Bloodstream infections in patients with liver cirrhosis

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ABSTRACT
Bloodstream infections are a serious complication in patients with liver cirrhosis. Dysregulated intestinal bacterial translocation is the predominant pathophysiological mechanism of infections in this setting. For this reason enteric Gram-negative bacteria are commonly encountered as the first etiological cause of infection. However, through the years, the improvement in the management of cirrhosis, the recourse to invasive procedures and the global spread of multidrug resistant pathogens have importantly changed the current epidemiology. Bloodstream infections in cirrhotic patients are characterized by high mortality rate and complications including metastatic infections, infective endocarditis, and endotipsitis (or transjugular intrahepatic portosystemic shunt-related infection). For this reason early identification of patients at risk for mortality and appropriated therapeutic management is mandatory. Liver cirrhosis can significantly change the pharmacokinetic behavior of antimicrobials. In fact hypoproteinaemia, ascitis and third space expansion and impairment of renal function can be translated in an unpredictable drug exposure.

KEYWORDS
bacteremia; bloodstream infections; epidemiology; liver cirrhosis; pathophysiology; therapeutic management

Introduction
Liver cirrhosis (LC) is the 10th most common cause of death in Western world. Infections are among the most important complications of end-stage liver disease (ESLD), in term of incidence, severity and impact on the overall outcome. Indeed, they represent the primary cause of admission at emergency department among patients with LC. About 20–30% of hospital admissions for acute decompensation are related to an infection, or complicated with an infection during the in-hospital stay. In those cases, 10% of patients have more than one episode within the same hospitalization. Moreover, the need for frequent exposure to healthcare environment due to the complication of LC, make this population prone to develop healthcare related infections typically characterized by difficult-to-treat and multidrug resistant pathogens.

Infection-related mortality is high in patients with ESLD, approaching 30% within 30 days and 66% within 1 year from the hospital admission. For this reason, infection is considered an important prognostic marker in patients with ESLD.

Bloodstream infections (BSIs) are a common complication in patients with ESLD, affecting 4–21% of patients, making them 10 times more common in cirrhotic than in non-cirrhotic patients. The increased gut permeability and the cirrhosis associated immune dysfunction (CAID) make this population prone to develop BSI by endogenous route, particularly during acute-on-chronic liver failure (ACLF). Frequent need for hospitalization, invasive procedures and, use of indwelling devices such as central venous line or transjugular intrahepatic portosystemic shunt (TIPS), give to the exogenous route an additional pathogenetic rule, further increasing the overall risk, mainly in the setting of Health Care Associated or Hospital Acquired infections.

BSIs in LC are also associated with high mortality, prolonged hospitalization and faster escalation of the liver disease. In different studies including both cirrhotic and non-cirrhotic patients with bacteremia or candidemia, LC was found to be an independent predictor of mortality. The present review focuses on epidemiology, risk factors for mortality, complication of BSI and therapeutic principles in patients with LC. All these aspects are closely related to the unique pathophysiology of the infectious risk in this patient population.
Pathophysiology of BSIs in patients with liver cirrhosis: intestinal translocation and cirrhosis-associated immune dysfunction

The epidemiology and high mortality rate of BSIs in cirrhotic patients are hypothesized to be a consequence of two interconnected pathophysiological conditions: dysregulated intestinal bacterial translocation and cirrhosis-associated immune dysfunction (CAID). This latter summarizes both local and systemic immune system alterations in LC that play a pivotal role in determining the high incidence of infections and the ominous infection-related mortality in this patient population.11

