Bacterial Infections in Cirrhosis

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Abstract

Bacterial infections are the most common trigger of acute decompensation of cirrhosis. The occurrence of infections in cirrhosis is associated with the development of organ dysfunctions, failures and acute on chronic liver failure. The combination of infections and organ dysfunction/acute on chronic liver failure dramatically increases the mortality risk in these patients. Infections in cirrhosis are a big challenge for clinicians, since the mortality from sepsis is increasing in these patients worldwide. The rapid and progressive spread of multiresistant bacteria has been blamed for the increased mortality rate. Several studies have shown that early diagnosis and appropriate administration of antibiotic treatment are crucial for improving prognosis in these patients. Moreover, the prevention and treatment of acute kidney injury and organ failures are fundamental parts of management of infections in cirrhosis. Herein we provided a concise and updated review of the literature on bacterial infections in patients with cirrhosis.

Keywords:
sepsis; septic shock; liver cirrhosis; liver transplantation; multidrug resistant
Introduction

Liver cirrhosis is a leading cause of death worldwide. Patients with cirrhosis have several biological and immunological alterations that predispose to the development of infections.1 These changes involve both a lack of producing an effective immune response and an increase in the exposure of the immune system to gut derived pathogens (Figure 1).2 In cirrhosis, portal hypertension causes an alteration of gut tight junctions, with an increased intestinal permeability, which favors translocation of bacteria from the gut to the systemic circulation.3 In addition, changes in quality and quantity of bacteria (intestinal bacterial overgrowth and proliferation of pathogenic bacteria such as Enterobacteriaceae and Enterococcaceae) further favor this pathological bacterial translocation, predisposing patients with cirrhosis to the development of infections.4 Cirrhosis of the liver is also associated with immune dysfunction that involves both the innate and adaptive immune system, resulting in an ineffective immune response.5 In particular, recent studies identified CD8+ T cell functional and transcriptional alterations in patients with cirrhosis, as well as a reduced count of memory lymphocytes, CD8+ T cells and NK cells, which can contribute to immunosuppression.6,7

The inadequate immune response, the failure of physiological barriers and changes in the microbiome make patients with cirrhosis highly predisposed to the development of bacterial infections, which is the most common precipitating event of decompensation in hospitalized patients with cirrhosis.8

Bacterial infections dramatically impair prognosis in patients with cirrhosis, which is associated with decompensation9 and organ failures,8,10,11 and results in a 4-fold increased mortality risk.12 Infections are the most common trigger of acute on chronic liver failure (ACLF), a condition characterized by acute decompensation of cirrhosis, organ failures and high short-term mortality.8

Strikingly, in recent years, mortality risk has increased in patients with cirrhosis and sepsis, in spite of a reduction in mortality risk from other complications of cirrhosis, such as variceal bleeding and/or hepatorenal syndrome.13 The spread of multidrug resistant (MDR) infections has been blamed as responsible for the increase in mortality risk in cirrhosis.14 Therefore, improvement in the management of bacterial infections represents an absolute priority for patients with cirrhosis.

The purpose of this review is to provide an updated and concise review of the literature on the epidemiology and management of bacterial infections in patients with cirrhosis.

Epidemiology of infections and antimicrobial resistance

Patients with cirrhosis have a 2- to 3-fold higher risk of having bacterial infections and sepsis than other patients admitted to the hospital.15 Approximately 32%-40% of hospitalized patients with cirrhosis develop bacterial infections either at admission or during the hospitalization.16-18 Among these infections, 32%-50% are community acquired, 25%-41% are healthcare-associated and 25%-37% are nosocomial.16,18-24 Importantly, about 25% of patients with cirrhosis and bacterial infections develop secondary infections during hospitalization, which can further complicate the clinical course of these patients, leading to
an increase in short-term mortality. The most common infections in patients with cirrhosis are spontaneous bacterial peritonitis (20%-35%; SBP), urinary tract infections (14%-41%; UTIs), pneumonia (8%-17%), spontaneous bacteremia (8%-21%) and skin and soft tissues infections (6%-13%). Notably, the specific type of infections can be very heterogeneous according to the local epidemiology.

