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**EDITORIAL**

- 4297 Circadian rhythms in the pathogenesis of gastrointestinal diseases

Codoñer-Franch P, Gombert M

- 4304 Challenge to overcome: Nonstructural protein 5A-P32 deletion in direct-acting antiviral-based therapy for hepatitis C virus

Sato K, Uraoka T

REVIEW

- 4311 Management of bacterial and fungal infections in end stage liver disease and liver transplantation: Current options and future directions

Righi E

MINIREVIEWS

- 4330 Towards hepatitis C virus elimination: Egyptian experience, achievements and limitations

Omran D, Alborai M, Zayed RA, Wifi MN, Naguib M, Eltabbakh M, Abdellah M, Sherief AF, Maklad S, Eldemellawy HH, Saad OK, Khamiss DM, El Kassas M

ORIGINAL ARTICLE**Basic Study**

- 4341 Temporal clinical, proteomic, histological and cellular immune responses of dextran sulfate sodium-induced acute colitis

Nunes NS, Kim S, Sundby M, Chandran P, Burks SR, Paz AH, Frank JA

- 4356 Analysis of the nitric oxide-cyclic guanosine monophosphate pathway in experimental liver cirrhosis suggests phosphodiesterase-5 as potential target to treat portal hypertension

Schaffner D, Lazaro A, Deibert P, Hasselblatt P, Stoll P, Fauth L, Baumstark MW, Merfort I, Schmitt-Graeff A, Kreisel W

- 4369 Sex-specific effects of *Eugenia punicifolia* extract on gastric ulcer healing in rats

Périco LL, Rodrigues VP, Ohara R, Bueno G, Nunes VV, Santos RC, Camargo AC, Justulin LA, de Andrade SF, Steimbach VM, da Silva LM, da Rocha LR, Vilegas W, dos Santos C, Hiruma-Lima CA

Retrospective Study

- 4384 Practical fecal calprotectin cut-off value for Japanese patients with ulcerative colitis

Urushikubo J, Yanai S, Nakamura S, Kawasaki K, Akasaka R, Sato K, Toya Y, Asakura K, Gonai T, Sugai T, Matsumoto T

Observational Study

- 4393 Liver stiffness reversibly increases during pregnancy and independently predicts preeclampsia

Ammon FJ, Kohlhaas A, Elshaarawy O, Mueller J, Bruckner T, Sohn C, Fluhr G, Fluhr H, Mueller S



- 4403** Hepatitis C virus related cirrhosis decreased as indication to liver transplantation since the introduction of direct-acting antivirals: A single-center study

Ferrarese A, Germani G, Gambato M, Russo FP, Senzolo M, Zanetto A, Shalaby S, Cillo U, Zanusi G, Angeli P, Burra P

CASE REPORT

- 4412** *FANCA* D1359Y mutation in a patient with gastric polyposis and cancer susceptibility: A case report and review of literature

Huang JP, Lin J, Tzen CY, Huang WY, Tsai CC, Chen CJ, Lu YJ, Chou KF, Su YW

Contents

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Management of bacterial and fungal infections in end stage liver disease and liver transplantation: Current options and future directions

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Abstract

Patients with liver cirrhosis are susceptible to infections due to various mechanisms, including abnormalities of humoral and cell-mediated immunity and occurrence

of bacterial translocation from the intestine. Bacterial infections are common and represent a reason for progression to liver failure and increased mortality. Fungal infections, mainly caused by *Candida* spp., are often associated to delayed diagnosis and high mortality rates. High level of suspicion along with prompt diagnosis and treatment of infections are warranted. Bacterial and fungal infections negatively affect the outcomes of liver transplant candidates and recipients, causing disease progression among patients on the waiting list and increasing mortality, especially in the early post-transplant period. Abdominal, biliary tract, and blood-stream infections caused by Gram-negative bacteria [e.g., *Enterobacteriaceae* and *Pseudomonas aeruginosa* (*P. aeruginosa*)] and *Staphylococcus* spp. are commonly encountered in liver transplant recipients. Due to frequent exposure to broad-spectrum antibiotics, invasive procedures, and prolonged hospitalizations, these patients are especially at risk of developing infections caused by multidrug resistant bacteria. The increase in antimicrobial resistance hampers the choice of an adequate empiric therapy and warrants the knowledge of the local microbial epidemiology and the implementation of infection control measures. The main characteristics and the management of bacterial and fungal infections in patients with liver cirrhosis and liver transplant recipients are presented.

Key words: Liver cirrhosis; Liver transplant recipients; Bacterial infections; Fungal infections; Multidrug resistant organisms; Management

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Core tip: Infections are frequent in patients with liver cirrhosis, liver transplant candidates, and liver transplant recipients and are associated with increased morbidity and mortality. Knowledge of the risk factors, etiology, and type of infections is paramount for the management of severe bacterial and fungal infections in these pa-

tient populations. Increasing rates of infections due to multidrug-resistant pathogens have been reported worldwide and particularly affect liver transplant recipients. The type of bacterial and fungal infections along with their risk factors, management, and future research in patients with liver cirrhosis and liver transplant recipients are presented in the review.

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INTRODUCTION

Liver cirrhosis (LC) represents a dynamic clinical entity characterized by various stages of progression^[1]. From a clinical perspective, LC includes compensated and decompensated stages of disease characterized by different features, prognoses, and predictors of death. Specifically, decompensated cirrhosis is associated with portal hypertension or liver insufficiency and their related complications, including recurrent variceal hemorrhage, refractory ascites, hyponatremia, and/or hepatorenal syndrome. All these clinically evident complications can be further aggravated by the occurrence of infections^[1].

Various mechanisms predispose patients with LC to infections. Impairment of immune function has been well documented and is characterized by multiple immune deficiencies, involving not only local liver damage but also deficiencies in systemic innate and acquired immunity^[2]. Increased gastrointestinal (GI) permeability and pathological bacterial translocation are considered key factors leading to increased infection susceptibility in LC (Figure 1)^[3,4]. Although a clear correlation between bacterial translocation and spontaneous bacterial peritonitis (SBP, one of the most frequent infections in cirrhosis) has not been universally reported^[5,6], various factors support this relationship. A GI pathogen such as *Escherichia coli* (*E. coli*), for example, represents a commonly isolated pathogen in cirrhosis and also a major cause of SBP (Table 1)^[7,8]. Furthermore, a higher number of pathogenic bacteria, especially Enterobacteriaceae, have been found in the mucosal microbiota composition of the sigmoid in cirrhotic patients compared to healthy controls^[9]. Host-related, hospital-related, and drug-related factors also contribute to increased susceptibility to infections in this population (Figure 1). The presence of concomitant comorbidities associated with liver disease, including obesity, alcohol consumption, malnutrition, viral hepatitis and/or HIV infection predisposes to bacterial and fungal infections^[10]. Frequent and prolonged hospitalizations along with the use of invasive devices (e.g., urinary and central venous catheters, CVC) pose patients at risk of nosocomial infections such as pneumonia,

CVC-related bacteremia, and urinary tract infections. Furthermore, the use of immunosuppressive agents remains frequent in this population^[11].

