Published in final edited form as:
Gut. 2012 August ; 61(8): 1219–1225. doi:10.1136/gutjnl-2012-302339.

Bacterial infections in end-stage liver disease: current challenges and future directions

Jasmohan S Bajaj[1], **Jacqueline G O'Leary**[2], **Florence Wong**[3], **K Rajender Reddy**[4], and **Patrick S Kamath**[5]

[1]Department of Medicine, Virginia Commonwealth University and McGuire VA Medical Center, Richmond, Virginia, USA

[2]Department of Medicine, Baylor University Medical Center, Dallas, Texas, USA

[3]Department of Medicine, University of Toronto, Toronto, Ontario, Canada

[4]Department of Medicine, Canada University of Pennsylvania, Philadelphia, Pennsylvania, USA

[5]Department of Medicine, Mayo Clinic School of Medicine, Rochester, Minnesota, USA

INTRODUCTION

Bacterial infections continue to be a leading cause of mortality and acute-on-chronic liver failure in end-stage liver disease (ESLD). The consequences of infection include prolonged hospitalisation, acute kidney injury (AKI), death, de-listing from liver transplant and susceptibility to further infections. The diagnosis of infections in cirrhosis is fraught due to the background of a partial systemic inflammatory response syndrome (SIRS) state and negative cultures in 30–50% of patients. Furthermore, the lack of multi-center studies limits the generalisability of currently available results. The modulation of infections by the underlying immune state, gut barrier function and super-imposed medications such as beta-blockers, proton pump inhibitors and antibiotics is required. A rational approach to the diagnosis and prevention of AKI associated with infection, with judicious use of crystalloids and albumin, is also needed. Changes in bacteriology including emergence of multi-resistant organisms and Clostridium difficile have also recently changed the approach for prophylaxis and therapy of infections. Effective strategies for the prevention, diagnosis, and management of infections in ESLD form a large unmet need. A systematic approach to study the epidemiology, bacteriology, resistance patterns, and procedure and medication utilisation specific to ESLD is needed to improve outcomes.

Bacterial infections in patients with end-stage liver disease affect candidacy for liver transplantation. Up to one-third of all hospitalised patients with cirrhosis are infected.[1–5] With sepsis, mortality increases to more than 50% and is associated with significant costs.[6] A recent systematic review demonstrated a fourfold increased risk of death in infected cirrhotic patients compared with their non-infected counterparts.[7] More importantly, intensive care unit (ICU) mortality of patients with cirrhosis has remained unchanged over 50 years, unlike disease states such as cardiac failure where mortality has decreased.[8]

Correspondence to: Dr Jasmohan S Bajaj, Associate Professor, Division of Gastroenterology, Hepatology and Nutrition, Virginia Commonwealth University and McGuire VA Medical Center, 1201 Broad Rock Boulevard, Richmond, VA 23249, USA; jasmohan@gmail.com.

Contributors All authors contributed equally to the design, writing, drafting and final approval of the submitted text.

Competing interests None.

Provenance and peer review Not commissioned; externally peer reviewed.

Therefore the prevention, diagnosis and management of infections in patients with end-stage liver disease form a large unmet need. This commentary briefly reviews infections in patients with cirrhosis, and outlines specific areas that need to be addressed in such patients hospitalised with infections.

SCOPE OF THE PROBLEM

The magnitude of the problem of infections in cirrhosis is not quantifiable for many reasons. Infections are often difficult to recognise in patients with cirrhosis because 30–50% of infections, such as spontaneous bacterial peritonitis (SBP), can remain culture negative.[9] Conventional risk-scoring strategies, such as the systemic inflammatory response syndrome (SIRS) criteria, cannot reliably differentiate sepsis (SIRS plus infection) from noninfectious SIRS.[10] This is important because a partial SIRS-like state is present in most patients with decompensated end-stage liver disease and therefore in itself cannot be used to differentiate between infected and uninfected patients. There are also difficulties diagnosing the presence of infections, especially in hospitalised cirrhotic patients.[5] Strategies such as measuring C-reactive protein and procalcitonin may be helpful in selected patients, but a specific differentiator is still needed.[1112] Time-appropriate strategies are needed to suspect infections and send cultures early so as to initiate appropriate antimicrobial therapy. Also a heightened suspicion of potentially resistant organisms is required in order to change therapy as needed.[2] In addition, most current studies are single centre, and there are limited data on the emergence of multi resistant strains and healthcare-associated (which develop <48 h after admission in patients with previous exposure to healthcare services in the preceding 90 or 180 days) and nosocomial (which develop >48 h after admission) infections.

Some idea of the magnitude of the problem may be obtained from the US nationwide inpatient sample (NIS), which analyses data from 20% of acute care hospitals and includes 8 million discharge records from 38 states. The NIS identified 65 072 patients in 2006 with a discharge diagnosis of cirrhosis. The total costs incurred were approximately US$14 billion per year. Of the hospitalized patients, 26 300 had presumed infection and required ICU support, as identified by mechanical ventilation and invasive cardiovascular monitoring. The in-house mortality of the hospitalised cirrhotic patients was 53%, or 13 800 deaths a year nationwide. The mean length of hospitalisation was 13.8 days. The total costs associated with ICU admissions in cirrhotic patients with presumed infection were US$3 billion, with mean costs of US $116 200 per admission and average daily costs of US$16 589 in non-survivors.