Low-grade bacterial translocation is common in healthy patients and it is neutralized by gut-associated lymphoid tissue, systemic immunity, or directly by the liver. Liver exerts a surveillance function against bacteria and plays a primary role for the immune homeostasis of the whole organism. In experimental models impairment of Kupffer cells function resulted in the lower ability in clearing bacteria from the bloodstream and preventing uncontrolled bacteremia, especially when it originates from gut translocation.19,20 In another animal model, a structural damage due to septal and sinusoidal fibrosis compromised the immune filter activity of the liver and promoted the occurrence of infections, mainly BSI and SBP. 15 Moreover, the liver is responsible for the production of complement proteins which act in the regulation and effector phase of adaptive immune response.21 Liver disease can also affect the blood concentration of acute phase proteins (i.e. C Reactive Protein and lypopolysaccharide-binding protein, soluble CD14) and pattern recognition receptors (such as toll-like receptors) which are key element of the innate immune system.22,23 Several other abnormalities of the immune system cells have been described, including impaired phagocytosis, myeloperoxidase production and chemotaxis of neutrophils to the infection site; dysfunction and reduction of B cell lymphocytes; presence of T cell lymphopenia with impairment of cell mediated immunity.11,21,24-26

In patients with LC dysregulated bacterial translocation is facilitated by three factors: i) bacteria overgrowth, ii) the impairment of intestinal barrier function and iii) the dysfunction of local immune defenses.

Bacterial overgrowth and the related intestinal dysbiosis represent an imbalance of intestinal ecosystem, with a decrease in overall microbial diversity and a shift from the physiological abundance of Firmicutes and Bacteroidetes phyla to an abundance of Proteobacteria phylum (which includes Enterobacteriaceae).27-29

In animal models of LC, portal hypertension and intestinal hypo-mobility lead to bacterial overgrowth in the small bowel and is considered the primus movens of translocation in these models.30 In a clinical study of 24 patients with liver cirrhosis the bacterial overgrowth was enhanced by portal hypertension, as suggested by animal models.31 In addition progressive intestinal dysbiosis was identified in patients with LC especially in advanced stages of the disease.32 Interestingly, drugs that may alter the microbiota (i.e. proton pump inhibitors) or that affect the intestinal mobility (β-blockers) can have a role modifying the rate of bacterial infections in this setting.33

The alterations in intestinal barrier permeability along with local immune dysfunction play a key role in determining an increase in bacterial translocation. Experimental and clinical studies have demonstrated that intestinal hyper-permeability is common in LC, especially in advanced disease acting as an independent predictor of the risk for spontaneous bacterial peritonitis.34,35 In a study including 80 cirrhotic patients and 24 controls assessed for intestinal permeability, the risk of SPB and BSI were directly related to the grade of intestinal barrier dysfunction measured by the expression of tight junction protein Claudin-2.36

Etiology

Etiological distribution of BSIs in cirrhotic patients can be described in terms of pathophysiological and historical points of view.

In terms of pathophysiology, because the main route of bacteremia in cirrhotic patients is endogenous seeding from the gastrointestinal tract, Gram-negative enteric bacilli, anaerobes, and Enterococcus spp. are the leading causes of BSI.

However, owing the improvement in the management of LC with an increased use of invasive procedures, exogenous route of infection (central venous catheter, TIPS etc) has become common. As a consequence, the incidence of staphylococcal BSI has been increasing over the last 10 years.9,37 Moreover, the extended use of antibiotic prophylaxis, mainly with norfloxacin, has exercised a selective pressure on both gut and hospital environment, resulting in an increasing rates of multi-drug-resistant (MDR) bacteria, extensively drug-resistant (XDR), and fungi.38-41

Drawing a historical timeline (Fig. 1), the etiology of BSI was predominated by Gram-negative bacteria (GNB) until the 1990s. Then, the already mentioned changes in the supportive care of cirrhotic patients and the extended use of quinolone prophylaxis, drove a shift toward Gram-positive bacteria (GPP) infections, mainly staphylococci.9,37 However, in the following years, GNB have been re-emerging as causes of BSI in cirrhotic patients as
a consequence of multiple factors impacting in the whole hospital setting. They include i) improvement in the prevention of hospital-acquired infections, mainly those devices-related, has reduced the incidence of staphylococcal infections; ii) quinolones have lost activity against Gram-negative due to widespread and extended use; iii) the increased use of broader-spectrum antibiotics created ideal conditions for the selection and transmission of MDR/XDR GNB in hospitals worldwide.38-41