Risk factors for the development of infections are gastrointestinal bleeding, the presence of ascites, low protein content on ascitic fluid and previous episodes of infections. More recently, other clinical characteristics such as ACLF and relative adrenal insufficiency have been found to be associated with the risk of development of bacterial infections and sepsis. Finally, genetic polymorphisms of toll like receptor 2 and nucleotide-binding oligomerisation domain 2, two pathogen pattern recognition receptors, have been shown to be strongly associated with risk of infection.

Enterobacteriaceae such as *Escherichia coli* and *Klebsiella pneumoniae* are the most frequent pathogens responsible for SBP and UTIs, although Gram-positive bacteria such as enterococci are becoming more prevalent. As for the general population, Gram-positive bacteria are more commonly found to be responsible for pneumonia, while in bloodstream infections the prevalence of Gram-positive cocci (including *Staphylococcus aureus*) and Gram-negative bacteria (mainly Enterobacteriaceae) is almost the same. Fungal infections can be found in 4%-7% of patients, although their occurrence in community acquired infections is rare, their prevalence in nosocomial episodes and in alcoholic hepatitis is higher. Among fungal infections, risk factors for invasive candidiasis are previous antibiotic use, gastrointestinal endoscopy, ACLF and presence of a central venous catheter.

MDR bacteria (ie, bacteria with acquired non-susceptibility to at least one agent in three or more antimicrobial categories) are a relevant concern in patients with cirrhosis. In recent years, their prevalence dramatically increased. In a 10-year period, Fernandez et al. showed an increase in the prevalence of MDR from less than 10% to 23% and more recently data from the GLOBAL study and PREDICT study showed that MDR bacteria are responsible for almost one third of infections in cirrhosis cases. Several factors have been blamed for these findings, namely exaggerated use of broad-spectrum antibiotics, quinolone prophylaxis for SBP and frequent hospitalization in patients with cirrhosis. Prevalence of MDR bacteria is quite heterogeneous among different geographic areas, exceeding 70% in India and being lower than 20% in the US. Other factors, such as the over-the-counter access to antibiotics, the use of antibiotics in livestock, and a lack of regulation governing discharge of expired antibiotics, have been attributed to this heterogeneity.

The immediate consequence of the spread of MDR organisms is the reduced efficacy of commonly used empirical antibiotic treatment, which is associated with an increase in mortality rate in patients.

The most common MDR bacteria in patients with cirrhosis are extended-spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae, methicillin-resistant *S. aureus* (MRSA) and vancomycin resistant enterococci. Furthermore, extensively drug-resistant bacteria (ie, bacteria non-susceptible to at least one agent in all but two or fewer antimicrobial categories), such as carbapenemase-producing Enterobacteriaceae and carbapenem-resistant
Acinetobacter baumannii, are a relevant issue worldwide, being highly prevalent in some geographic areas, such as India and Greece. Clinical predictors of infections sustained by MDR organisms are important in clinical practice, because they can guide the selection of empirical antibiotic treatment. Among them, the most important are: nosocomial infections, hospitalization for at least 2 days in the last 3 months, use of antibiotics in the last month, being carriers of MDR bacteria, and being in an area with high prevalence of MDR bacteria. Unfortunately, most epidemiological studies on risk factors for MDR bacteria did not focus on specific type of MDR (eg, ESBL-producing Enterobacteriaceae or MRSA), and future studies should address this issue to guide clinicians in the appropriate selection of empirical antibiotic treatment.

