes, susceptibility to LPS-induced lung edema, and death. All these factors, added to the hyperproduction of proinflammatory cytokines and NO during infection, could explain the high incidence of the acute respiratory distress syndrome (ARDS) in cirrhosis. Patients with cirrhosis and sepsis are more likely to die with ARDS compared to individuals with ARDS who did not have cirrhosis or sepsis. Patients with cirrhosis requiring mechanical ventilation have mortality rates well above 50% and as high as 100% in one series.

Coagulation Failure. Cirrhosis is associated with a decrease in hepatic synthesis of zymogen forms of procoagulant factors (V, VII, X, and prothrombin) and anticoagulant factors (protein C, protein S, and antithrombin). Moreover, thrombocytopenia is common in cirrhosis due to hypersplenism and/or the production of autoantibodies. Severe sepsis, via tissue factor activation, accentuates the deficiency of factors V, VII, X, prothrombin, protein C, antithrombin, and thrombocytopenia in cirrhosis. Fibrin-degradation products are present in 40% of patients with cirrhosis with severe sepsis compared to 14%-32% in the general population with severe sepsis.

Neurological Failure. Acute deterioration of neurological status, called septic encephalopathy, is common in sepsis. Presence of neurological symptoms are observed in 21%-33% of patients with cirrhosis with sepsis and 60%-68% in those with septic shock. Some data suggest a synergism between systemic inflammation and mechanisms that induce hepatic encephalopathy. Provoked hyperammonemia induces significant neuropsychological impairment in patients with cirrhosis who have a systemic inflammatory response syndrome (SIRS), which involves high levels of TNF-α, IL-1β, IL-6, and NO metabolites; this effect is not observed after the resolution of SIRS. Moreover, LPS administration in cirrhotic rats alters consciousness and exacerbates brain edema, an effect which is not observed in control rats. The development of encephalopathy in patients with cirrhosis who have sepsis worsens the prognosis.

Abdominal Compartment Syndrome. Intra-abdominal hypertension is common in patients without cirrhosis with severe sepsis (Supporting Table 2), and may be due to increased gut permeability, vigorous fluid resuscitation, and visceral edema. Intra-abdominal compartment syndrome can induce (1) renal failure by impairing kidney perfusion, (2) respiratory failure by increasing thoracic pressure, and (3) circulatory failure. This syndrome is an independent predictor of mortality. In uninfected patients with cirrhosis, tense ascites increases abdominal pressure and may decrease creatinine clearance. The impact of the intra-abdominal hypertension secondary to ascites in patients with cirrhosis and severe sepsis is unknown.

Management of Severe Sepsis and Septic Shock in Patients with Cirrhosis

Patients with severe sepsis and septic shock require emergency care during the early stage of sepsis (the first 6 hours) followed by critical care in later stages (Fig. 3).

I. Antibiotics

In septic patients, the early initiation of appropriate antibiotics is associated with higher survival rate. A retrospective study by Kumar et al. suggested that each hour of delay decreased survival by 7.6%. The choice of an adequate empiric antimicrobial treatment improves the outcome of patients, and misuse doubles mortality rate.

The use of a strategy which associates urgent diagnostic paracentesis and prompt initiation of adequate empiric broad-spectrum, non-nephrotoxic antibiotic treatment when ascitic fluid neutrophils are >250/mm³ has a beneficial effect on survival in patients with SBP and no shock. Thus, early diagnosis of the site of infection is critical and should be performed in parallel to resuscitation (Fig. 3). Empiric antibiotic treatments for classical
community-acquired bacterial infections in cirrhosis are shown in Table 3. If the causative organism is identified (30%-50% of patients with cirrhosis and sepsis have negative cultures), then the antibiotic regimen should be narrowed to decrease the likelihood of the emergence of resistant organisms.

II. Hemodynamic Therapy

Early Hemodynamic Therapy. In the general population, it may be beneficial during the first 6 hours of severe sepsis and septic shock to maintain mean arterial pressure >65 mm Hg, central venous pressure of 8-12 mm Hg, hematocrit >30%, and central venous oxygen saturation >70%. These goals are achieved using fluids, vasopressors, inotropes, and blood transfusion (Table 4).

Patients with cirrhosis and septic shock have a lower baseline arterial pressure, are more hyperdynamic, have higher central venous oxygen saturation, and lower hematocrit than patients without cirrhosis who have severe sepsis. Therefore, specific goals for early hemodynamic therapy should be established in patients with cirrhosis with severe sepsis and septic shock.