The increasing prevalence of MDR/XDR GNB, in particular, should be kept in mind when empirical antibiotic treatment is prescribed. The spread of these strains in fact is a leading cause of failure of antimicrobial empirical treatment in LC.42 We recently analyzed 162 cirrhotic patients with BSI hospitalized at our hospital from 2008 to 2012.38 GNB, which caused 64% of episodes, were classified as MDR and XDR in 25% and 21% of cases, according to the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and consensus definitions.43 Considering isolate susceptibility, the frontline use of a third generation cephalosporin for empirical coverage of GNB, was adequate in only 60% of BSI episodes. Not surprisingly, inadequate treatment defined by MIC sensitivity was significantly associated to in-hospital mortality in our series. [adjusted HR 0.37 (95% CI 0.20-0.70) - P = 0.002]

Although our data are referred to a single institution, poor antibiotic coverage provided by cephalosporines was observed also in studies conducted in countries with low prevalence of ESBL producing Enterobacteriaceae.44

Candida spp should not be forgotten among the pathogens involved in LC related BSIs. Candidemia may arise both endogenously and exogenously in patients with LC, but nearly always occurs when a prolonged antibiotic exposure is documented. In our series, Candida species accounted for 10% (16/162) of BSIs.38 Candida BSIs were more common in cirrhotic patients with more than 6 days of hospital stay prior to developing BSI (P = 0.009), hospital-acquired BSI (P = 0.03), prior surgery (P = 0.013), central venous catheter (P = 0.004), neutropenia (P = 0.05), or prior piperacillin-tazobactam (P = 0.05) or fluoroquinolone (P = 0.013) antibiotic therapy. Of the 11 patients with primary BSI, 9 (81%) were exposed to prolonged (> 5 days) broad spectrum antibiotic therapy within the 30 days before candidemia. In addition, Candida BSI had the strongest association with inappropriate empirical therapy. Of note, although the increasing incidence of candidemia among patients hospitalized in internal medicine departments is a topic of the present literatures, none of published studies have analyzed the incidence and characteristics of candidemia in cirrhotic patients. Thus this could represent a topic for future epidemiological investigations.
Finally, patients with LC are at risk to develop streptococcal BSI including pneumococcal invasive disease and group B streptococcal invasive disease.\textsuperscript{45,46}

Table 1 summarizes published studies describing the etiology of BSI in cirrhotic patients. Notably, all of the published series are single center and mostly retrospective, thus generalizability of their results may be limited by the local epidemiology and the studied population (severity of cirrhosis, community vs. healthcare or hospital acquired infections). To overcome these limitations, a multicentre prospective observational study on cirrhotic patients with BSI is ongoing in 6 countries. Preliminary data show that the main pathogens of BSI are Enterobacteriaceae (43%), \textit{Staphylococcus} spp (23%) and \textit{Enterococcus} spp (19%). Among Enterobacteriaceae, 53% and 5% resulted to be MDR and XDR, respectively. \textit{Candida} spp was isolated in 8% of BSI.\textsuperscript{47}

\textbf{Clinical findings and complications}

Early recognition of infection severity in patients with LC can be difficult. Systemic inflammatory response syndrome criteria defining severe sepsis in non-cirrhotic patients\textsuperscript{48} may be less accurate and applicable then in patients with liver cirrhosis.\textsuperscript{49} Indeed, cirrhotic patients, even if not infected, often present hypotension and hyperdynamic circulatory state, have low white blood cell count as a result of hypersplenism, and may exhibit a reduced production of acute-phase proteins, especially C-reactive protein, in response to infection.\textsuperscript{50,51} In a study enrolling patients with ACLF admitted to ICU, SIRS was not an independent factor for mortality at multivariate analysis.\textsuperscript{52}