Infections as a trigger of acute decompensation and ACLF

As previously stated, bacterial infections are the most common trigger of acute decompensation and ACLF in patients with cirrhosis. The reason why bacterial infections are so important in patients with cirrhosis concerns the systemic inflammation induced by the interactions between the host and the pathogens. Indeed, the current belief is that most complications of cirrhosis are the consequences of an exaggerated inflammatory response and/or a reduced tolerance of the host to systemic inflammation. In fact, biomarkers of systemic inflammation increase from patients with compensated cirrhosis to those with decompensated cirrhosis and the highest levels are observed in patients with ACLF. Interaction of bacteria with antigen presenting cells, such as monocytes, macrophages or dendritic cells, induces inflammatory responses and recruitment of leukocytes (neutrophils and lymphocytes). Their activation further enhances the inflammatory response and induces the production of nitric oxide and reactive oxygen species (Figure 2). The former is responsible for worsening of splanchnic arterial vasodilation and reduction of effecting circulating volume, and it also induces myocardial dysfunction resulting in a cardiocirculatory dysfunction, while the latter induces oxidative stress causing organ dysfunction and/or failure. Finally, inflammatory cytokines, reactive oxygen species and nitric oxide can induce mitochondrial dysfunction, compromising cellular energy production through oxidative phosphorylation. In this regard, high-throughput metabolomics and lipidomics performed with the sera of patients with acute decompensation of cirrhosis and ACLF showed a marked inhibition of mitochondrial oxidative phosphorylation in patients with ACLF. The aforementioned hypotheses are supported by the following findings: a) patients with cirrhosis and bacterial infections have higher levels of inflammatory cytokines; b) patients with cirrhosis and bacterial infections have higher levels of nitric oxide and carbon monoxide; c) levels of reactive oxygen species increase following stimulation with lipopolysaccharide in experimental cirrhosis; d) patients with cirrhosis and spontaneous bacterial peritonitis have reduced peripheral vascular resistance and higher plasma renin activity; e) levels of inflammatory cytokines and markers of oxidative stress predict the development of organ failure; and f) metabolic fingerprints suggesting mitochondrial dysfunction is commonly observed in patients with cirrhosis and bacterial infections.
Moving on clinical ground, patients with cirrhosis and bacterial infections more frequently develop acute kidney injury (AKI), hepatorenal syndrome, hepatic encephalopathy, and organ dysfunctions and failures. The occurrence of organ dysfunction and/or failure is the most important predictor of mortality in patients with cirrhosis and bacterial infections, with the highest mortality observed in patients with ACLF. The occurrence of ACLF is also associated with a high instrumentation of patients and further worsening of immune dysfunction, which predispose the patients to the development of further infections. Therefore, when ACLF is associated with bacterial infections, its prognosis is quite worse than when it is not.

**Diagnosis of infections in patients with cirrhosis**

The prompt identification and diagnosis of infections is crucial in patients with cirrhosis. In the early phase of infection, signs and symptoms are frequently subtle in these patients and the onset of complications of cirrhosis (ascites, hepatic encephalopathy, gastrointestinal bleeding) or worsening of renal function can be the sole sign of infection. Therefore, all patients admitted to the hospital with decompensated cirrhosis should be considered potentially infected until proven otherwise. If clinical signs of infection are missing, other parameters may be helpful in evaluating infections in these patients. Acute phase proteins such as C-reactive protein or procalcitonin have been proven to be useful in predicting infections in patients with cirrhosis, being as accurate in cirrhosis as in the general population.

All patients admitted to the hospital for decompensated cirrhosis and/or showing deterioration of liver/kidney function should be investigated for infections. An adequate workup for infections includes an accurate physical examination, a diagnostic paracentesis, blood and urine culture, urinalysis and chest X-ray. The diagnostic criteria for infection in cirrhosis are the same as those used in the general population; however, diagnostic criteria for SBP deserve a specific mention. SBP is defined as an infection of peritoneal fluid without evidence of an abdominal, surgically-treatable source. SBP is diagnosed by means of paracentesis, and a neutrophil count > 250 cells/µl in ascitic fluid is required to diagnose SBP. Paracentesis should not be delayed in hospitalized patients with cirrhosis and ascites, because a delay in performing paracentesis has been associated with lower survival in patients with SBP.

A small proportion of patients with cirrhosis and ascites (<5%) may develop secondary bacterial peritonitis. The indicators for secondary peritonitis include a lack of response to antimicrobial therapy, multiple organisms in ascitic fluid culture, and the combination of at least 2 of the following findings in ascitic fluid: i) glucose levels <50 mg/dl; ii) protein concentrations > 10 g/l; or iii) lactate dehydrogenase concentrations above normal serum levels.