Another study from the NIS showed that *Clostridium difficile* infection in patients with cirrhosis was associated with a significantly higher mortality, length of stay and total costs compared with patients admitted with cirrhosis without *C difficile* and patients with *C difficile* without cirrhosis. This is striking because the mean age of the patients with *C difficile* without cirrhosis was significantly higher than that of patients with *C difficile* and cirrhosis.[13] In the Korean National database, patients with cirrhosis and bacteraemia were significantly more likely to die than those without cirrhosis.[14] Bacteraemia in cirrhotic patients was more likely to be due to intra-abdominal infections and *Klebsiella pneumoniae*, and less likely to be due to coagulase-negative *Staphylococcus*. Multivariate analysis confirmed cirrhosis as an independent risk factor for mortality (HR 2.11, 95% CI 1.43 to 3.13).[14]

The North American Consortium for the Study of End-Stage Liver Disease (NACSELD) currently includes 12 centres throughout North America focused on determining outcomes after infections in patients with cirrhosis.[15] Preliminary data from the NACSELD study noted that, in 176 patients from nine sites, the majority of infections were SBP and urinary

tract infection (UTI), followed by spontaneous bacteraemia, skin, respiratory and *C difficile* infections. Gram-positive (36%) organisms were the most common, followed by Gram-negative (30%) organisms. The remainder were either fungal (4%) in origin or infections without an isolated organism. The death rate was highest for respiratory (44%), bacteraemia (38%) and *C difficile* (41%) infections, and lowest for urinary (21%) and skin (29%) infections or SBP (17%). The index infections were healthcare-associated (56%) or nosocomial (20%), and, importantly, 28% of patients developed a second infection during hospitalisation. The overall mortality was 25%, and patients who died had a higher Model for End-Stage Liver Disease (MELD) score at admission (25±8 vs 19±7, $p<0.001$) and were more likely to have hepatic encephalopathy (HE), hepatorenal syndrome (HRS), mechanical ventilation and ICU stay during hospitalisation (all $p<0.0001$). There was a higher incidence of second infections during hospitalisation in patients who died than in patients who survived (53% vs 20%, $p=0.0001$). Patients who developed a second infection were more likely to have a Gram-negative first infection, an ICU stay, lower albumin, greater length of hospitalisation and higher MELD score. Multivariate analysis showed that only second infection ($p=0.0009$) and MELD score ($p<0.0001$) were associated with death. Therefore there is a need to develop early diagnostic and prognostic markers, including biomarkers, for a better understanding of infections so as to improve outcomes.

CONTRIBUTION OF DRUGS SUCH AS ANTIBIOTICS, PROTON PUMP INHIBITORS (PPIS) AND β BLOCKERS TO INFECTIONS AND UNDERLYING IMMUNE STATUS

Changes in gut bacteria in cirrhosis can lead to bacterial overgrowth with subsequent enhanced bacterial translocation from the gut to the systemic circulation and as cites, identified by bacterial DNA or by isolating bacteria in systemic biofluids. Bacterial translocation is the major pathogenetic factor for infections.[516–18] Bacterial translocation can be silent or can result in florid infections.[19] Even in the absence of infection, bacterial translocation can increase mortality.[2021] It is also a process that is facilitated by acid suppression[2223] and increased intestinal permeability in cirrhosis, specifically with advanced disease. Sepsis as a result of bacterial translocation and small-bowel bacterial overgrowth is a key component of the natural history of infections.[20] However, one of the key modulators of outcomes of infections is the underlying immune status, which is negatively affected at multiple levels in cirrhosis. Specifically, the neutrophil burst, phagocytosis and opsonisation are impaired.[21] Recent evidence has also indicated that antimicrobial peptides and *NOD2* genetic variants are altered in patients with cirrhosis.[2425] A deeper understanding of the bacterial–immune interface either at the intestinal wall or within the ascitic fluid or mesenteric lymph nodes is important for developing biomarkers that would predict development of infection with an overall view to prevention.[26]

Single-centre studies have associated the use of PPIs with SBP and *C difficile*.[1327] This is an important observation, as PPIs are some of the most overprescribed drugs for cirrhosis.[28] An appropriate indication for PPI use exists in fewer than half of the patients.[29] PPIs predispose to bacterial overgrowth and adversely affect immune function.[30] Another seemingly contradictory association is the effect of non-selective β blockers (NSBBs) on the negative outcomes in cirrhosis. While a meta-analysis showed a reduced development of SBP in previous studies, a recent non-randomised study demonstrated a worse survival in the subset with refractory as cites.[3132] The effect of NSBBs on cirrhosis outcomes has led to the formulation of a ‘window hypothesis’, which suggests that NSBBs only improve outcomes in a narrow window of the cirrhosis natural history between those who have medium to large varices before the development of end-stage liver disease.[33] Therefore the clinical role of NSBBs in cirrhosis needs to be elucidated further.

The role of non-absorbable antibiotics, such as rifaximin, in the modulation of infections in cirrhosis is also emerging. Whereas the pivotal HE trial did not show a significant difference in the rate of infections between groups, subsequent small studies reported a protective role of rifaximin against endotoxaemia and SBP.[34–36] Out patient prophylaxis using fluoroquinolones or sulfamethoxazole/trimethoprim in patients with previous SBP has been clearly shown to reduce subsequent episodes of SBP, but not survival.[37] It is not completely clear whether these agents can improve outcomes in subgroups of patients with as cites fluid albumin <1.0 g/dl. SBP prophylaxis has been associated with the development of *C difficile* in a single-centre study.[13] The study of SBP prophylaxis becomes more nuanced, especially when the emergence of multiresistant strains is considered.[2] Further studies into the use of antibiotics are required to determine their role in reducing infections and mortality.

Thus several lines of evidence suggest the influence of outpatient medication on infection risk. Considering the small sample size and retrospective nature of most of these studies, further evaluation of drugs such as PPIs, non-absorbable antibiotics (such as rifaximin) and NSBBs is needed to determine their role in infections.