Other well-known scores for BSI severity, such as the Pitt score has not been validated in the LC population, but probably could have many of the same limitations of sepsis score, being based on fever, hypotension, mechanical ventilation, cardiac arrest and altered mental status.\textsuperscript{53}

On the other hand the cirrhosis-specific scores, such as the Child Pugh and MELD have been reported to be useful to predict infection severity in LC setting.\textsuperscript{54} In a large cohort study involving cirrhosis patients with community acquired pneumonia, Viasus et al. showed that the MELD score predicted both patient mortality and the need for ICU admission better than the Pulmonary Severity Index (PSI) and CURB-65 (Confusion-Urea-Respiratory rate-Blood pressure-65 older age) score. Moreover, the MELD was the only predictor of severe infection (OR 1.22, 95\%CI 1.04–1.42, \(p = 0.01\)) in multivariate analysis.\textsuperscript{55}

In the above mentioned study on LC patients with BSI performed at our center, we evaluated the MELD score prior BSI, the MELD score at BSI and the APACHE II score at BSI, finding that the \(\Delta\)MELD (difference between the MELD at BSI onset and the baseline MELD) was the best predictor of 30-day crude mortality. This result may be partially explained by the fact that infection changes the history of ESLD, increasing the morbidity and mortality of patients with liver cirrhosis.\textsuperscript{38}

Recently, a new liver disease score, the chronic liver failure-sequential organ failure assessment (CLIF-SOFA) for predicting the short-term mortality in patients with ACLF. The CLIF-SOFA categorizes patients in 4 different stages according to the number of organ system failures. It was proposed and validated in a large prospective multicentre study. The overall 28-day mortality rate in 415 patients with ACLF was 32.8\%, ranging from 23.3\% to 74.5\% for grade 1 to 3. Mortality in cirrhotic patients with no ACLF was 1.9\%.\textsuperscript{56} Of note, in the validation study, one third of the ACLF episodes were triggered by infection. Unfortunately, the authors did not investigate the differences in accuracy of CLIF-SOFA among patients with and without infection. Therefore, the value of CLIF-SOFA score as a prognostic index for BSI in cirrhotic patients requires further validation.

The high propensity of cirrhotic population to develop BSI may enhance the incidence of BSI-related complications, including metastatic infections, infective endocarditis (IE), and endotipsitis.

A population based study performed in Taiwan, compared 40,803 cirrhotic patients with 40,841 randomly selected control subjects with similar age and sex distribution. Overall 192/81,644 (0.24\%) patients experienced IE within 3 years of follow-up. Of these, 121 were cirrhotic patients (0.30\%) and 71 were controls (0.17\%) (\(p < 0.001\)). Thus, the study demonstrated a 2-fold higher risk to develop IE in LC.\textsuperscript{57} In a case-series enrolling 316 patients with IE, 10\% of patients had an underlying LC.\textsuperscript{58} In another study of \textit{S.aureus} BSI, 2\% of patients with LC were diagnosed as having staphylococcal IE.\textsuperscript{59}

Because of the majority of data regarding IE in LC come from small single-center retrospective series without any stratification regarding cirrhosis severity and evolutionary stage, the question whether a diagnosis of IE should be routinely excluded in all the cirrhotic patients with BSI, at least if a GBP is isolated, is still unresolved. In addition, it has to be considered that the referral diagnostic tool for IE diagnosis, the trans-esophageal echocardiography, could be contraindicated or dangerous in a proportion of LC patients for the risk of upper gastrointestinal bleeding.