In all patients with infections, the presence of sepsis should be evaluated, assessing the increase ≥ 2 points in the sequential organ failure assessment (SOFA) score. In patients with cirrhosis who frequently have jaundice and thrombocytopenia, a baseline SOFA score is required for an accurate diagnosis of sepsis. When a baseline SOFA score is not available, the
combination of a SOFA score $\geq 2$ points and a quick SOFA (qSOFA) score $\geq 2$ is suggested to identify patients with sepsis.\textsuperscript{20}

**Treatment of infections**

*Antibiotic treatment*

Once the diagnosis of bacterial infection is made, empiric antibiotic therapy should be initiated as soon as possible. In fact, a delay in starting an effective antimicrobial therapy is associated with an increased risk of mortality in patients with cirrhosis and septic shock.\textsuperscript{63} In addition to empiric antibiotic treatment, sepsis and septic shock should be treated with an adequate resuscitation protocol.\textsuperscript{64} Blood, urine and, if present, ascites cultures should be collected before the administration of antibiotics. Ascitic fluid cultures should be collected in blood culture bottles immediately after paracentesis, to improve the detection of microorganisms.\textsuperscript{65}

The choice of the empirical antibiotic treatment should be tailored to the clinical scenario. The type, site and severity of the infection, the local epidemiology and the risk factors for MDR bacteria drive the selection of empirical antibiotic treatment (Figure 3).\textsuperscript{2,66}

Recommendations for the treatment of pneumonia, UTIs and skin and soft tissue infections follow the ones provided for general population; however, the use of aminoglycosides should be avoided in patients with cirrhosis, since these drugs are associated with a high risk of nephrotoxicity.\textsuperscript{67} In patients with sepsis/ACLF, a broad-spectrum empirical antibiotic treatment (eg, those provided for nosocomial episodes) should be considered, because failure of antibiotic treatment dramatically increases mortality.\textsuperscript{18,57}

In patients with SBP and spontaneous bacterial empyema, third-generation cephalosporins (ceftriaxone 2g once a day, or cefotaxime 2g twice a day) are the first-line treatment in community acquired episodes. Amoxicillin/clavulanic acid is considered an equivalent alternative. In patients with community acquired SBP and sepsis/ACLF, a broad-spectrum treatment (eg, piperacillin/tazobactam) should be considered. The use of carbapenems has been shown to be associated with a lower mortality rate than third-generation cephalosporins in patients with organ dysfunction (ie, CLIF-SOFA score $\geq 7$), while no benefit was found in patients without.\textsuperscript{68} Although not randomized, this study suggests that carbapenem use should be limited to patients with a high risk of mortality.

In patients with nosocomial SBP, third-generation cephalosporins are poorly effective and a broader spectrum treatment ensuring coverage for ESBL-producing Enterobacteriaceae, MRSA and Enterococci should be considered.\textsuperscript{24,37} Piano et al. showed that a combination of meropenem (1g three times a day) plus daptomycin (6 mg/kg once a day) is more effective than ceftazidime in the treatment of nosocomial SBP (87\% vs 25\%), and that the efficacy of empirical antibiotic treatment is associated with increased survival.\textsuperscript{37} Of course, this strategy cannot be universally applied, but should be adapted to local epidemiology. In patients with healthcare-associated infections (recent hospitalization, nursing home resident, etc), the use of a broad-spectrum treatment should be considered, given the high risk of failure of treatment with third-generation cephalosporins. In this setting, Merli et al. found a broad-spectrum treatment associated with a lower mortality rate.\textsuperscript{38} Finally, extended/continuous
infusion of beta-lactam antibiotics should be considered, since it may increase the time of plasma antibiotic concentration above the minimal inhibitory concentration and has been associated with better survival in patients with cirrhosis and bloodstream infections.69

Whenever microbiological cultures allow identification of bacteria responsible for infections, antibiotic therapy should be modified according to the antimicrobial susceptibility tests.2 In those with negative cultures, antibiotic treatment should be adapted to clinical course. In patients with negative cultures, no clinical improvement and no reduction of acute phase proteins, an escalation of antibiotic treatment should be considered.66 In patients with SBP, a diagnostic paracentesis after 48 hours from the beginning of the treatment is useful to predict response to treatment. In fact, a reduction of neutrophil count in ascitic fluid of less than 25% of the baseline suggests a failure of antibiotic treatment.