Infections remain one of the principal causes of morbidity and mortality also among liver transplant recipients (LTR)^[12]. Bacterial and fungal infections following LT are frequent, occurring in more than 50% of patients mainly due to the type of surgical procedures that, compared to other solid organ transplants, are more complex and may presents complications such as abdominal abscess, bile leaks, and hepatic artery stenosis^[13]. Bacterial infections account for up to 70% of all infections in LTR, followed by fungal and viral infections^[14]. The interplay among key factors such as patients' net state of immunosuppression, environmental exposure to specific organisms (e.g., nosocomial pathogens), and development of surgical complications affects the timing of specific post-LT infections^[14]. The organism's virulence, along with intensity and timing of the exposure, can also impact infections' severity and outcome. Factors known to increase the risk of infections after LT include a Model for End-Stage Liver Disease (MELD) score greater than 30, reoperation (including retransplantation), renal replacement therapy, prolonged intensive care unit (ICU) stay, and older age^[15].

An appropriate management of infections in patients with cirrhosis and following liver transplantation implies the knowledge of predisposing risk factors for infections in order to identify high-risk patients, the prompt use of correct diagnostic tools to recognize atypical disease presentations, and early adequate antimicrobial treatment and source control.

The possible etiologies of infections among patients with LC and LTR are diverse and may range from common bacterial and viral pathogens to opportunistic pathogens that are clinically relevant only for immunocompromised patients. In this review, the most common challenges and main principles for the management of bacterial and fungal infections are discussed. The review focuses mainly on nosocomial infections, including those caused by multidrug resistant organisms (MDRO), while other opportunistic infections are not presented in details.

BACTERIAL INFECTIONS IN PATIENTS WITH LIVER CIRRHOSIS

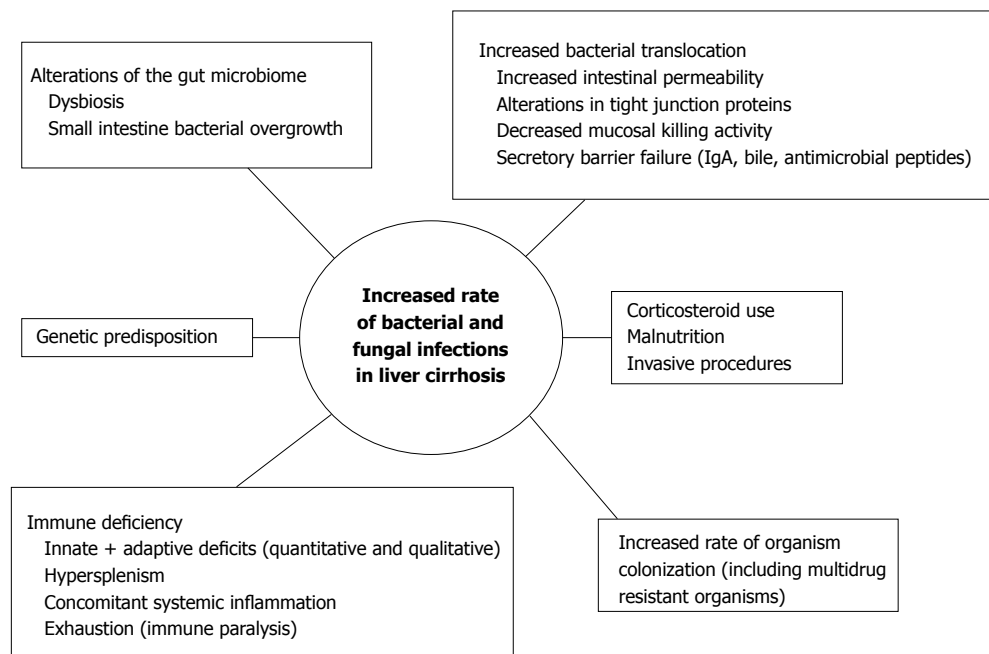
Epidemiology

Bacterial infections are common in patients with LC and can occur at various stages of liver disease, representing the primary cause of admission to emergency departments in this patient population^[16]. Among patients admitted to emergency departments, increasing rates of SBP and hepatorenal syndrome have been documented^[16]. Patients with LC present a high prevalence of bacterial infections, with 10% reporting more than one episode of infection within the same hospitalization^[17,18]. Second infections were reported as independent predictors of mortality in hospitalized patients

Table 1 Main studies reporting the characteristics and mortality rates associated with infections in patients with liver cirrhosis

Year	Prevalence of infections (%); patient <i>n</i>	Main infection sites (%)	Most common pathogens (%)	Mortality rates (%)	Ref.
2018	NR; <i>n</i> = 312	Only BSI included; primary (32), SBP (16), UTI (11)	GNB (53)	25	[28]
2017	61; <i>n</i> = 852	Only BSI included; primary (60), abdominal (33), UTI (7), pneumonia (6)	GNB (60)	23	[22]
2015	38; <i>n</i> = 401	Pneumonia (22), UTI (21), SBP (19)	<i>E. coli</i> (72)	31	[23]
2012	51; <i>n</i> = 207	UTI (52), SBP (23), BSI (21)	GPB (56)	24	[19]
2010	33; <i>n</i> = 150	UTI (37), pneumonia (22), BSI (13)	GNB (62)	37	[18]
2007	45; <i>n</i> = 233	UTI (43), pneumonia (25), SBP (16)	GNB (65)	18	[20]
2003	25; <i>n</i> = 135	UTI (31), SBP (26), pneumonia (25)	NR	9	[25]
2002	22; <i>n</i> = 70	BSI (16), CVC-BSI (9), liver abscess (3)	GPB (67)	29	[24]
2002	32; <i>n</i> = 507	SBP (24), UTI (19), pneumonia (14), CVC-BSI (8)	GPB (47)	22	[17]
2001	34; <i>n</i> = 361	UTI (41), SBP (23), BSI (21), pneumonia (17)	<i>E. coli</i> (25)	15	[8]
1994	39; <i>n</i> = 132	SBP (44), UTI (26), pneumonia (16)	GNB (65), <i>E. coli</i> (62)	29	[27]
1993	47; <i>n</i> = 170	SBP (31), UTI (25), pneumonia (21)	GNB (72)	17	[26]

NR: Not reported; BSI: Bloodstream infections; SBP: Spontaneous bacterial peritonitis; UTI: Urinary tract infections; CVC: Central venous catheter; GNB: Gram-negative bacteria; GPB: Gram-positive bacteria.

**Figure 1** Factors leading to increased susceptibility to infections in patients with liver cirrhosis.

with LC and appeared preventable in the majority of cases^[19].

According to reports from different countries, the overall prevalence of bacterial infections in hospitalized patients with LC varies from 22% to 51% (Table 1)^[17-28]. Multiple factors have been associated with the occurrence of infections, including increased MELD scores, alcoholic liver disease, protein malnutrition, and GI bleeding^[7,8,19,21,29]. Infections often represent the trigger for clinical deterioration or progression to liver decompensation^[18,20]. For example, bacterial infections remain a leading cause of acute on chronic liver failure^[19]. In a study including 50 cirrhotic patients, the presence of an infectious episode worsened liver function in 62% of cases^[18]. Patients with infections were more likely to develop ascites, hepatic encephalopathy, hyponatremia,

hepatorenal syndrome, or septic shock compared to noninfected ones. Furthermore, SBP can lead to severe renal failure, which is also associated with poor clinical outcomes^[20,30]. In a report encompassing 104 cirrhotic patients with bacterial infections, 34% presented infection-induced renal failure associated with GI infections and SBP. Multivariate analysis confirmed that lack of infection resolution was an independent factor for renal failure ($P = 0.03$)^[20].

On the other hand, clinical complications of LC can represent a risk factor for development of infections. Examples are GI bleeding, associated with bacterial infections in up to 45% of patients^[7] and SBP, usually reported in patients with ascites, showing prevalence rates that vary between 15% and 25%^[8]. Besides SBP, other frequent infections in cirrhotic patients include

urinary tract infections, pneumonia, and skin and soft tissue infections (SSTI) (Table 1)^[18,20].