PROGNOSIS AND MANAGEMENT IN THE ICU

Several precipitating factors are associated with deterioration in cirrhosis leading to multiple organ failure. These include infection, gastrointestinal bleeding, alcoholic hepatitis, superimposed viral hepatitis, drug-induced hepatotoxicity, and surgery. The response to infection in patients with cirrhosis is often exaggerated, leading to ICU admission because of sepsis, severe sepsis and septic shock.[38] MELD score has been validated as a predictor of mortality in cirrhotic patients in the ICU and may have better prognostic capacity than the Child–Turcotte–Pugh score and the Simplified Acute Physiology Score II. The Acute Physiology and Chronic Health Evaluation III score is another predictor of early ICU mortality. The Sequential Organ Failure Assessment score correlates with mortality: failure of two organ systems is associated with a mortality of 55%, and failure of three or more organs with almost 100% mortality.[39] Even when supportive measures are introduced, the underlying immune dysfunction state (immune paralysis following the first infection which contributes to secondary infections), poor nutrition, ongoing portal hypertension-related systemic haemodynamic changes, HE and gastrointestinal bleeding prevent recovery in these patients. Liver transplantation is ultimately an effective form of therapy for these patients, and worsening liver and renal function increase the MELD score, but ongoing infection and multiorgan system dysfunction make them generally poor candidates.

The ‘sepsis bundle’ has been accepted as the standard of care in patients with severe sepsis in the ICU.[40] It is not clear whether these recommendations apply to patients with cirrhosis and severe sepsis. For example, arterial lines and central venous catheters are recommended for monitoring of mean arterial pressure and central venous pressure in severe sepsis. However, in critically ill cirrhotic patients, such vascular access may be associated with a significantly increased risk of bleeding. Red blood cell transfusions are recommended to increase central venous oxygen saturation. However, red blood cell transfusions in cirrhotic patients may be associated with an increased risk of variceal bleeding. Thus the role of the sepsis bundle in cirrhosis needs validation.

The key areas of need in the management of cirrhotic patients in the ICU is the prevention of nosocomial and second infections, reduction of unnecessary instrumentation, judicious use of antibiotic and antifungal agents, and validation of prognostic scores that take into account the underlying liver disease severity. Additional areas that need to be addressed are whether albumin is the preferred volume expander, how coagulopathy should be corrected, the optimal vasopressor support, the methodology for determining adrenal insufficiency, and the

situations in which steroids should be given and the doses that should be used.[6] Finally, the role of artificial and bioartificial liver support devices needs to be determined in this population.[41]

PREVENTION AND TREATMENT OF ACUTE KIDNEY INJURY (AKI) IN INFECTED PATIENTS WITH CIRRHOSIS

A critical need is to prevent and adequately treat renal dysfunction in infected cirrhotic patients. This is because renal dysfunction with AKI has emerged as a major determinant of mortality in patients with cirrhosis.[4243] AKI, including HRS, is associated with a markedly shorter survival. In patients with decompensated cirrhosis admitted to hospital, increased creatinine concentration within 24 h of admission is associated with poorer survival. Even more profound is the requirement of renal replacement therapy, which is associated with 94% in-hospital mortality.[44] While most cases of functional renal impairment respond to volume challenge, with return of renal function to baseline levels, approximately one-third of patients are not volume responsive; these include patients with HRS or acute tubular necrosis.[45] Therefore the first line of management of AKI in hospitalised cirrhotic patients is volume expansion, the response to which can determine the prognosis and subsequent management—for example, the use of vasoconstrictors would be indicated for volume-unresponsive cases of AKI such as HRS. Acute or type 1 HRS is defined as renal failure, which is characterised by a doubling of the initial serum creatinine to a level of >2.5 mg/dl in <2 weeks, which has been reported in about 10% of cirrhotic inpatients. Chronic or type 2 HRS is characterised by moderate renal failure, with serum creatinine between 1.5 and 2.5 mg/dl.[45] Whereas type 2 HRS is usually associated with refractory as cites and follows a steady declining course, type 1 HRS is usually precipitated by an acute event and is often part of multiorgan system failure.[46] The most common precipitating factor of type 1 HRS is bacterial infection,[4748] and this may occur despite clearance of the bacterial infection. The inflammatory response to bacterial infections increases systemic arterial vasodilatation, with further reduction of the effective arterial blood volume and further renal vasoconstriction, leading to renal failure.

SBP was the first bacterial infection recognised to be associated with a high incidence of renal failure in cirrhosis. This occurs in approximately one-third of patients despite resolution of the infection,[4849] and is associated with an in-hospital mortality of 42–67%.[4950] However, it was soon recognised that any bacterial infection could precipitate renal failure in cirrhosis.[51] Patients who develop renal failure with bacterial infection have a higher MELD score and lower mean arterial pressure.[47] Biliary or gastrointestinal tract infections are more likely to be associated with the development of renal failure, followed by SBP and UTI, although other infections such as pneumonia or even skin infections are associated with the development of renal failure. Once renal failure develops, it can be transient, resolving with the clearance of the infection, or it can persist, or even progress despite the clearance of infection.[51] Biliary or gastrointestinal infectioninduced renal failure is most likely to progress, followed by SBP- and UTI-related renal failure.[47] Once renal failure sets in, the probability of survival at 3 months is only 31%, and decreases with higher MELD scores.[52]