Fluid Therapy. Optimal fluid resuscitation is of great importance in severe sepsis. Currently, there is no evidence that colloids are better than crystalloids. In patients with cirrhosis, an open-label unblinded randomized clinical trial (RCT) in patients with SBP (without shock) treated with cefotaxime showed that the intravenous administration of a 20% albumin solution reduced the incidence of renal failure and decreased mortality rates from 29% to 10%. This effect was not observed in patients with a low risk of mortality (total bilirubin <4 mg/dL and creatinine <1 mg/dL). A recent small unblinded RCT suggested that a 20% albumin solution improved systemic hemodynamics better than a 6% hydroxyethylstarch solution in SBP. There are no data on the effects of intravenous albumin in patients with cirrhosis and bacterial infections unrelated to SBP.
Vasopressors. Norepinephrine and dopamine are first-line vasopressors to correct hypotension in septic shock. In patients with septic shock, mortality rates are similar with the combination of norepinephrine plus dobutamine compared to epinephrine alone. Sepsis-elicited vasopressin deficiency may play a role in the mechanism of septic shock refractory to catecholamine administration. A large double-blind RCT compared the effects of low-dose vasopressin to those of norepinephrine in patients with septic shock who were receiving open-label conventional (catecholamine) vasopressor therapy. Results show that mortality rates were similar in both groups.

### Table 3. Empiric Antibiotic Therapy for Common Community-Acquired Bacterial Infections in Cirrhosis

<table>
<thead>
<tr>
<th>Sites</th>
<th>Organisms</th>
<th>Antibiotics</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP</td>
<td>Escherichia coli</td>
<td>Cefotaxime (2 g/6 hours or 2 g/12 hours IV)</td>
</tr>
<tr>
<td></td>
<td>Streptococcus Viridans</td>
<td>or amoxicillin/clavulanic acid (1-0.2 g/8 hours then 0.5-0.125 g/8 hours PO)</td>
</tr>
<tr>
<td></td>
<td>Enterobacter spp</td>
<td>or ofloxacin (400 mg/12 hours PO)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>or ciprofloxacin (200 mg/12 hours IV then 500 mg/12 hours PO)</td>
</tr>
<tr>
<td>Urinary tract infections</td>
<td>Escherichia coli</td>
<td>Ciprofloxacin (500 mg/12 hours PO)</td>
</tr>
<tr>
<td></td>
<td>Klebsiella pneumoniae</td>
<td>or cotrimoxazole (160-800 mg/12 hours PO)</td>
</tr>
<tr>
<td></td>
<td>Enterococcus spp</td>
<td>or Amoxicillin/clavulanic acid (1.0-2 g/8 hours IV)</td>
</tr>
<tr>
<td>Pneumonia *</td>
<td>Streptococcus pneumoniae</td>
<td>Amoxicillin/clavulanic acid (1.0-2 g/8 hours IV) and macrolide</td>
</tr>
<tr>
<td></td>
<td>Staphylococcus aureus</td>
<td>or moxifloxacin (400 mg/24 hours PO)</td>
</tr>
<tr>
<td>Soft tissue infections</td>
<td>Staphylococcus aureus</td>
<td>Ceftazidim (2 g/8 hours IV) + oxacillin 2 g/6 hours IV</td>
</tr>
<tr>
<td></td>
<td>Streptococcus pyogenes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Klebsiella pneumoniae</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Escherichia coli</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pseudomonas aeruginosa</td>
<td></td>
</tr>
</tbody>
</table>

*Liver disease is considered as severe comorbidity for community-acquired pneumonia in guidelines.

Microbiological samples must be taken as early as possible and before starting empiric antibiotic therapy. Empiric antibiotic therapy must be adapted to local epidemiology, prevalence of antibiotic resistance and results of bacterial cultures. The durations of antibiotic therapy vary between types of infection. For SBP, antibiotic must be given during 5-7 days. Patients with complicated cystitis must be treated for at least 5 days. In case of pyelonephritis, antibiotic therapy must be prolonged for 10-14 days. Patients with community-acquired pneumonia must be treated for a minimum of 5 days. Soft tissue infections must be treated for a minimum of 10 days. In all cases, the duration of antibiotic therapy depends on response to treatment and resolution of infection.