Few reports have also documented high rates of bacterial meningitis among patients with cirrhosis compared to those without liver disease, including pneumococcal infections^[31]. Increased creatinine serum levels were associated with mortality in cirrhotic patients with meningitis^[32]. The overall incidence of bacteremia, urinary tract infections, pneumonia, meningitis, tuberculosis, and liver abscess appeared increased more than tenfold in LC, and mortality rates of each episode were 3 to 10 times higher than in non-cirrhotic patients^[33]. A 10-fold higher risk of bloodstream infections (BSI) in LC compared to the general population was identified in a Danish study showing 47%, 45%, and 8% of Gram-negative, Gram-positive, and polymicrobial BSI, respectively, with overall 30-d case-fatality rate of 0.53^[34]. BSI in cirrhotic patients can lead to complications such as deep-seated metastatic infections, including endotipitis (in patients with transjugular intrahepatic portosystemic shunt) and infective endocarditis^[35]. *Streptococcus bovis* endocarditis, in particular, has been associated with advanced liver disease^[36]. Types, etiology, and mortality of bacterial infections in LC are reported in Table 1.

Diagnosis and treatment

Due to the increased risk of sepsis and multiorgan failure among cirrhotic patients, prompt identification of symptoms and signs of septic shock and assessment of organ function is paramount^[37]. The diagnostic workup should also aim at identifying the source of infection by blood cultures, urine culture, chest X-ray, and lung or abdominal CT scan according to patients' medical history and clinical presentation. Performance of paracentesis with neutrophil count and microbiological culture of ascitic fluid is recommended in all cirrhotic patients hospitalized with ascites to rule out SBP^[38,39]. Other microbiological tests include sputum and/or bronchoalveolar lavage cultures if pneumonia is suspected, stool cultures (including assays for *Clostridium difficile* diagnosis) in case of GI symptoms, and wound - or intra-abdominal - cultures, when indicated^[37].

Data on antimicrobial treatment options in LC are limited, thus recommendations are often based on expert opinion or inferred from studies in non-cirrhotic populations^[37]. A study analyzing bloodstream infections in patients with cirrhosis found that timely initiation of an appropriate antimicrobial therapy had a major impact on patients' outcome^[40]. Multidrug resistance is a major predictor of inappropriate therapy in LC. For these reasons, antimicrobial treatment should be promptly initiated and, when possible, adjusted according to the microbiological results. Empirical treatment should take into consideration the local epidemiology, including the rates of antimicrobial resistance, the site of infection, and patients' clinical presentation (e.g., septic shock).

Patients with SBP usually have infections caused by enteric pathogens, such as Enterobacteriaceae and

Enterococcus spp.; infections due to *P. aeruginosa* are also possible, especially among hospitalized patients^[11]. Third generation cephalosporins (e.g., ceftriaxone, ceftotaxime, or the antipseudomonal cephalosporin ceftazidime) or beta-lactam/beta-lactamase inhibitor combinations such as piperacillin/tazobactam (active also against *Enterococcus* spp.) are frequently used to treat SBP^[11]. Although ciprofloxacin represents a potential option for SBP treatment, rates of resistances associated to quinolone use remains high at various centers and among patients receiving long-term norfloxacin prophylaxis^[37]. Tigecycline presents good intra-abdominal penetration and is active against *Enterococci* [including *Enterococcus faecium* (*E. faecium*)], *Staphylococcus aureus* (*S. aureus*) and Enterobacteriaceae; nevertheless, its bacteriostatic activity and reduced serum concentrations limit tigecycline use in patients with sepsis. Other broad-spectrum antibiotics, such as carbapenems, should be reserved to the treatment of severe infections or in areas with a high prevalence of ESBL-producing strains^[11,37]. Enterobacteriaceae and *Enterococcus* spp. are also common causes of urinary tract infections and can be treated with a third generation cephalosporin or beta-lactam/beta-lactamase inhibitor combinations^[11]. In uncomplicated, non-bacteremic infections, oral options such as cotrimoxazole or nitrofurantoin can be used, according to the pathogen's susceptibility. The use of quinolones, however, should be limited due to their high potential for antimicrobial resistance selection.

Nosocomial pneumonia represents a frequent life-threatening infection in LC. Antimicrobial options include a beta-lactam (e.g., ceftazidime, a beta-lactam/beta-lactamase inhibitor combination, or a carbapenem) with or without a quinolone such as ciprofloxacin^[11]. If risk factors for MRSA are documented (e.g., MRSA colonization or previous infection), treatment with vancomycin or linezolid can be considered. SSTI, most frequently cellulitis, can be caused by both Gram-negative and Gram-positive pathogens in cirrhotic patients^[41].

In severe nosocomial infections, the association of a broad-spectrum antibiotic active against Gram-negative bacilli (e.g., piperacillin/tazobactam or meropenem) with an anti-MRSA drug (e.g., vancomycin, daptomycin) is recommended^[11].

Outcome

Although the diagnosis and treatment of infections have improved over the decades, their occurrence still significantly impact on the mortality of patients with liver cirrhosis^[29]. In these patients, GI bacterial overgrowth and translocation favor the occurrence of various infections, while the increase of endotoxins levels and cytokines can induce systemic inflammatory responses leading to septic shock, multiorgan dysfunction, and death^[29].

A systematic review including 178 studies showed better outcomes in noninfected compared to infected patients with cirrhosis (OR = 3.75, 95%CI: 2.12-4.23)^[42].

Mortality of infected patients was 30% at 1 mo and increased to 63% after 12 mo following an infection. Infections and mortality appeared more frequent in patients with Child-Pugh C compared to A or B stage ($P = 0.003$ and $P = 0.0002$, respectively)^[21]. A prospective study including 312 BSI (53% due to Gram-negative and 47% due to Gram-positive bacteria) showed 30-d mortality rates of 25%^[40]. Risk factors associated with mortality included delayed (> 24 h) antibiotic treatment ($P < 0.001$), inadequate empirical therapy ($P < 0.001$), and increased Chronic Liver Failure-Sequential Organ Failure Assessment (CLIF-SOFA) score ($P < 0.001$). A study analyzing the characteristics of infections in cirrhotic compared to non-cirrhotic patients hospitalized in ICU identified higher prevalence of infections (59% vs 51%, $P < 0.01$), increased rates of abdominal infections, and higher number of Gram-positive infections (including methicillin-resistant *Staphylococcus aureus*, MRSA) in the LC group^[43]. In a study showing mortality rates of 37% among LC patients with hospital-acquired infections, sepsis was an independent factor for hospital death ($P = 0.005$; 95%CI: 1.7-21.4)^[18]. Another study identified higher in-hospital mortality in cirrhotic compared to non-cirrhotic patients (42% vs 24% respectively, $P < 0.001$) and among those with septic shock (30% vs 49%, $P < 0.05$)^[43]. Based on these data, a novel prognostic stage in the course of cirrhosis was proposed, defining the group of "critically ill decompensated patients", characterized by a risk of progression to death or liver transplant of 60%^[42].

FUNGAL INFECTIONS IN LC

Fungal infections in patients with liver cirrhosis are mainly caused by *Candida* spp. and could represent, if not promptly recognized, a cause of treatment failure^[44,45]. Studies on fungal infections in LC often refer only to *Candida* spp., are usually limited to retrospective cohorts, and can be biased by underreporting and under diagnosis. Nevertheless, data shown in the few available reports appear worrisome in terms of unfavorable outcomes.