With the already reported limitations, IE in the setting of cirrhosis seems to have similar features of non-cirrhotic population. In fact, in LC, like in general population, predisposing valve diseases and left-side endocarditis are
Table 1. Studies assessing the epidemiology and outcome of bloodstream infections in patients with liver cirrhosis

| Author/year (ref.) | Study design | Study Population | N episodes and incidence | Onset | Site of infection | GPC | GNB | Yeasts and polymicrobial BSI | MDR pathogens | Mortality rate |
|-------------------|--------------|------------------|--------------------------|-------|-------------------|-----|-----|----------------------------|---------------|---------------|
| Thulstrup/2000    | Retrospective observational, multicenter. Patients identified with discharge records. | 1339 patients with LC (54% with alcoholic LC) | 117 BSI 18.3 cases per 1000 person-year | 45% CA 55% HA | Not reported | 53/113 (47%) - Staphylococcus aureus 26/113 (23%) - Streptococcus pneumoniae 16/113 (14%) | 55/113 (48%) - Escherichia coli 46/113 (41%) - Other enteric bacteria 6/113 (5%) | Candida spp 1/113 (1%) Polymicrobial BSI 8/113 (7%) | Not reported | 30-day mortality rate 53% |
| Campillo/200227   | Prospective, single-center enrolling patients with nosocomial infection | 200 cirrhotic patients with either SBP and BSI (87% with alcoholic LC) | 119 BSI 194 SBP | All NA | Not reported | 87/119 (73%) - S.aureus 39% Streptococcus spp 17% CoNS 9% Enterococcus spp 8% | 31/119 (26%) Enterobacteriaceae 21% (E.coli 18%) Non-fermenting bacilli 4% | Not reported | MRSA 34% In-hospital mortality 58% |
| Karvellas/201022  | Retrospective, single-center | 184 ICU patients with ACLF (alcoholic in 48% cases) | 99 BSI episodes in 67 patients | All NA | 13 % SBP 9 % LRTI | 36% | Enterobacteriaceae | Candida 6% | | In-ICU mortality 75% |
| Hsieh/201436     | Retrospective, single-center | 246 cirrhotic patients (HBV 46%; HCV 34%) | 246 community-onset BSI | All CA IAI 45% Primary BSI 17% UTI 16% | 50/246 (20%) Streptococcus spp 12% S.aureus 8% | 196/246 (80%) E.coli 33% K.pneumoniae 24% | Polymicrobial BSI 12 | MRSA 3% BSI Among Enterobacteriaceae FQ resistance 12%; ESBL production in 6% | 28-day mortality 23% |
| Bartoletti/201418 | Retrospective, single-center | 162 Patients with LC (HCV 51% Alcholic 32%) and BSI | 162 BSI | CA 7% HCA 20% HA 73% | Primary 72% LRTI 9% SBP 8% UTI 7% | 62/162 (38%) Enterococcus spp 16% S.aureus 12% | 104/162 (64) E.coli 29% K.pneumoniae 18% Non fermenting bacilli 15% | Candida spp 9% Polymicrobial 18% | MRSA 3% E.faecium 7% 30-day mortality 29% |

(continued)
Table 1. (Continued)

| Author/year (ref.) | Study design | Study Population | N* episodes and incidence | Onset | Site of infection | GPC* | GNB* | Yeasts and polimicrobial BSI* | MDR pathogens* | Mortality rate |
|--------------------|--------------|------------------|---------------------------|-------|------------------|------|------|----------------------------|----------------|---------------|
| Park/2015[40]     | Retrospctive, single-center, observational | 72 patients with LC (47% with alcoholic LC) | 102 BSI | CA 22% HCA 3% HA 68% | Primary BSI 33% SBP 30% UTI 17% | 52/102 (51%) S. aureus 13% CoNS 21% | 50/102 (49%) K. pneumoniae 18% E. coli 16% Non-fermenting bacilli 8% | Not reported | 15% KPC producing K. pneumoniae 8% | Not reported | 30-day mortality 30% |
| Brandolini/2015[41] | Retrospctive, single-center. Patients identified with discharge records. | 1161 patients with LC or chronic hepatitis | 148 BSI 0.60 episodes for 100 days of hospital stay | CA 43% HA 57% | 62/148 (42%) S. aureus 13% Enterococcus spp 11% | 80/148 (54%) E. coli 23% K. pneumonia 6% Non-fermenting bacilli 9.5% | Candida spp 4% | MRSA 2% E. faecium 4% In-hospital | Carbapenemase production 6% |