Although the duration of antibiotic treatment has not been specifically investigated in patients with cirrhosis, a 5- to 7-day course is considered appropriate for the majority of infections. In patients with SBP, a 5-day course has been associated with a similar efficacy than a 10-day course of treatment.70

As MDR bacteria continue to evolve, new antibiotic strategies are being developed in order to provide effective treatment for extensively drug-resistant bacteria. This is particularly relevant for carbapenem-resistant Gram-negative bacteria. New carbapenemase inhibitors, such as vaborbactam, avibactam and relebactam, have been combined with cephalosporins (ie, ceftazidime) or carbapenems to ensure high efficacy against Gram-negative MDR bacteria producing carbapenemases.71 These carbapenemase-inhibitors are effective against the Klebsiella pneumoniae carbapenemase (avibactam, varbobactam, relebactam) and the OXA-48-type carbapenemase (avibactam), but are not effective against metallo-β-lactamases. In this regard, cefiderocol seems to be a relevant new asset.72 In addition, alternatives to carbapenems for ESBL-producing Enterobacteriaceae, such as ceftolozane/tazobactam, are available and may help to reduce the exposure to carbapenems. Despite the widespread use and proven efficacy of these new drugs in the general population, currently, there is a paucity of data about their use in patients with liver cirrhosis.

**Prevention of AKI**

As hinted before, cirrhotic patients with bacterial infections have an increased risk of developing AKI, which is associated with a high risk of mortality.73 Therefore, non-steroidal anti-inflammatory drugs and aminoglycosides should be avoided in these patients. For the same reason, beta-blockers should be used with caution, since they seem to be associated with a high incidence of AKI and short-term mortality in patients with SBP.74 Moreover, the administration of albumin (1.5 g per kg of body weight on day-1 and 1 g per kg of body weight on day-3) together with antibiotics seems to be associated with a lower risk of developing AKI and a lower mortality risk in patients with SBP.75 This is probably related to its oncotic, immunomodulant and antioxidant properties.76 The beneficial effects of albumin in preventing AKI have not been clearly proved in patients with infections other than SBP. In fact, in the study by Guevara et al.,77 the administration of human albumin was associated with an improvement in renal function and survival in patients with infections other than SBP. Subsequently, Thevenot et al.78 did not show a difference in the 3-month renal failure
rate and survival rate between patients who received albumin and patients who did not. Moreover, they reported some cases of pulmonary oedema in the group of patients treated with albumin. More recently, the INFECIR-2 trial was early terminated for low recruitment rate and lack of differences in survival after interim analysis. 79 However, improvement in circulatory and renal function as well as resolution of ACLF was significantly more common in the albumin group than in the control group. In spite of strong rationale, current evidences do not support the routine use of albumin in patients with cirrhosis and infections unrelated to SBP.

**Prevention of bacterial infections**

Considering the deep negative impact of bacterial infections in patients with cirrhosis, prevention of infections can be crucial in the management of the disease.

Antibiotic drugs have been extensively investigated for this purpose. Antibiotic prophylaxis is currently recommended for three patient categories: a) patients with a previous episode of SBP; b) patients with gastrointestinal bleeding; and c) patients at high risk of SBP, ie, patients with ascites protein levels <15 g/L and at least one among the following: Child-Pugh score ≥9 with serum bilirubin ≥3 mg/dL, serum creatinine ≥1.2 mg/dL, blood urea nitrogen ≥25 mg/dl or serum sodium ≤130 mEq/L. 60

In patients with a previous episode of SBP, the risk of recurrence is almost 70% within one year. Norfloxacin (400 mg once a day) significantly reduces the recurrence rate of SBP. 80 In addition, in patients with advanced cirrhosis and low ascitic protein level (ie, < 15 g/L), norfloxacin reduced the incidence of SBP and hepatorenal syndrome and showed a trend toward an improvement in survival. 81 These results led other authors to investigate the use of norfloxacin in all patients with advanced cirrhosis (ie, Child-Pugh class C). However, norfloxacin did not improve survival in these patients and a survival benefit was shown only in the subgroup of patients with ascitic protein levels < 15 g/L. 82

Bacterial infections are observed in more than 50% of patients with cirrhosis and gastrointestinal bleeding, being associated with failure to control bleeding, rebleeding and mortality. 60 In these patients, antibiotic prophylaxis with norfloxacin (400 mg twice a day for 7 days) is effective in reducing both the incidence of severe infections (SBP and/or bloodstream infections) and mortality. 83 However, in patients with advanced cirrhosis (at least 2 of the following: ascites, severe malnutrition, encephalopathy or bilirubin >3 mg/dL) and gastrointestinal hemorrhage, ceftriaxone (1 g once a day) has been shown to be more effective than oral norfloxacin in preventing bacterial infections. 84 Rifaximin has been proposed as an alternative to norfloxacin in the prophylaxis of bacterial infections in cirrhosis considering that its use in hepatic encephalopathy has not been associated with the development of MDR bacteria. 85,86 However, its real efficacy in this context is still to be determined.