Prevention of renal failure in the setting of infections remains a challenge. With SBP, patients given albumin have a lower incidence of renal failure, associated with improved survival.[53] Underlying liver and renal function determine the risk of developing renal dysfunction associated with SBP. In one study, using the definition of high risk as plasma urea ≥60 mg/dl and serum bilirubin ≥4 mg/dl, almost 30% of patients who presented with SBP could be regarded as low risk for the development of renal failure and therefore were not given albumin. Renal failure only developed in 4.7% of the low-risk group, which had a

3.1% mortality. In contrast, 40% of the patients with SBP in the high-risk group (70% of the entire cohort) already had renal failure at the time of SBP diagnosis, while an additional 26% developed renal failure before SBP resolution.[54] Those in the high-risk group treated with albumin had a significantly improved 90-day survival (p=0.01). The number of patients needed to treat in the high-risk group to avoid one death was 5.5. Similar findings were also reported by Sigal *et al*[55] and Terg *et al.* [56] Thus the need for universal administration of albumin for the treatment of SBP needs to be re-evaluated. The need for albumin to prevent the development of renal failure in other bacterial infections also needs to be examined.

A small study assessed the effects of 2 mg/day terlipressin (a systemic vasoconstrictor) in addition to ceftriaxone (1 g every 12 h) on systemic haemodynamics and clinical outcome in patients with SBP.[57] This regimen improved the hyper-dynamic circulation compared with ceftriaxone alone. There was a significant increase in SBP reversal and a reduction in mortality with terlipressin at 48 h. Therefore the use of a vasoconstrictor should be investigated as a potential alternative, or additive, to albumin in the prevention of renal impairment in SBP.

Renal dysfunction, especially HRS type 1, is treated with vasoconstrictors and albumin infusion. The choice of vasoconstrictor depends on local availability: midodrine in North America in combination with octreotide, and terlipressin for most other parts of the world.[45] Given the poor survival of patients with cirrhosis, bacterial infections and established renal failure,[47] there is now a trend towards treating renal impairment at an earlier stage than defined type 1 HRS. One challenge has been to define an early stage of renal dysfunction, as serum creatinine is an inaccurate measure of renal function.[5859]

A new definition of AKI in cirrhosis has been proposed,[60] which is an increase in serum creatinine of 0.3 mg/dl in <48 h (table 1).[61] The exact prevalence of AKI according to this new definition is unknown, but is an important question because it appears that such small increases in serum creatinine in patients with cirrhosis may negatively affect survival.

Several newer concepts are helping to shape treatment strategies. These include the understanding that both the acute deterioration in renal function and the background chronic renal dysfunction can be functional or structural in nature, and the recent recognition that the inflammatory response to bacterial infection may be partly responsible for the development of renal failure.

MEASURES FOR PREVENTION, SURVEILLANCE AND IDENTIFICATION OF HEALTHCARE-ASSOCIATED AND NOSOCOMIAL INFECTIONS AND MULTIRESISTANT BACTERIA AND *C DIFFICILE*

The emergence of multiresistant species and the looming spectre of nosocomial and healthcare-associated infections are concerning. Nosocomial infections in the general population are estimated to affect 1.7 million persons a year, cost at least US $5 billion annually, and are the sixth leading cause of death in the USA.[62–65] Although healthcare-associated and nosocomial infections are different, they both increase length of stay, cost and mortality, and occur more commonly in ‘sicker’ patients following procedures such as surgery or in those who need mechanical ventilation or vascular or urinary catheters.[66] The organisms responsible are often resistant to the ‘first line’ antibiotics often given for similar community-acquired infections, making empiric antibiotic treatment decisions more challenging and expensive.[267–69]

Nosocomial infections in non-cirrhotic patients are usually broken down into four categories[6266–68] as shown in table 2. However, there has been little published on

nosocomial infections in patients with cirrhosis. Fernandez *et al* studied multiresistant organisms and nosocomial infections occurring in a single centre over three time periods: 1998–2002 (n=572), 2005–2007 (n=507) and 2010–2011 (n=162).[23] Infection was present in one-third of hospital admissions: 25–32% healthcare associated and 36–45% nosocomial. Community-acquired infections were most commonly SBP (35%) and cellulitis (19%), healthcare-associated infections were most commonly SBP (28%) and UTIs (24%), and nosocomial infections were dominated by UTIs (31%).[2] *C difficile* was not studied. Overall, multidrug-resistant (MDR) organisms caused 4% of community-acquired, 14% of healthcare-associated and 35% of nosocomial infections ($p<0.001$).[2] This high risk of MDR organisms decreased the efficacy of their 'standard of care' antibiotic regimens to 40% in nosocomial infections, and doubled mortality in patients infected with MDR organisms. In another European single-centre study, Merli and colleagues found that one-third of 150 hospitalised patients with cirrhosis experienced at least one infection; 78% were healthcare-associated or nosocomial infections.[4] UTIs were most common, and 64% were caused by MDR organisms. MDR organisms were predominantly Gram-negative isolates in SBP, such as *Escherichia coli* and *K pneumoniae* with extended spectrum β lactamase activity. The change in bacteriology also reflects an emergence of Gram-positive pathogens. A disturbing trend is the increased isolation of methicillin-resistant *Staphylococcus aureus*.[70] *Enterococcus faecalis* and *Enterococcus faecium* have been isolated in 10–24% of infections in the setting of cirrhosis and are associated with a mortality of 25%. Focusing on specific infections, it has been found that SBP is an important cause of both community-acquired and nosocomial infections in patients with cirrhosis.[7172] Whereas community-acquired SBP is more commonly caused by Gram-negative rods, nosocomial SBP has an increased prevalence of Gram-positive cocci. In addition, nosocomial acquisition increases the risk of resistance to cephalosporin and fluoroquinolone and significantly increases mortality. Although previous reports on nosocomial infections did not include *C difficile* infection, it was a common nosocomial infection found in the NACSELD study and had the highest risk of mortality (28%).[15] This is similar to the previous *C difficile* National Database study in cirrhosis in which length of stay doubled, mortality markedly increased, and cost increased by US$43 665/infected admission.[13]