**IV, intravenous; PO, per os; SBP, spontaneous bacterial peritonitis.**

### Table 4. Results of Randomized, Controlled Trials in the General ICU Population

<table>
<thead>
<tr>
<th>Group</th>
<th>Authors</th>
<th>No. of Patients</th>
<th>Intervention Group</th>
<th>Control Group</th>
<th>28-Day Mortality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with severe sepsis and septic shock</td>
<td>Rivers et al.⁵⁰</td>
<td>263</td>
<td>Early, goal-directed therapy</td>
<td>Standard therapy</td>
<td>33</td>
</tr>
<tr>
<td>Patients with acute lung injury and ARDS†</td>
<td>ARDS Clinical Trials Network⁵⁹</td>
<td>861</td>
<td>Low tidal volume (6 mL/kg of ideal body weight)</td>
<td>High tidal volume (12 mL/kg of ideal body weight)</td>
<td>31</td>
</tr>
<tr>
<td>Patients with severe sepsis and septic shock</td>
<td>Bernard et al.⁶⁰</td>
<td>1690</td>
<td>Activated protein C</td>
<td>Placebo</td>
<td>25</td>
</tr>
<tr>
<td>Patients with severe sepsis and low risk of death‡</td>
<td>Abraham et al.⁶¹</td>
<td>2640</td>
<td>Activated protein C</td>
<td>Placebo</td>
<td>18</td>
</tr>
<tr>
<td>Patients with septic shock</td>
<td>Annane et al.⁵⁴</td>
<td>299</td>
<td>Hydrocortisone plus fludrocortisone</td>
<td>Placebo</td>
<td>55</td>
</tr>
<tr>
<td>Patients with septic shock§</td>
<td>Sprung et al.⁶⁶</td>
<td>499</td>
<td>Hydrocortisone</td>
<td>Placebo</td>
<td>34</td>
</tr>
<tr>
<td>Patients with septic shock¶</td>
<td>Russell et al.⁵⁷</td>
<td>778</td>
<td>Vasopressin</td>
<td>Norepinephrine</td>
<td>35</td>
</tr>
<tr>
<td>Patients with severe sepsis¶</td>
<td>Brunkhorst et al.⁶⁸</td>
<td>537</td>
<td>Intensive insulin (to maintain glucose level of 80-110 mg/dL)</td>
<td>Conventional insulin (to maintain glucose level of 180-200 mg/dL)</td>
<td>25</td>
</tr>
</tbody>
</table>

*P < 0.05 versus intervention group. †Most patients had sepsis. ‡Low risk of death was defined by an Acute Physiology and Chronic health evaluation (APACHE II) ≥25 or single-organ failure. §Because of slow recruitment and expiry of the supply of study drug, the trial was stopped after only 499 of the planned 800 patients had been recruited. ¶ Patients were treated with open-label vasopressors. †The trial was stopped for safety reasons.
groups (Table 4). A subgroup analysis suggested vasopressin administration may reduce mortality rates in patients with shock of lesser severity.

Patients with cirrhosis and severe sepsis or septic shock are known to be hyporeactive to vasopressor therapy. There are no data on plasma arginine-vasopressin levels and no RCT of vasopressor therapy in these patients.

### III. Protective-Ventilation Strategy for Acute Lung Injury–ARDS

Ventilation strategy for ARDS to reduce barotrauma and volutrauma should include ventilation with low tidal volumes and limited end-inspiratory plateau pressures (Table 4).

There are no RCTs of mechanical ventilation for ARDS in cirrhosis.

### IV. Recombinant Human Activated Protein C (rhAPC)

In a double-blind RCT, the administration of recombinant human activated protein C (rhAPC) for 4 days in patients with severe sepsis significantly reduced the 28-day mortality (Table 4). This effect was more evident in patients with high risk for death.

The principal side effect of rhAPC administration is serious bleeding (3.5%-3.9%).

Patients with cirrhosis or portal hypertension were excluded from RCTs with rhAPC for severe sepsis because of potential increase in the risk of severe bleeding. It should be noted that patients with cirrhosis and portal vein thrombosis who are on the waiting list for liver transplantation receive anticoagulation. The risk of bleeding seems very low (5%) during a long period of anticoagulation (8 months). Thus, the use of rhAPC might be safe in patients with cirrhosis and severe sepsis, but this needs to be studied.