Candidemia may arise both endogenously and exogenously in patients with LC, but nearly always occurs when prolonged antibiotic exposure is documented^[40,44]. The use of antibiotics for prevention of SBP, in particular, is frequent and may favor an excessive growth of fungi in the intestinal flora, potentially causing fungal translocation in the peritoneal cavity and development of spontaneous fungal peritonitis (SFP)^[46]. SFP is characterized by PMN counts of ≥ 250 cells/mm³ in the ascitic fluid along with positive fungal cultures (with or without concomitant SBP) and no apparent intraabdominal sources of infection, while fungal ascites is defined by lower PMN counts^[47]. Culture positivity ranged from 0 to 11% in various studies^[47]. SFP is mainly caused by *C. albicans*, is frequently nosocomial, and appears associated to higher mortality compared to PBS^[47]. Advanced liver disease and GI bleeding have been advocated as risk factors for SFP,

since higher GI permeability may be required to favor the translocation of large pathogens such as fungi^[47]. SFP should also be considered in the diagnostic workup of hospitalized cirrhotic patients with impaired renal function, such as those with refractory ascites^[45]. Other risk factors for SFP include prolonged hospitalizations and performance of invasive procedures^[48]. Fungal infections characterized by high mortality have been described in LC patients hospitalized in ICU and in those with alcoholic hepatitis^[44,45,49,50]. A retrospective analysis of 120 cirrhotic patients identified the presence of fungal colonization as an independent factor for mortality ($P = 0.047$)^[49]. A study including 185 patients with culture-positive infections documented *Candida* spp. in 19 (10%) cases. Of these, 58% were SFP and 42% candidemia. Only 47% of fungal infections were diagnosed and treated with antifungal agents, while the remaining patients died. Mortality rates at one month were 58% and 29% in patients with fungal infections compared to those with bacterial infection, respectively ($P = 0.001$)^[44]. Similarly, another study encompassing 126 cirrhotic patients with culture-positive ascites identified SFP in 14/126 (11%) patients. Only 43% of patients with cultures positive for fungi received antifungal treatment^[45]. In a prospective multicenter study, *Candida* spp. represented 7% of all BSI and was associated with prolonged hospitalizations, prior surgery, CVC placement, neutropenia, and prior antimicrobial use^[40]. Compared to other infections, *Candida* BSI had the strongest association with inappropriate empirical therapy^[28]. Bassetti et al^[51] previously analyzed 169 episodes of candidemia and 72 intra-abdominal candidiasis in cirrhotic patients, showing high rates of ICU admission (50%), non-albicans *Candida* infections (46%), and occurrence of septic shock (35%). Thirty-day mortality was 35.3% and was independently associated with candidemia (OR = 2.2, 95%CI: 1.2-4.5), septic shock (OR = 3.2, 95%CI: 1.7-6), and absence of adequate antifungal treatment (OR = 0.4, 95%CI: 0.3-0.9)^[51].

These data emphasize the importance of performing fungal cultures and maintaining a high level of suspicion in patients with LC, especially those with impaired renal function and/or receiving antimicrobial treatment with limited clinical response, to ensure early treatment and ultimately reduce mortality (Table 2)^[52-54].

Early administration of antifungal treatment has been associated with improved outcomes, especially in patients with severe infections^[55,56].

Novel molecules (e.g., azoles such as isavuconazole) and new antifungal classes (e.g. echinocandines) have become available for the treatment of invasive fungal infections in the last decades. In patients with LC concerns in the efficacy and safety of antifungals appear linked to resistance to antifungals, patients' reduced tolerance, and altered drug pharmacokinetics caused by advanced liver disease.

Although fluconazole is still widely used due to its favorable pharmacokinetics and tolerability, a shift to non-albicans strains showing lower fluconazole sus-

Table 2 Management of fungal infections in patients with liver cirrhosis

Type	Characteristics	Management	Ref.
SFP, fungemia, disseminated fungal infection (mainly <i>Candida</i> spp.)	Delayed diagnosis and therapy. Lack of clinical signs and suspicion. Frequent concomitant SBP. High mortality.	Suspect if peritonitis is not improved after 48 h of empirical antibiotic treatment. Perform fungal cultures (ascites and blood).	[44,45,52,53]
Antifungal prophylaxis	Factors influencing mortality less known. Mortality higher than SBP due to delayed diagnosis.	Indicated for SBP (high risk, previous episode, GI bleeding). No clear indication for fungal infections. Consider in: ICU patients without improvement > 48 h, high prevalence (> 5%) regions, risk factors (corticosteroids, prolonged microbial use, CVC, TPN, high APACHE score, dialysis). Prompt initiation.	[48,54]
Antifungal treatment	Recommendations for fungal infections in LC.	Echinocandins as first-line treatment (e.g., fungemia, nosocomial SFP or critically ill with CA-SFP). Fluconazole indicated if less severe infections. De-escalation if patient is stable and sensitivity tests available.	[52-54]

SFP: Spontaneous fungal peritonitis; SBP: Spontaneous bacterial peritonitis; GI: Gastrointestinal; CVC: Central venous catheter; TPN: Total parenteral nutrition; APACHE: Acute Physiology and Chronic Health Evaluation; LC: Liver cirrhosis; CA: Community-acquired.

ceptibility has been reported^[57]. Echinocandins are currently recommended as first line treatment in critically ill patients and in case of reduced susceptibility to fluconazole^[58]. Despite evidence of resistance has emerged especially in *C. glabrata*, overall resistance rates to echinocandins remains low^[59]. Compared to azoles such as voriconazole, echinocandins present reduced liver toxicity and better tolerability^[60]. While dose adjustments are not recommended for any severity of liver disease for micafungin and anidulafungin, reduction of caspofungin maintenance dose from 50 to 35 mg/d is suggested^[61]. This dose reduction, however, may not be appropriate in critically ill patients who may have sub-therapeutic exposure and efficacy. In patients with liver cirrhosis receiving voriconazole, therapeutic drug monitoring is recommended due to the correlation between trough plasma concentration and occurrence of adverse effects^[62].

MANAGEMENT OF INFECTIONS IN CIRRHOTIC PATIENTS

As a general rule, an infection should be suspected in all cirrhotic patients with unexpected clinical deterioration (e.g., new onset of porto-systemic encephalopathy, worsening of renal or liver function tests) due to the known impact of infections on liver disease progression^[37].

A prompt diagnosis of infectious processes in patients with liver disease can be hampered by various factors that may act as confounders or mask bacterial and/or fungal infections, thus potentially delaying an effective treatment. Due to the immune impairment that accompanies LC, systemic responses and classical symptoms of infections may be reduced and difficult to diagnose. Furthermore, LC itself may be a cause of low-grade fever in up to 20% of patients^[63]. Opportunistic infections can also occur and their recognition may be less immediate, or require longer times to obtain culture

positivity. Targeted microbiological cultures (blood, urine and ascites cultures) before administration of antimicrobials are recommended, and the use of markers (e.g., galactomannan, beta-D-glucan) could be considered if fungal infections are suspected^[64]. Similarly to other immunocompromised patients, high-resolution chest CT should be preferred to X-rays for pulmonary infections^[37]. Besides prompt diagnosis, early appropriate antimicrobial and/or antifungal treatment remain key factors in the management of LC patients with severe infections.