We propose, on the basis of our and other previous work in this area, that healthcare-associated and nosocomial infections in cirrhosis be broken down into six categories: spontaneous bloodstream infections unrelated to interventions or infections at other sites, UTIs, pulmonary infections, SBP, *C difficile* and intervention-related infections (table 3). Although up to one-third of all nosocomial infections should be preventable,[73] 'success in curbing their emergence remains elusive.'[74] It should be emphasised that the data available on healthcare-associated and nosocomial infections in cirrhosis are largely limited to single centres, although smaller multicentre studies exist.[1–413717275–80]

SUMMARY

Because of the high morbidity and mortality in patients with cirrhosis who become infected (many of whom may be denied liver transplantation because of multiple organ failure) and the paucity of data in this field, we propose the studies outlined in table 4. Only through systematic study of epidemiology, bacteriology, resistance patterns, and procedure and medication utilisation specific to patients with cirrhosis will we discover how to routinely accomplish this in the most cost-effective way.

Acknowledgments

Funding This was partly funded by the NIH grant NIDDK RO1DK087913 and partly from an educational grant from Grifols Pharmaceuticals.

REFERENCES

1. Borzio M, Salerno F, Piantoni L, et al. Bacterial infection in patients with advanced cirrhosis: a multicentre prospective study. Dig Liver Dis. 2001; 33:41–48. [PubMed: 11303974]
2. Fernandez J, Acevedo J, Castro M, et al. Prevalence and risk factors of infections by multiresistant bacteria in cirrhosis: a prospective study. Hepatology. 2012; 55:1551–1561. [PubMed: 22183941]
3. Fernandez J, Navasa M, Gomez J, et al. Bacterial infections in cirrhosis: epidemiological changes with invasive procedures and norfloxacin prophylaxis. Hepatology. 2002; 35:140–148. [PubMed: 11786970]
4. Merli M, Lucidi C, Giannelli V, et al. Cirrhotic patients are at risk for health care-associated bacterial infections. Clin Gastroenterol Hepatol. 2010; 8:979–985. [PubMed: 20621200]
5. Tandon P, Garcia-Tsao G. Bacterial infections, sepsis, and multiorgan failure in cirrhosis. Semin Liver Dis. 2008; 28:26–42. [PubMed: 18293275]
6. Olson JC, Wendon JA, Kramer DJ, et al. Intensive care of the patient with cirrhosis. Hepatology. 2011; 54:1864–1872. [PubMed: 21898477]
7. Arvaniti V, D'Amico G, Fede G, et al. Infections in patients with cirrhosis increase mortality four-fold and should be used in determining prognosis. Gastroenterology. 2010; 139:1246–1256. e1–e5. [PubMed: 20558165]
8. Kim W, Shah N, Kamath P. Economic impact of critical care in patients with cirrhosis in the US. Hepatology. 2010; 52:910A.
9. Runyon BA, Canawati HN, Akriviadis EA. Optimization of ascitic fluid culture technique. Gastroenterology. 1988; 95:1351–1355. [PubMed: 3049220]
10. Cazzaniga M, Dionigi E, Gobbo G, et al. The systemic inflammatory response syndrome in cirrhotic patients: relationship with their in-hospital outcome. J Hepatol. 2009; 51:475–482. [PubMed: 19560225]
11. Li CH, Yang RB, Pang JH, et al. Procalcitonin as a biomarker for bacterial infections in patients with liver cirrhosis in the emergency department. Acad Emerg Med. 2011; 18:121–126. [PubMed: 21276124]
12. Fernandez J, Gustot T. Management of bacterial infections in cirrhosis. J Hepatol. 2012; 56(Suppl 1):S1–S12. [PubMed: 22300459]
13. Bajaj JS, Ananthakrishnan AN, Hafeezullah M, et al. Clostridium difficile is associated with poor outcomes in patients with cirrhosis: a national and tertiary center perspective. Am J Gastroenterol. 2010; 105:106–113. [PubMed: 19844204]
14. Kang CI, Song JH, Chung DR, et al. Liver cirrhosis as a risk factor for mortality in a national cohort of patients with bacteremia. J Infect. 2011; 63:336–343. [PubMed: 21835195]
15. Bajaj J, O'Leary JG, Olson JC, et al. In hospital mortality in cirrhosis is related to infections independent of MELD score: a prospective multi-center study from the North American Consortium for the study of end-stage liver disease (NACSELD). Hepatology. 2011; 54 Abstract, 300A.
16. Garcia-Tsao G. Spontaneous bacterial peritonitis: a historical perspective. J Hepatol. 2004; 41:522–527. [PubMed: 15464231]
17. Cirera I, Bauer TM, Navasa M, et al. Bacterial translocation of enteric organisms in patients with cirrhosis. J Hepatol. 2001; 34:32–37. [PubMed: 11211904]
18. Garcia-Tsao G. Bacterial translocation: cause or consequence of decompensation in cirrhosis? J Hepatol. 2001; 34:150–155. [PubMed: 11211893]
19. Navasa M, Rodes J. Bacterial infections in cirrhosis. Liver Int. 2004; 24:277–280. [PubMed: 15287849]
20. Thabut D, Massard J, Gangloff A, et al. Model for end-stage liver disease score and systemic inflammatory response are major prognostic factors in patients with cirrhosis and acute functional renal failure. Hepatology. 2007; 46:1872–1882. [PubMed: 17972337]
21. Manakkat Vijay GK, Taylor NJ, Shawcross DL. The quest for the elusive factors that underpin neutrophil dysfunction in cirrhosis goes on. J Hepatol. 2012; 56:1212–1213. [PubMed: 22127281]