Notes: * percentages among all BSI
Abbreviations: GPC Gram-positive cocci
GNB Gram-negative bacteria
BSI bloodstream infection
MDR multidrug resistant
LC liver cirrhosis
CA community acquired
HA hospital acquired
HCA healthcare associated
SBP spontaneous bacterial peritonitis
UTI urinary tract infection
CoNS coagulase-negative staphylococci
MRSA methicillin-resistant Staphylococcus aureus
ICU: intensive care unit
ACLF acute-on chronic liver failure
HBV hepatitis B virus
HCV hepatitis C virus
IAI intra-abdominal infection
FQ fluoroquinolones
ESBL extended spectrum β-lactamase
LRTI lower respiratory tract infection
KPC Klebsiella pneumoniae carbapenemase
common (48% aortic valve IE, 45% mitral valve IE) and S. aureus is the main pathogen accounting for 30-80% of cases followed by Streptococcus spp. On the other hand, compared with non-cirrhotic population, IE in patients with liver disease is associated with higher rates of renal failure and worse outcome, and less frequently is managed with valve replacement.

Endotipsitis is a rare complication of TIPS insertion. Despite the first description of the disease dates back to 1998, the absence of a standard case definition for endotipsitis or TIPS-related infection could have contributed to an underestimation of its true incidence, which is estimated to affect 1 to 5% of patients.

Endotipsitis should be considered if sustained bacteremia is present in a patient with TIPS, with or without thrombus or vegetation plus either no other identifiable infective primary focus after an exhaustive diagnostic workup. Of note, together with S. aureus and coagulate-negative Staphylococci, GNB are commonly isolated in patients with suspected TIPS-related infection, reflecting the common endogenous route of infection and the epidemiology of BSI of patients with LC. The mortality rate of endotipsitis without liver transplantation, which could represent the only definitive treatment for this kind of infection, is very high, approximately of 24-60% of cases and seems to be higher in case of S. aureus and Candida spp. infection.

**Therapeutic management - antimicrobial pharmacokinetics/pharmacodynamic issues in liver cirrhosis**

Ensuring a prompt and appropriate empirical antimicrobial treatment for BSIs is essential in LC.

The concept of appropriateness for empirical and targeted antimicrobial treatment relies on a right antimicrobial coverage associated to an appropriate exposure consistent with the drugs’ pharmacokinetic-pharmacodynamic (PK/PD) features. Pharmacokinetic variability is a major contributor to therapeutic failure: therefore to guarantee a correct exposure to antibiotics, timely administration of the right dose at the right schedule, according to the pathophysiological and immunological status of the patient, is required.

Patient with LC have several unique pathophysiological characteristics that can alter the PK/PD behavior and the in vivo activity of antimicrobial agents. These characteristics include: i) hypoalbuminemia and reduction binding to proteins; ii) altered distribution; iii) altered clearance of the antimicrobial.

The reduction of antimicrobial protein binding is a consequence of decreased albumin production and accumulation of antibiotic binding inhibitors (such as bilirubin or α-acid glycoprotein) in patients with LC. Depending on the degree of antibiotic protein binding, patients with LC may have, both in plasma and tissues, a higher fraction of unbound drug. This is the microbiologically active drug, but also the fraction that is cleared more rapidly through renal or hepatic pathways. Hence, patients with hypoalbuminemia have a higher proportion of drug “escaping” from the bloodstream and distributing into tissues, translating to increased distribution volume (Vd) and reduced or sometimes sub-therapeutic bloodstream concentrations required to treat severe infection.