Infections caused by multidrug resistant organisms (MDRO) may represent a cause of treatment failure favoring poor outcomes. Prevalence of MDRO in LC patients reflects the global resistance burden of different countries, thus knowledge of the local patterns of susceptibility is paramount to optimize empirical and targeted therapy in severe infections. Two studies in Italy and Greece identified prevalence rates of MDR infections of 27% and 19%, respectively, mainly caused by ESBL-producing *E. coli* and carbapenem-resistant *K. pneumoniae*^[65,66]. MDRO accounted for nearly one-third of BSI in cirrhotic patients in a European multicenter study that identified inadequate empirical therapy as an independent cause of 30-d mortality^[40]. Infections were associated with previous antimicrobial exposure and invasive procedures. Most common MDRO were ESBL-producing Enterobacteriaceae (14%), while the highest mortality rates (> 40%) were associated with carbapenem-resistant Enterobacteriaceae, *Candida* spp., and *E. faecium*.

INFECTIONS IN PATIENTS ON THE TRANSPLANT WAITING LIST

Patients on the waiting list are frail and often require multiple hospitalizations, which in turn can favor in-

Table 3 Management of infections in liver transplant recipients

Population/ infection	Risk factor and type of infection	Management	Ref.
Liver transplant candidates/ all infections	Donor-derived. Active/latent infections. Vaccine-preventable infection.	Donor screening. Careful patient history and physical examination. Identification of infections requiring therapy. Immunization.	[160-165]
Liver transplant recipients/ bacterial	Nosocomial infections (ICU, invasive devices). Recurrent infections (anatomical defects). Immunosuppression.	Peri-transplant antibiotic prophylaxis (< 48 h). Prompt diagnostic workup (uncommon presentations, opportunisms). Source control when needed.	[76,83,160]
Liver transplant candidates and recipients/MDRO	Colonization (MRSA, VRE, CRE) linked to increased risk of infections. Risk of transmission between patients and across wards.	Surveillance cultures (CRE, VRE, MRSA) and decolonization (MRSA). Infection control (hand hygiene, isolation, contact precautions).	[102,112,164]

LT: Liver transplantation; ICU: Intensive care unit; MDRO: Multidrug-resistant organisms; MRSA: Methicillin-resistant *Staphylococcus aureus*; VRE: Vancomycin-resistant *enterococci*; CRE: Carbapenem-resistant Enterobacteriaceae.

fections and deteriorate liver function or lead to multi-organ failure. Occurrence of severe infections put patients at risk of dropout from transplant waiting lists, potentially reducing the possibility to undergo LT and causing a destructive impact on the natural progression of cirrhosis. A prospective study evaluating 136 LT candidates developing bacterial infections showed that the majority were delisted or died (42%), while 35% underwent LT^[67]. Similarly, occurrence of SBP was documented as a cause of death or removal from the waiting list in 38% of patients with advanced cirrhosis^[68]. Although higher post-transplant mortality has not been clearly correlated with occurrence of pre-transplant infections, other factors such as increased MELD score, prolonged post-LT intubation and hospitalization were documented among infected LT candidate compared with noninfected ones^[69]. Various studies investigating the outcome of LTR after recovery from an infection prior to LT showed an increase length of hospital stay, higher rates of postoperative infections and increased isolation of MDRO compared to patients without infection, although similar survival rates were reported^[70]. Careful management of these patients, especially in case of repeated hospitalization, is warranted.

INFECTIONS IN LIVER TRANSPLANT RECIPIENTS

Bacterial infections: Timing

Bacterial infections, especially those caused by nosocomial pathogens, are more common during the early post-transplant period (0-1 mo). Surgical complications can lead to wound infections, peritonitis, hepatic artery thrombosis, and biliary tract ischemia that can cause biloma or strictures, increasing the risk of recurrent cholangitis^[12,71,72]. Other factors contributing to bacterial infections in the early postoperative period include mechanical ventilation, prolonged ICU stay, alteration of the mucocutaneous barrier, vascular and urinary catheterization, and profound immunosuppression^[73]. A retrospective study including 463 LTR over a 3-year period

identified at least one infection in 41% of cases, with biliary tract infections and infections due to staphylococci representing the most common types^[72].

Complications occurring during transplantation that imply a more complex and prolonged surgical procedure, such as development of ischemia-reperfusion injury and high amount of blood transfused intraoperatively, may favor surgical site infections^[74,75]. A prospective study including LTR with BSI identified CVC-BSI (31%), pneumonia (24%), and abdominal and/or biliary infections (14%) as most common sources of bacteremia. Diabetes mellitus ($P = 0.03$) and serum albumin level less than 3.0 mg/dL ($P = 0.02$) were predictors of bacteremia. Mortality at 14 d was higher in patients with BSI compared with nonbacteremic infections (28% vs 4%, $P = 0.03$)^[75]. Risk factors for mortality among patients with BSI after LT include ICU stay, abnormal laboratory findings (e.g., greater serum bilirubin level and prothrombin time) and lack of febrile response^[75].

Infections in the donors, if controlled, are not considered a contraindication for transplant. However, since they may represent a source of post-transplant bacterial infections, an accurate screening of donors is recommended (Table 3)^[76,77]. Opportunistic infections (e.g., herpesvirus infections, nocardiosis, tuberculosis, etc.) are considered more common between 1 and 6 mo post-transplant, although pneumonia and intra-abdominal infections can still occur during this period. Risk factors that may favor bacterial infections during the intermediate post-transplantation period include over-immunosuppression, allograft rejection, biliary tract complications, and re-transplantation^[73]. In a study analyzing early (< 6 mo) vs late post-transplant infections (> 6 mo), the incidence decreased from 11.5 episodes/1000 transplant-days in the first month to 1.9 and 0.3 between 1 mo and 6 mo and after 6 mo, respectively^[78]. Gram-positive and Gram-negative bacteria-related infections were equally distributed (14.8% of all infections). A specific risk factor for late infections was the performance of a biliary derivation to jejunum, favoring cholangitis and secondary peritonitis in

LTR. Risk for late bacterial infections varies according to the recipient's graft and immune status, with high-risk patients characterized by recurrent rejection and allograft dysfunction requiring intense immunosuppression^[73]. Community-acquired infections, however, remain common following LT even among low-risk patients. A high level of suspicion for late bacterial infections should be maintained due to potentially atypical or less expected infection presentations.

Management of infections in LTR includes prompt initiation of antimicrobial treatment and adequate source control (e.g., CVC removal, surgical debridement).

Type of post-transplant bacterial infections

Bloodstream infections: BSI represent an important cause of mortality in LTR^[79]. BSI mainly occur during the first post-operative month and appear to be predictors of long-term survival in transplant recipients. A study encompassing 704 LTR at a single center over a 10-year period showed an incidence of BSI of 37% with an overall mortality of 16%^[79]. The majority of BSI (39%) occurred within 10 d after LT. Most frequently isolated pathogens were Enterobacteriaceae (41%), *S. aureus* (19.8%), Enterococci (13.1%), *P. aeruginosa* (8.8%), and yeasts (7.1%). A similar study including only Gram-negative bloodstream infections identified an incidence of 210/1000 person-years within the first month following transplantation. Compared to kidney transplant recipients, LTR were more likely to develop early infections and had higher BSI-associated mortality^[80]. Potential sources of BSI include intra-abdominal infections (IAI), CVC-BSI, pneumonia, and, less frequently, urinary tract infections. Need for re-operation, prolonged use of indwelling vascular catheters, and acute graft rejection represent predisposing factors for BSI^[79]. Gram-negative bacilli such as *E. coli*, *K. pneumoniae*, and *P. aeruginosa* are often the most commonly isolated pathogens, although enterococci, viridans streptococci, and polymicrobial infections are frequently reported among LTR^[79-81]. Blood cultures from CVC and peripheral vein represent the gold standard for the diagnosis of BSI and CVC-BSI. If pneumonia or urinary tract infections are suspected, additional cultures (e.g., sputum, bronchoalveolar lavage, or urine cultures) and imaging (e.g., chest CT scan or kidney imaging) should be performed. Management of persistent BSI also warrants the investigation of deep-seated infections (e.g., endocarditis, intra-abdominal abscesses, etc.) and, when possible, prompt source control measures such as removal of vascular catheters and drainage of collections^[37].