22. Frances R, Zapater P, Gonzalez-Navajas JM, et al. Bacterial DNA in patients with cirrhosis and noninfected as cites mimics the soluble immune response established in patients with spontaneous bacterial peritonitis. Hepatology. 2008; 47:978–985. [PubMed: 18306221]
23. Jun DW, Kim KT, Lee OY, et al. Association between small intestinal bacterial overgrowth and peripheral bacterial DNA in cirrhotic patients. Dig Dis Sci. 2010; 55:1465–1471. [PubMed: 19517230]
24. Nischalke HD, Berger C, Aldenhoff K, et al. Toll-like receptor (TLR) 2 promoter and intron 2 polymorphisms are associated with increased risk for spontaneous bacterial peritonitis in liver cirrhosis. J Hepatol. 2011; 55:1010–1016. [PubMed: 21356257]
25. Teltschik Z, Wiest R, Beisner J, et al. Intestinal bacterial translocation in rats with cirrhosis is related to compromised paneth cell antimicrobial host defense. Hepatology. 2012; 55:1154–1163. [PubMed: 22095436]
26. Wiest R, Krag A, Gerbes A. Spontaneous bacterial peritonitis: recent guidelines and beyond. Gut. 2012; 61:297–310. [PubMed: 22147550]
27. Bajaj JS, Zadvornova Y, Heuman DM, et al. Association of proton pump inhibitor therapy with spontaneous bacterial peritonitis in cirrhotic patients with as cites. Am J Gastroenterol. 2009; 104:1130–1134. [PubMed: 19337238]
28. Chavez-Tapia NC, Tellez-Avila FI, Garcia-Leiva J, et al. Use and overuse of proton pump inhibitors in cirrhotic patients. Med Sci Monit. 2008; 14:CR468–CR472. [PubMed: 18758417]
29. Goel GA, Deshpande A, Lopez R, et al. Increased rate of spontaneous bacterial peritonitis among cirrhotic patients receiving pharmacologic acid suppression. Clin Gastroenterol Hepatol. 2012; 10:422–427. [PubMed: 22155557]
30. Kedika RR, Souza RF, Spechler SJ. Potential anti-inflammatory effects of proton pump inhibitors: a review and discussion of the clinical implications. Dig Dis Sci. 2009; 54:2312–2317. [PubMed: 19714466]
31. Serste T, Melot C, Francoz C, et al. Deleterious effects of beta-blockers on survival in patients with cirrhosis and refractory as cites. Hepatology. 2010; 52:1017–1022. [PubMed: 20583214]
32. Senzolo M, Cholongitas E, Burra P, et al. Beta-blockers protect against spontaneous bacterial peritonitis in cirrhotic patients: a meta-analysis. Liver Int. 2009; 29:1189–1193. [PubMed: 19508620]
33. Krag A, Wiest R, Albillos A, et al. The window hypothesis: haemodynamic and non-haemodynamic effects of beta-blockers improve survival of patients with cirrhosis during a window in the disease. Gut. 2012; 61:967–969. [PubMed: 22234982]
34. Bass NM, Mullen KD, Sanyal A, et al. Rifaximin treatment in hepatic encephalopathy. N Engl J Med. 2010; 362:1071–1081. [PubMed: 20335583]
35. Kalambokis GN, Tsianos EV. Rifaximin reduces endotoxemia and improves liver function and disease severity in patients with decompensated cirrhosis. Hepatology. 2012; 55:655–656. [PubMed: 22030839]
36. Vlachogiannakos J. Long-term administration of rifaximin improves the prognosis of patients with alcohol-related decompensated cirrhosis: a case-control study (abstract). Hepatology. 2010; 52:328A.
37. Rimola A, Garcia-Tsao G, Navasa M, et al. Diagnosis, treatment and prophylaxis of spontaneous bacterial peritonitis: a consensus document. International As cites Club. J Hepatol. 2000; 32:142–153. [PubMed: 10673079]
38. Levesque E, Hoti E, Azoulay D, et al. Prospective evaluation of the prognostic scores for cirrhotic patients admitted to an intensive care unit. J Hepatol. 2011; 56:95–102. [PubMed: 21835136]
39. Lehner S, Stemmler HJ, Muck A, et al. Prognostic parameters and risk stratification in intensive care patients with severe liver diseases. J Gastrointestin Liver Dis. 2010; 19:399–404. [PubMed: 21188331]
40. Jain R, Kralovic SM, Evans ME, et al. Veterans affairs initiative to prevent methicillin-resistant Staphylococcus aureus infections. N Engl J Med. 2011; 364:1419–1430. [PubMed: 21488764]
41. Hassanein TI, Tofteng F, Brown RS Jr, et al. Randomized controlled study of extracorporeal albumin dialysis for hepatic encephalopathy in advanced cirrhosis. Hepatology. 2007; 46:1853–1862. [PubMed: 17975845]