The most important drawback of antimicrobial prophylaxis is the risk to promote antimicrobial resistance. 87 Therefore, non-antibiotic strategies are strongly needed. Preclinical studies showed interesting data about the combination of antioxidants and probiotics, 88 prokinetics 89 and farnesoid X receptor agonists, 90 all being shown to prevent
either bacterial translocation or bacterial overgrowth in experimental models of cirrhosis. However, randomized controlled trials should prove their efficacy on clinical ground. Finally, studies on some drugs used for the treatment of complications of cirrhosis, such as albumin and non-selective beta-blockers, showed interesting results in preventing infections. Albumin was shown to restore immune function in cirrhosis and the long term use of albumin (40 g per week) reduces the incidence of infections and improves survival in patients with uncomplicated ascites and refractory ascites. However, these data were not confirmed when albumin was used at lower doses and for a shorter time. More recently, China et al. investigated whether the use of daily infusions of 20% human albumin solution to target a serum albumin level of 30 g/L would reduce the incidence of infections in patients admitted to the hospital for complications of cirrhosis. The results showed that albumin is not more beneficial than standard care and is associated with side effects. The discrepancy between the outcomes reported in the ANSWER trial and the ATTIRE trial deserves some comments. The populations selected in the two studies were quite different. In particular, patients enrolled in the ANSWER trial all had ascites, a better liver function (lower MELD score) and were more stable (ie, no renal failure, no bacterial infections in the previous 7 days, and no variceal bleeding in the previous 14 weeks). The enrolment of patients with acute decompensation of cirrhosis, which were quite unstable and heterogeneous, may have affected study results in the ATTIRE trial. Moreover, the doses of albumin used (adapted to albumin concentration in the ATTIRE trial and fixed in the ANSWER trial) and the duration of treatment were quite different (the administration of albumin lasted for 18 months in the ANSWER trial and for 14 days in the ATTIRE trial). It is likely that the administration of albumin for a short time was not sufficient to exert clinically meaningful effects. In this regard, it is worth noting that in the ANSWER trial the survival curves begun to separate after 2-3 months of albumin treatment. Finally, the higher intensity of medical supervision during weekly infusion of albumin could have been responsible for better outcomes in the ANSWER trial. Anyhow, the implementation of albumin use apart from clearly established indications is still a debated topic that should be addressed in the future.

As far as non-selective beta-blockers are concerned, their use has been shown to decrease intestinal permeability and the incidence of SBP.

**Conclusion**

Bacterial infections are a very important complication in patients with cirrhosis, since they are associated with an increased risk of mortality. The early detection and effective treatment are of paramount importance to improve the prognosis of these patients. The increasing prevalence of MDR bacteria is probably the most serious threat that clinicians are facing in the management of cirrhosis nowadays. Therefore, new strategies should be developed to improve their diagnosis and treatment. In this regards, priority areas for future research are: a) development of new tools to allow a faster identification of strains responsible for infections and their antibiotic susceptibility; b) development of biomarkers to identify early-stage infections in asymptomatic patients and guide duration of treatment; c) the discovery of new broad-spectrum antibiotics; d) strategies to prevent organ failure and ACLF in patients with infections; and e) new prophylactic strategies to prevent infections in cirrhosis.
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**Figure legend**

**Figure 1. Factors predisposing patients with cirrhosis to bacterial infections.** GI, gastrointestinal.
Figure 2. Pathophysiology of organ failures in patients with cirrhosis and bacterial infections. NO, nitric oxide; ROS, reactive oxygen species.

Figure 3. Management of infections in hospitalized patients with cirrhosis. *, ascites, gastrointestinal bleeding, hepatic encephalopathy, acute kidney injury; †, broad spectrum antibiotics including the use of carbapenems (+ glycopeptides/lipopeptides if risk of MRSA, or oxazolidinones if risk of VRE); #, patients with nosocomial infections should be treated with broad spectrum antibiotics; patients with healthcare-associated infections should be treated according to local epidemiology and risk factors (previous exposure to antibiotics). Modified from Piano et al.94 with permission from the authors.