Surgical site infections: Surgical site infections (SSI) can occur in up to 10% of patients undergoing LT. SSI are more frequently associated to the early post-transplant period and are mainly caused by *Enterococcus* spp., *E. coli*, and *S. aureus*^[82,83]. Although they carry a relatively low mortality risk, SSI are associated with increased

morbidity and length of hospital stay. In patients with suspected SSI, obtaining purulent discharge cultures and appropriate imaging (e.g., ultrasounds or CT scan) of a collection is important to achieve a timely diagnosis. Management of SSI is usually based on a combined approach, including surgical debridement and targeted antimicrobial therapy. A prospective study including 107 (9%) patients developing SSI identified as independent risk factors choledochojejunal or hepaticojejunal reconstruction, previous liver or kidney transplant, and transfusion of more than 4 red blood cell units^[83].

Intra-abdominal infections: IAI represent common infections, accounting for up to 50% of early bacterial infections following LT, and include intraabdominal abscesses, peritonitis, and cholangitis^[84-86]. IAI can be polymicrobial and are mainly caused by Enterococci, staphylococci, *Pseudomonas* spp., Enterobacteriaceae, and anaerobes^[84]. Risk factors for IAI are often related to complications during transplantation and their severity is increased by hepatic artery thrombosis and arterial stenosis^[84,87]. Compared with SSI, IAI can have a major impact on patients' outcome. A study encompassing 57 LTR with biloma showed higher rates of mortality, graft loss and need for re-transplantation compared to patients without IAI^[84,87]. Predictors of mortality were renal insufficiency ($P = 0.02$) and infections due to *Candida* spp. or Gram-negative bacteria.

Adequate imaging, such as ultrasounds, CT scan, or MRI, along with prompt source control are often essential to assure an appropriate management of IAI. Surgical approaches include percutaneous drainage of infected foci and control of peritoneal contamination by diversion or resection (e.g., biliary strictures or stones). Patients with diffuse peritonitis from a perforated viscus should undergo prompt emergency surgery. Intraoperative samples and cultures from recently (< 48 h) inserted drains or ascitic fluid collected in blood culture vials should always be performed to achieve a microbiological diagnosis.

Difficult-to-treat bacteria and MDRO

Although any bacteria can potentially be isolated after LT, infections are mainly caused by Enterobacteriaceae, *P. aeruginosa*, enterococci (including *E. faecium*), viridans streptococci, and *S. aureus*^[88-90]. Even if an increase in Gram-negative pathogens responsible for infections in LTR has been documented, Gram-positive bacteria remain the most frequent agents of CVC-BSI^[91].

Similar to liver cirrhosis, an increasing number of antimicrobial resistant bacteria has been documented among LTR, with prevalence rates varying significantly according to the geographic areas and among different centers^[92]. Most case series reporting rates of MDR Gram-negative in solid organ transplant recipients, however, were from endemic areas, resulting in relatively high percentages ranging from 18% to 50%^[93,94]. Very few reports specifically documented the rates of resistance

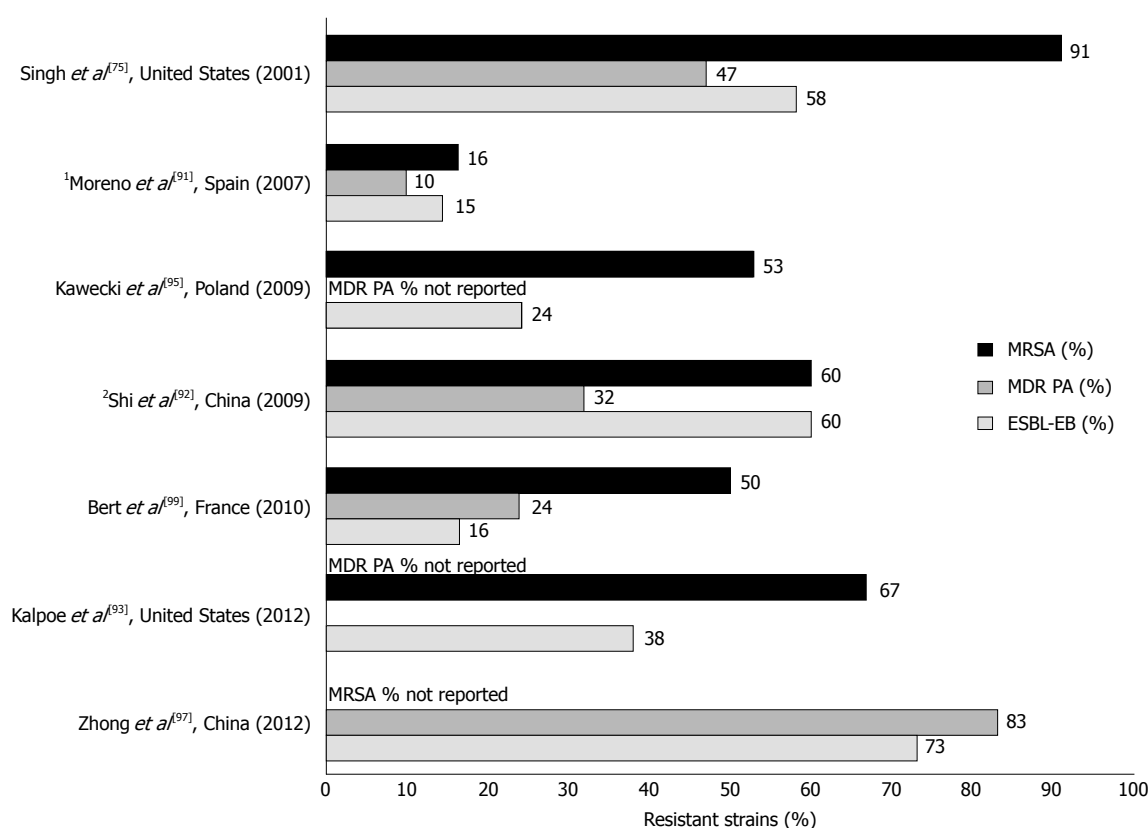


Figure 2 Studies reporting the percentage of infections caused by methicillin-resistant *Staphylococcus aureus*, MDR *Pseudomonas aeruginosa*, and extended-spectrum beta-lactamase-producing Enterobacteriaceae following liver transplantation^[79,91-93,95-97]. ¹Data reported for all solid organ transplants; ²MRSA data obtained from reference 98^[98]. MRSA: Methicillin-resistant *Staphylococcus aureus*; MDR-PA: Multidrug-resistant *Pseudomonas aeruginosa*; ESBL-EB: Extended-spectrum-beta-lactamase Enterobacteriaceae.

among the most frequently isolated pathogens in LTR (Figure 2)^[79,91-93,95-98], and larger prospective studies are necessary to understand the global impact of these infections. Table 4 summarizes the current antimicrobial options to treat MDRO.