42. Garcia-Tsao G, Parikh CR, Viola A. Acute kidney injury in cirrhosis. Hepatology. 2008; 48:2064–2077. [PubMed: 19003880]
43. Belcher JM, Garcia-Tsao G, Sanyal AJ, et al. Association of AKI with mortality and complications in hospitalized patients with cirrhosis. Hepatology. Published Online First: 27 March 2012.
44. Mackle IJ, Swann DG, Cook B. One year outcome of intensive care patients with decompensated alcoholic liver disease. Br J Anaesth. 2006; 97:496–498. [PubMed: 16849386]
45. Salerno F, Gerbes A, Gines P, et al. Diagnosis, prevention and treatment of hepatorenal syndrome in cirrhosis. Gut. 2007; 56:1310–1318. [PubMed: 17389705]
46. Guevara M, Arroyo V. Hepatorenal syndrome. Expert Opin Pharmacother. 2011; 12:1405–1417. [PubMed: 21480763]
47. Fasolato S, Angeli P, Dallagnese L, et al. Renal failure and bacterial infections in patients with cirrhosis: epidemiology and clinical features. Hepatology. 2007; 45:223–229. [PubMed: 17187409]
48. Follo A, Llovet JM, Navasa M, et al. Renal impairment after spontaneous bacterial peritonitis in cirrhosis: incidence, clinical course, predictive factors and prognosis. Hepatology. 1994; 20:1495–1501. [PubMed: 7982650]
49. Angeli P, Guarda S, Fasolato S, et al. Switch therapy with ciprofloxacin vs. intravenous ceftazidime in the treatment of spontaneous bacterial peritonitis in patients with cirrhosis: similar efficacy at lower cost. Aliment Pharmacol Ther. 2006; 23:75–84. [PubMed: 16393283]
50. Tandon P, Garcia-Tsao G. Renal dysfunction is the most important independent predictor of mortality in cirrhotic patients with spontaneous bacterial peritonitis. Clin Gastroenterol Hepatol. 2011; 9:260–265. [PubMed: 21145427]
51. Terra C, Guevara M, Torre A, et al. Renal failure in patients with cirrhosis and sepsis unrelated to spontaneous bacterial peritonitis: value of MELD score. Gastroenterology. 2005; 129:1944–1953. [PubMed: 16344063]
52. Martin-Llahi M, Guevara M, Torre A, et al. Prognostic importance of the cause of renal failure in patients with cirrhosis. Gastroenterology. 2011; 140:488.e4–496.e4. [PubMed: 20682324]
53. Sort P, Navasa M, Arroyo V, et al. Effect of intravenous albumin on renal impairment and mortality in patients with cirrhosis and spontaneous bacterial peritonitis. N Engl J Med. 1999; 341:403–409. [PubMed: 10432325]
54. Poca M, Concepcion M, Casas M, et al. Role of albumin treatment in patients with spontaneous bacterial peritonitis. Clin Gastroenterol Hepatol. 2012; 10:309–315. [PubMed: 22094025]
55. Sigal SH, Stanca CM, Fernandez J, et al. Restricted use of albumin for spontaneous bacterial peritonitis. Gut. 2007; 56:597–599. [PubMed: 17369392]
56. Terg R, Gadano A, Cartier M, et al. Serum creatinine and bilirubin predict renal failure and mortality in patients with spontaneous bacterial peritonitis: a retrospective study. Liver Int. 2009; 29:415–419. [PubMed: 18803587]
57. Chelarescu O, Chelarescu D, Stratan I, et al. Terlipressin influence in spontaneous bacterial peritonitis (abstract). J Hepatol. 2004; 40:67.
58. Caregaro L, Menon F, Angeli P, et al. Limitations of serum creatinine level and creatinine clearance as filtration markers in cirrhosis. Arch Intern Med. 1994; 154:201–205. [PubMed: 8285815]
59. Sherman DS, Fish DN, Teitelbaum I. Assessing renal function in cirrhotic patients: problems and pitfalls. Am J Kidney Dis. 2003; 41:269–278. [PubMed: 12552488]
60. Wong F, Nadim MK, Kellum JA, et al. Working Party proposal for a revised classification system of renal dysfunction in patients with cirrhosis. Gut. 2011; 60:702–709. [PubMed: 21325171]
61. Mehta RL, Kellum JA, Shah SV, et al. Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. Crit Care. 2007; 11:R31. [PubMed: 17331245]
62. Peleg AY, Hooper DC. Hospital-acquired infections due to gram-negative bacteria. N Engl J Med. 2010; 362:1804–1813. [PubMed: 20463340]
63. Klevens RM, Edwards JR, Richards CL Jr, et al. Estimating health care-associated infections and deaths in U.S. hospitals, 2002. Public Health Rep. 2007; 122:160–166. [PubMed: 17357358]