In patients with advanced LC, splanchic congestion and fluid retention due to hypoalbuminemia and reduced renal blood flow can further increase the Vd for relatively hydrophilic antibiotics, such as β-lactams, aminoglycosides, and vancomycin. As a result most of the patients with ACLF presents with edema, ascites and third space expansion resulting in inadequate blood levels of these antibiotics. Therefore larger loading and daily doses are often required for hydrophilic antibiotics to achieve therapeutic blood levels.

On the other hand, increased Vd may also prolong the drug elimination irrespective of the clearance rates. In some patients with LC, antibiotics half-life is increased, paradoxically causing drug accumulation and potential for toxicity.

Finally, the PK of antibiotics can be affected by liver disease related changes in renal function that are very common in this population. Renal failure in LC is mainly due to a reduced renal perfusion secondary to a vasodilatation in the splanchnic circulation without a compensation of cardiac output. Although clearance of creatinine is widely accepted as a viable method for renal function assessment, several studies demonstrate that measured creatinine clearance from timed urine collection may overestimate the glomerular filtration rate in LC even in patients without hepatorenal syndrome.

Unfortunately, antibiotic PK/PD is rarely studied in patients with liver dysfunction, especially in patients with advanced cirrhosis and ascites (i.e., Child-Pugh Class C). Consequently, there is currently little or no scientific basis for antibiotic doses currently administered to treat life-threatening infections in patients with advanced cirrhosis. Given the unpredictable drug exposure, therapeutic drug monitoring (TDM) might play a pivotal role for individualizing doses, both in lowering exposure-dependent toxicity and in ensuring an optimal drug exposure, especially for the treatment of serious infections or MDR pathogens.
Conclusions and remarks for empirical antimicrobial treatment

The choice of antimicrobial coverage should be made taking into account several items such as i) local epidemiology, ii) site of infection onset (community vs. healthcare and hospital acquire infections), iii) individual patient risk factors for multidrug resistant infections (e.g. prior antibiotic exposure, colonization status), iv) clinical severity and v) infection source.

Taking in mind the above exposed algorithm, without pretending to be a clinical guideline, some basic tips for clinicians about empirical antimicrobial treatment in patients with LC, could be drawn:

1. avoid third generation cephalosporines and fluoroquinolones in healthcare-associated and hospital acquired infections;
2. use a β-lactam/β-lactamase inhibitor in setting with low-intermediate prevalence of ESBL producing strains;
3. start with a carbapenem in settings with high prevalence of ESBL producing strains attempting to de-escalate if possible as soon as culture results become available;
4. provide anti-MRSA coverage in patients with suspected device related infections;
5. if time-dependent drugs (e.g., β-lactams) are administered, provide a loading dose and continuous or extended infusion;
6. assess, whenever possible, drug exposure by TDM.

Abbreviations

| Abbreviation | Definition |
|--------------|------------|
| LC           | liver cirrhosis |
| ESLD         | end-stage liver disease |
| BSI          | bloodstream infection |
| ACLF         | acute-on-chronic liver failure |
| CAID         | cirrhosis associated immune dysfunction |
| TIPS         | transjugular intrahepatic portosystemic shunt |
| SBP          | spontaneous bacterial peritonitis |
| MDR          | multidrug resistant |
| GNB          | Gram-negative bacteria |
| GPB          | Gram-positive bacteria |
| XDR          | extensively drug resistant |
| ICAAC        | interscience conference on antimicrobial agent and chemotherapy |
| ICU          | intensive care unit |
| OR           | odds ratio |
| CLIF-SOFA    | chronic liver failure-sequential organ failure assessment |
| IE           | infective endocarditis |
| ESBL         | extended spectrum β-lactamase |
| KPC          | Klebsiella pneumoniae carbapenemase |
| Vd           | volume of distribution |
| PK           | pharmacokinetics |
| TDM          | therapeutic drug monitoring |

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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