Methicillin-resistant *S. aureus*: *S. aureus* is an important cause of BSI, pneumonia, wound infections and IAI in LTR, especially within the first 3 post-transplant months^[88]. Isolation of methicillin-resistant *S. aureus* (MRSA) in LTR varies across centers and may cause up to 50% of BSI, with important implications for empirical therapy that may result inadequate^[99]. MRSA isolation has been linked to several risk factors, including recent surgery (< 2 wk), cytomegalovirus primary infection, extended ICU stay, concomitant major post-transplant infections, peritonitis, and increased prothrombin time^[99-101]. *S. aureus* carriers who are transplant candidates have a higher risk (24% to 87%) of post-LT infections and may benefit from decolonization prior to transplantation^[102-104]. Pre-transplant identification of colonized patients and subsequent eradication of MRSA may be a valuable strategy for limiting *S. aureus* infections. Decolonization, however, is not permanent; hence it is difficult to determine the optimal timing to decolonize a patient. MRSA colonization is also possible following LT, according to local MRSA pre-

valence rates, infection control policies, and recipients' general state of illness^[105]. Infection control strategies aiming to reduce the transmission of MRSA through multifaceted interventions such as active surveillance, contact isolation, hand hygiene, environmental cleaning, decolonization of carriers, and antimicrobial stewardship are mandatory (Table 3)^[106]. Each transplant program, however, should consider the local epidemiology as a key parameter to implement the infection control practices.

Although vancomycin remains the mainstay for treatment of MRSA, various limitations have been associated with its use, including lower efficacy for strains with MIC > 1.0 mg/L and MSSA-mediated infections, reduced tissue penetration, and increased renal toxicity compared to other available options^[88,107,108]. Valid alternatives to vancomycin include linezolid, especially in the treatment of MRSA-related pneumonia, and daptomycin (Table 4)^[108-111]. Furthermore, novel anti-MRSA options have recently become available for the treatment of MRSA, although most of them have only been approved for SSTI and real-world data, especially in the field of organ transplantation, are still limited^[109].

Vancomycin-resistant Enterococci: Enterococcal infections are usually associated to CVC-BSI, catheter-associated urinary tract infections, and SSTI^[112]. Vancomycin resistance among Enterococci (VRE), especially

Table 4 Treatment options for multidrug resistant organisms in liver transplant recipients

Pathogens	Recommendation	Antimicrobial regimens	Ref.
MDR Gram-positives			
MRSA	Nasal decolonization with mupirocin. Daptomycin highly bactericidal in BSI; non effective in pulmonary infections. Linezolid and tigecycline bacteriostatic.	Vancomycin ¹ /linezolid OR Daptomycin OR Tigecycline OR Novel anti-MRSA cephalosporins (ceftaroline, ceftobiprole) ² .	[107-111]
VRE	Daptomycin highly bactericidal in BSI; non effective in pulmonary infections. Linezolid and tigecycline bacteriostatic.	Linezolid OR Daptomycin OR Tigecycline.	[113,121,122]
MDR Gram-negatives			
ESBL-producing Enterobacteriaceae	Conflicting data on carbapenem superiority <i>vs</i> BLBLI. Meropenem recommended for high inoculum infections and unstable patients.	Carbapenems OR Piperacillin/tazobactam.	[175-177]
Carbapenem-resistant Enterobacteriaceae	Test antimicrobial susceptibility (also on colonizing strains). Some evidence of better outcomes with combination therapy <i>vs</i> monotherapy. New molecules promising but scarce data in LT.	Ceftazidime/avibactam, OR Combination regimen (at least two active drugs) including colistin/polymyxin B, tigecycline, aminoglycosides ¹ (gentamycin, amikacin), IV fosfomycin, high-dose prolonged infusion carbapenems. For uncomplicated UTI, consider monotherapy (aminoglycosides, fosfomycin).	[127,137,138,175,178]
MDR <i>P. aeruginosa</i>	Test antimicrobial susceptibility. New molecules promising but scarce data in LT.	Combination regimen (at least two active drugs) including colistin, an anti-pseudomonal beta-lactam (if susceptible), aminoglycosides ¹ , fosfomycin OR Ceftolozane/tazobactam, ceftazidime/avibactam	[175,179,180]

¹Therapeutic drug monitoring recommended; ²Approved for skin and soft tissue infections and community-acquired pneumonia (ceftaroline), community-acquired and hospital-acquired pneumonia excluding ventilator-associated pneumonia (ceftobiprole). MDR: Multidrug resistant; BLBLI: Beta-lactam/beta-lactamase inhibitor combination; BSI: Bloodstream infections; LT: Liver transplantation; MDRO: Multidrug-resistant organisms; MRSA: Methicillin-resistant *Staphylococcus aureus*; VRE: Vancomycin-resistant *enterococci*; CRE: Carbapenem-resistant Enterobacteriaceae.

E. faecium, currently represents a concern in various transplant centers^[113]. VRE-colonized transplant recipients act as reservoirs for VRE transmission and carry an increased risk of infection, ICU stay, and death^[114,115]. GI colonization with VRE among LTR is reported between 3% and 55%^[116,117], while reported rates of VRE infections among colonized LTR range between 12% and 32%^[114,116-118]. A study including LTR who developed bilomas in the early post-transplant period showed that the most common responsible pathogens were *Enterococci* (37%); of these, 50% were VRE^[87]. Common risk factors for VRE infections include antimicrobial use, biliary leaks and strictures, and surgical re-exploration or percutaneous drainage^[114-118]. Contact isolation in patients with VRE colonization and infection is recommended (Table 3). Daptomycin and linezolid are commonly used for VRE infections in solid organ transplant recipients, although reduced susceptibility to these antimicrobials has already been reported even in patients without previous exposure to these molecules^[119-122].

MDR Gram-negative bacteria: MDR among Gram-negative bacteria is particularly relevant in LTR due to the documented shift from Gram-positive to Gram-negative bacteria infections in the last decade^[71,81]. *E. coli*, *K. pneumoniae*, and *P. aeruginosa* currently represent commonly isolated bacteria in BSI after LT^[81,92]. Rates

of MDRO causing infections in LTR have exponentially increased worldwide, reaching up to 50% in some centers^[92,96]. Various risk factors have been associated with antimicrobial resistance, including reoperation, graft rejection, and abdominal infections^[96]. Unfortunately, MDRO infections are recognized to cause increased mortality compared to non-resistant infections^[79,92,96].

P. aeruginosa is an early nosocomial pathogen and represents a major cause of infection in LTR, accounting for about 6.5% of all BSI^[81]. BSI caused by MDR *P. aeruginosa* compared to susceptible strains appeared significantly more frequent in transplant recipients compared to non-transplanted patients. *P. aeruginosa* infections caused by MDR strains reached 43% in the United States and up to 52% in China^[92,123]. MDR *P. aeruginosa* causing nosocomial pneumonia in LTR has been reported between 50% and 65%^[124].