### V. Hydrocortisone

Patients without cirrhosis who have septic shock frequently have adrenal insufficiency, which is implicated in a reduced response to adrenergic agents and a higher mortality. In a double-blind RCT performed in patients with vasopressor-dependent septic shock, it was shown that the administration of hydrocortisone (50 mg intravenously every 6 hours) and fludrocortisone (50 μg orally once daily) to nonresponders to a corticotrophin test resulted in reduced 28-day mortality (Table 4). Another RCT that evaluated intravenous hydrocortisone did not find any significant effect of hydrocortisone on survival.

Steroid administration was associated with a more rapid resolution of circulatory shock, but there was a greater incidence of secondary infections. Nevertheless, it should be noted that although this trial was the largest in the field of corticosteroid therapy for sepsis, it was insufficiently powered to draw firm conclusions on the effect of hydrocortisone on survival of patients with septic shock.

Patients with cirrhosis and septic shock may have a high incidence of adrenal insufficiency (51%-68%) which may be related to a reduction in adrenal blood flow and high cytokine expression. A small uncontrolled study which assessed patients with severe cirrhosis (mean Child-Pugh scores of 11) with septic shock who are nonresponders to corticotrophin suggested that hydrocortisone could shorten the duration of shock resolution and improves survival compared with a retrospective matched cirrhotic cohort.

A large double-blind RCT is needed to evaluate hydrocortisone therapy in patients with cirrhosis who have septic shock.

### VI. Glucose Control

Hyperglycemia and insulin resistance are common in sepsis. Hyperglycemia may act as procoagulant, induce apoptosis, impair neutrophil function, and is associated with increased risk of death. Thus, insulin therapy may be useful in patients with sepsis. However, a RCT performed in patients with severe sepsis and septic shock showed that tight blood glucose control (80-110 mg/dL) with insulin therapy did not reduce mortality rates, but induced more hypoglycemic events compared to conventional strategy (180-200 mg/dL).

Moreover, a recent large multicenter RCT in a general population of intensive care unit (ICU) patients (21.6% with severe sepsis at admission) shows that intensive insulin therapy increased the 90-day mortality rate compared to targeting 144-180 mg/dL.

There are no RCTs of intensive insulin therapy in patients with cirrhosis and severe sepsis. However, it is not tempting to initiate such trials in these patients due to negative results obtained with intensive insulin therapy in a general population. Moreover, some patients with cirrhosis and septic shock may have spontaneous hypoglycemia due to severe liver failure.

### VII. Renal-Replacement Therapy and Liver-Support System

There is a continuing controversy about the type (intermittent or continuous) and the dose (conventional = 20 mL/kg body weight/hour or intensive = 35 mL/kg body weight/hour) of renal support to be recommended in critically ill patients. In a recent trial, intensive renal support, defined as continuous hemofiltration at 35 mL/kg/hour or daily intermittent hemodialysis, does not reduce 60-day mortality or improve recovery of kidney function compared with conventional less-intensive renal support. No RCTs assess different modalities of renal support.
support in patients with cirrhosis with sepsis-related renal failure. Renal replacement can be coupled to a liver support system—albumin dialysis, in the case of acute-on-chronic liver failure with HRS. In a small RCT, the Molecular Adsorbents Recirculating System (MARS) shows a greater improvement in survival of patients with decompensated cirrhosis with HRS compared with conventional hemofiltration.72 Larger studies in the field of sepsis in cirrhosis are needed.

**VIII. Selective Digestive Tract Decontamination and Selective Oropharyngeal Decontamination (SOD)**

Critically ill patients admitted to the ICU are prone to be infected secondarily, mainly to develop pneumonia. These acquired infections are associated with higher mortality rates.73 No studies specifically focus on selective digestive tract decontamination (SDD) in patients with severe sepsis or septic shock. In a large general ICU population in which the mortality rate associated with standard care was 27.5% at day 28, the rate was decreased by an estimated 3.5% with SDD and by 2.9% with selective oropharyngeal decontamination (SOD).74 SDD and SOD reduced the incidence of ICU-acquired bacteremia without obvious emergence of antibiotic-resistant microorganisms and *Clostridium difficile* toxin. SDD and SOD may have similar preventative effects in the septic population susceptible to nosocomial infections.

Although there is evidence of increased intestinal bacterial translocation in patients with advanced cirrhosis, there are no data on the effects of SDD or SOD in patients with cirrhosis who have severe sepsis or septic shock.75

**Prevention of Sepsis in Cirrhosis**

Bacterial infections are common and severe in patients with cirrhosis. Thus, it is important to prevent infections in patients who are at risk. Because infection is frequently due to translocation of GNB of intestinal origin, prevention is based on selective intestinal decontamination with a fluoroquinolone (e.g., norfloxacin).