64. Kung HC, Hoyert DL, Xu J, et al. Deaths: final data for 2005. Natl Vital Stat Rep. 2008; 56:1–120. [PubMed: 18512336]
65. Stone PW, Hedblom EC, Murphy DM, et al. The economic impact of infection control: making the business case for increased infection control resources. Am J Infect Control. 2005; 33:542–547. [PubMed: 16260329]
66. Kasper, DL.; Braunwald, E.; Fauci, AS., et al. Harrison's Principles of Internal Medicine. New York: McGraw-Hill; 2005.
67. Wisplinghoff H, Bischoff T, Tallent SM, et al. Nosocomial bloodstream infections in US hospitals: analysis of 24,179 cases from a prospective nationwide surveillance study. Clin Infect Dis. 2004; 39:309–317. [PubMed: 15306996]
68. Hidron AI, Edwards JR, Patel J, et al. Participating National Healthcare Safety Network Facilities. NHSN annual update: antimicrobial-resistant pathogens associated with healthcare-associated infections: annual summary of data reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2006–2007. Infect Control Hosp Epidemiol. 2008; 29:996–1011. [PubMed: 18947320]
69. Kallen AJ, Mu Y, Bulens S, et al. Health care-associated invasive MRSA infections, 2005–2008. JAMA. 2010; 304:641–648. [PubMed: 20699455]
70. Piroth L, Pechinot A, Minello A, et al. Bacterial epidemiology and antimicrobial resistance in ascitic fluid: a 2-year retrospective study. Scand J Infect Dis. 2009; 41:847–851. [PubMed: 19922067]
71. Cheong HS, Kang CI, Lee JA, et al. Clinical significance and outcome of nosocomial acquisition of spontaneous bacterial peritonitis in patients with liver cirrhosis. Clin Infect Dis. 2009; 48:1230–1236. [PubMed: 19302016]
72. Campillo B, Richardet JP, Kheo T, et al. Nosocomial spontaneous bacterial peritonitis and bacteremia in cirrhotic patients: impact of isolate type on prognosis and characteristics of infection. Clin Infect Dis. 2002; 35:1–10. [PubMed: 12060868]
73. Yokoe DS, Mermel LA, Anderson DJ, et al. A compendium of strategies to prvent healthcare-asscoiated infecitons in acute care hospitals. Infect Control Hosp Epidemiol. 2008; 29(Suppl 1):S12–S21. [PubMed: 18840084]
74. Perencevich EN, Lautenbach E. Infection prevention and comparative effectiveness research. JAMA. 2011; 305:1482–1483. [PubMed: 21486981]
75. Christou L, Pappas G, Falagas ME. Bacterial infection-related morbidity and mortality in cirrhosis. Am J Gastroenterol. 2007; 102:1510–1517. [PubMed: 17509025]
76. Bernard B, Cadranel JF, Valla D, et al. Prognostic significance of bacterial infection in bleeding cirrhotic patients: a prospective study. Gastroenterology. 1995; 108:1828–1834. [PubMed: 7768389]
77. Deschenes M, Villeneuve JP. Risk factors for the development of bacterial infections in hospitalized patients with cirrhosis. Am J Gastroenterol. 1999; 94:2193–2197. [PubMed: 10445549]
78. Campillo B, Dupeyron C, Richardet JP. Epidemiology of hospital-acquired infections in cirrhotic patients: effect of carriage of methicillin-resistant Staphylococcus aureus and influence of previous antibiotic therapy and norfloxacin prophylaxis. Epidemiol Infect. 2001; 127:443–450. [PubMed: 11811877]
79. Ortiz J, Vila MC, Soriano G, et al. Infections caused by Escherichia coli resistant to norfloxacin in hospitalized cirrhotic patients. Hepatology. 1999; 29:1064–1069. [PubMed: 10094947]
80. Campillo B, Dupeyron C, Richardet JP, et al. Epidemiology of severe hospital-acquired infections in patients with liver cirrhosis: effect of long-term administration of norfloxacin. Clin Infect Dis. 1998; 26:1066–1070. [PubMed: 9597225]

Table 1

Proposed definition of kidney disease in cirrhosis[60]

Diagnosis	Definition
Acute kidney injury	Rise in serum creatinine of ≥50% from baseline or a rise in serum creatinine of ≥26.4 μmol/l (≥0.3 mg/dl) in <48 h
	HRS type 1 is a specific form of acute kidney injury
Chronic kidney disease	Glomerular filtration rate of <60 ml/min for >3 months calculated using MDRD6 formula
	HRS type 2 is a specific form of chronic kidney disease
Acute-on-chronic kidney disease	Rise in serum creatinine of ≥50% from baseline or a rise in serum creatinine of ≥26.4 μmol/l (≥0.3 mg/dl) in <48 h in a patient with cirrhosis whose glomerular filtration rate is <60 ml/min for >3 months calculated using MDRD6 formula

HRS, hepatorenal syndrome; MDRD, Modification of Diet in Renal Disease.

Table 2

Categories of nosocomial infections in the non-cirrhotic population[66]

	Category	% of overall infections	Contributing factors
1	Bloodstream infections	25–35	Vascular catheters are the most common predisposing factor[68]
2	Urinary tract infections	30–40	≥2 days after insertion of urinary catheters, the risk of bacteriuria increases by 5–10% per day. Lowest risk of mortality
3	Pulmonary infections	15	Often caused by aspiration of Gram-negative oropharyngeal flora. Highest risk of mortality
4	Surgical site infections	18–25	Occur less commonly in patients with cirrhosis, as surgery is often avoided

Table 3

Proposed categories of nosocomial infections in cirrhosis

1	Spontaneous bloodstream infections (unrelated to interventions or infections at other sites)
2	Urinary tract infections
3	Pulmonary infections
4	Spontaneous bacterial peritonitis
5	*Clostridium difficile*
6	Intervention-related infections

Interventions are defined as urinary catheterisation, mechanical ventilation, central line placement, paracentesis, thoracentesis, renal replacement therapy, interventional radiology procedures, and intravenous nutrition.

Table 4

Challenges and future directions of bacterial infection management in cirrhosis

Challenge	Proposed future directions
Current limited single-centre experiences	Large, multicentre studies are needed to study predictors of mortality and nosocomial infections
Poly-pharmacy as a predictor of infections	Study the targeted role of proton pump inhibitors, rifaximin, non-absorbable antibiotics and β blockers in development of infections
Intensive care management of cirrhosis and sepsis	Design measures specifically targeting cirrhotic patients with sepsis and use of the ‘sepsis bundle’
Acute kidney injury in infections	Validate the prevalence of acute kidney injury using the new definition and determine the efficacy of volume expansion using albumin and, potentially, vasoconstrictors in prevention of acute kidney injury
Healthcare-associated and nosocomial infections	Determine the optimal antibiotic and non-antibiotic strategies to reduce further development of resistance
Multidrug resistant organisms	Redefine the role of spontaneous bacterial peritonitis prophylaxis and emphasise the role of non-antibiotic interventions