**Patients with Acute Gastrointestinal Hemorrhage.** In this context, bacterial infections are frequent. A meta-analysis of trials in patients with variceal hemorrhage has shown that antibiotic prophylaxis reduced the incidence of severe infection (SBP and/or septicemia) and decreased mortality.76 There is a decrease in mortality from variceal hemorrhage from 43% to 15% over a 20-year period and antibiotic prophylaxis is independently associated with improved survival.77 Oral norfloxacin (800 mg/day for 7 days) is commonly used.49 However, a RCT has shown that intravenous ceftriaxone (1 g/day for 7 days) was more effective than oral norfloxacin to prevent severe infections in patients with advanced cirrhosis (characterized by at least two of the following: ascites, severe malnutrition, encephalopathy, or bilirubin >3 mg/dL) and variceal bleeding.78

**Patients with Low Protein Ascitic Levels and No Prior SBP: Primary Prophylaxis.** Oral norfloxacin administration (400 mg/day) in patients with low protein ascitic levels (<1.5 g/dL) and advanced cirrhosis (Child-Pugh score ≥9 points with serum bilirubin level ≥3 mg/dL or impaired renal function [serum creatinine level ≥1.2 mg/dL, blood urea nitrogen level ≥25 mg/dL, or serum sodium level ≤130 mEq/L]) without prior SBP episode reduces the probability of SBP and HRS and improved the 3-month survival.79 Similarly, oral ciprofloxacin (500 mg/day) reduces the 1-year mortality rate in patients with ascitic protein levels <1.5 g/dL and without prior SBP episode.80

**Patients with Prior SBP: Secondary Prophylaxis.** After an episode of SBP, the cumulative recurrence rate at 1 year is 70%. Oral norfloxacin decreases the recurrence of SBP from ~70% to 20%.81

**Issues with Long-Term Antibiotic Therapy.** There is no consensus on the duration of long-term use of oral antibiotic therapy to prevent first SBP or its recurrence. However, antibiotic therapy is associated with the emergence of resistant organisms. This is why alternative approaches are needed. Interestingly, preliminary results of a large double-blind RCT show that oral pentoxifylline administration (1200 mg/day) significantly decreases the risk of bacterial infection in patients with advanced cirrhosis.82

**Catheter-Related Infections.** These infections are common in critically ill patients with cirrhosis. These patients may benefit from the following: appropriate hand hygiene, use of chlorhexidine for skin preparation, use of full-barrier precautions during the insertion of central venous catheters, use of the subclavian vein as the preferred site for insertion of the catheter, and the removal of unnecessary central venous catheters.83

**Areas of Future Research**

Obviously, specific information is lacking on patients with cirrhosis who have severe sepsis and septic shock. Table 5 summarizes the potential areas of future clinical research in these patients.

**Conclusions**

Despite extensive research and significant advances in understanding of the pathogenesis of sepsis, there are many unanswered questions and the outcome of these
Table 5. Potential Areas of Future Clinical Research on Severe Sepsis and Septic Shock in Patients with Cirrhosis

- Incidence of sepsis, severe sepsis and septic shock
- Improvement of diagnostic techniques to identify infective organisms
- Identify hemodynamic (or others) end points for resuscitation in the early phase of severe sepsis and septic shock
- Large RCTs on the efficacy of intravenous albumin in bacterial infections unrelated to SBP
- Large RCTs on the use of vasopressors
- Large RCTS on the use of hydrocortisone
- Pilot trials on efficacy and safety of recombinant human activated protein C
- Large RCTs on the use of renal-replacement therapies and liver-support systems
- Impact of ascites and compartmental syndrome on hemodynamics and renal function
- RCTs on nutrition, prevention for stress ulcer, sedation in the ICU
- Develop "nonantibiotic" approaches for primary prophylaxis of SBP

ICU, intensive care unit; RCT, randomized control trial; SBP, spontaneous bacterial peritonitis.

patients remains poor. The prognosis of sepsis is much worse in patients with cirrhosis. The specificities of the pathogenic process of sepsis in cirrhosis has only begun to be clarified. With actual well-defined prophylactic treatment for variceal bleeding, sepsis becomes a major cause of death for patients with advanced cirrhosis. Much effort is needed to define the specific management of sepsis in cirrhosis by designing and performing the proper trials in patients with advanced cirrhosis.

References