Rates of extended-spectrum beta-lactamases (ESBL)-producing Enterobacteriaceae in LTR vary between 6% to 13% according to the area, reaching up to 40% in endemic countries^[125,126]. Risk factors for ESBL-associated infections include pre-transplant colonization, advanced liver disease, and reoperation. In a study encompassing 317 LTR, independent factors associated with preoperative fecal carriage of ESBL-producing Enterobacteriaceae included exposure to a beta-lactam agent in the month preceding transplantation

($P < 0.001$) and a history of SBP ($P = 0.02$)^[125,126]. The occurrence of ESBL-associated infections has increased the use of carbapenems, that usually represent the last resort for antimicrobial therapy in immunocompromised patients. Carbapenem-resistance has subsequently developed, further complicating the management of LTR since the optimal treatment for carbapenem-resistant Enterobacteriaceae is not yet established^[127]. Carbapenem-resistant *K. pneumoniae* (CRKP), in particular, has emerged as a major threat for immunocompromised and hospitalized patients worldwide and is associated with significant mortality^[128,129]. A retrospective study evaluating 14 CRKP infection episodes after LT showed early onset of infection (median time from LT of 12 d) and mortality rates of 71%. Survival rates were significantly lower for patients with CRKP infections compared to those without (29% vs 86%, $P < 0.001$), and represented an independent risk factor for mortality along with MELD scores ≥ 30 ^[93]. Isolation of CRKP in LTR represents a public health threat in endemic countries^[94,130]. In one United States transplant center, CRKP accounted for 23% of all bacterial infections in LTR^[93,82]. Risk for acquisitions of CRKP in the general population that are also commonly encountered in LTR include exposure to broad-spectrum antibiotics, need for invasive devices, and ICU stay^[131]. Only recently, some studies have analyzed the presence of specific factors that can be predictive of CRKP infections in LTR. CRKP pre- and post-transplant colonization appeared as an important factor associated with CRKP infections. In a cohort of 41 CRKP rectal carriers (11 at LT and 30 post-LT), 20 patients developed CRKP infections^[132]. Compared with 2% of non-colonized patients, rates of infections were 18% and 47% among carriers before and after LT, respectively. Besides carrier status, renal replacement therapy, mechanical ventilation for > 48 h, and HCV recurrence appeared correlated with CRKP infections^[132]. Another recent study involving 54 patients with CRKP infections identified as independent risk factors for post-transplant infections the presence of CRKP colonization, reoperation, combined transplantation, MELD > 32 , and dialysis^[133].

There are currently no guidelines specifically addressing the management of MDRO infections in LTR. Recent recommendations from the Spanish group for the study of infection in transplant recipients (GESITRA) identified as a key point the characterization of the isolate's phenotypic and genotypic resistance profile in order to select a targeted therapy that can be adjusted according to susceptibility results^[134]. A specific surgical prophylaxis regimen is currently not recommended for patients colonized with carbapenem-resistant strains. Carrier status in LTR recipients, however, should be timely detected, and empirical therapy in case of infection should include active antibiotics based on available microbiological results. Even if donor and/or recipient colonization are associated with an increased risk of infection, carrier status currently do not represent a

contraindication to transplantation, but warrants contact isolation precautions and strict hand hygiene compliance. Due to the high-mortality of these infections and while awaiting real-world data on new antibiotic options, preventive strategies and antimicrobial stewardship programs remain key steps to curtail the impact of carbapenem-resistant infections in this cohort.

Novel molecules targeting MDR Gram-negative are currently available, although data on their use in immunocompromised patients remain scarce^[135]. Among new antimicrobial options, ceftazidime-avibactam has demonstrated promising activity against CRKP in preliminary studies^[136-138], and meropenem-vaborbactam has recently been approved for the treatment of complicated urinary tract infections caused by carbapenem-resistant Enterobacteriaceae. Both compounds, however, are not active against strains harboring metallo-beta-lactamases (MBLs) that are common in certain geographic areas^[139]. Results from observational studies including old antibiotics have shown better outcomes for combination therapy (Table 4), but these results remain conflicting and were not confirmed by all studies^[140-142]. New compounds targeting carbapenem-resistant strains, including MBLs (e.g., cefiderocol, aztreonam-avibactam) are currently under investigation^[143]. Regarding *Pseudomonas* spp., the novel beta-lactam/beta-lactamase inhibitor ceftolozane-tazobactam has shown good activity against MDR strains, including carbapenem-resistant isolates, with the exception of MBL producers^[144].

Fungal infections in liver transplant patients

Although better outcomes have been reported after the introduction of novel antifungals, invasive fungal infections remain an important cause of mortality in LTR, with reported rates between 25% and 81%^[145,146]. Fungal infections are frequent in absence of antifungal prophylaxis and can occur in up to 42% of LTR^[147,148]. Factors having an impact on the distribution and frequency of fungal infections include changes in surgical techniques, patient and donor organ characteristics, local fungal ecology and resistance, and the use of antifungal prophylaxis. The most common cause of invasive fungal infections in LTR is *Candida* spp. *Candida* infections, including candidemia, abdominal infections, and biliary infections, are mostly nosocomial and occur early after LT^[149]. A retrospective study in LTR identified an overall incidence of fungal infections of 12%, with non-albicans *Candida* accounting for 55% of the infections; of these, half were caused by fluconazole-resistant *C. parapsilosis*^[150]. One-year patient survival rates were significantly reduced among patients with fungal infections compared to those without (41% and 80%, respectively). Multivariate analysis showed that pre-transplant fungal colonization was associated with subsequent infections. Various other risk factors have been reported among patients developing fungal infections after LT, including high

blood product volumes during surgery, early surgical re-exploration, choledochojejunostomy, retransplantation, fulminant hepatic failure, and severe renal impairment^[145,147,148,151-153].

There is currently no consensus on pre-LT fungal prophylaxis regarding clinical indication, best regimens, and duration. Outcome benefits correlated with the use of antifungal prophylaxis among solid organ transplant recipients appear conflicting, and universal prophylaxis is currently not recommended^[154-157]. Pre-transplant risk assessment, however, appears useful to identify patients who are at high-risk for the development of fungal infections^[57,158].

Similar to liver cirrhosis, echinocandins and azoles are the most commonly used antifungals for the treatment of *Candida* spp. infections in LTR. Compared to the azoles, very few drug interactions have been reported with echinocandins. Only caspofungin use has been associated with relevant changes in the C_{max} of tacrolimus (up to 20% reduction) and cyclosporine (up to 35% increase in plasma concentration of caspofungin)^[159].

Lipid formulations of amphotericin B provide wide-spectrum options for patients that may be at risk of non-*Candida* infections. Voriconazole (and most recently, isavuconazole) remain the drug of choice for invasive aspergillosis, although limitations in its use in LTR and patients with compromised liver function are represented by significant drug interactions with immunosuppressants and occurrence of liver toxicity^[159].

Management of infections in LTR

Bacterial and fungal infections in LTR are often associated to surgical complications, involving pathogens that are typically encountered in nosocomial infections and, more recently, MDRO. Clinical presentations of common bacterial infections may be atypical, and clinical and/or radiological findings may not be evident due to an impairment of the inflammatory responses caused by immunosuppressive therapies. Graft rejection can also be confused with infections. Early diagnoses can therefore be challenging and often require invasive diagnostic procedures that remain key to identify the correct cause of infection and promote a potentially successful therapy. The choice of an appropriate antimicrobial regimen for LTR can be particularly challenging due to the need of an urgent empiric therapy in severe infections, the increased rates of antimicrobial resistance, and the risk of drug toxicity and drug-drug interactions. Knowledge of the local epidemiology is particularly important since the empiric antimicrobial treatment should take into account the coverage of resistant pathogens that colonize or have been previously isolated in LTR, especially in areas that are endemic for MDRO or during outbreaks. Table 3 summarizes the main principles for the management of infections in LTR^[160-164].

outcome of patients with liver cirrhosis, liver transplant candidates, and liver transplant recipients remain dramatic despite the advances in antimicrobial therapy and surgical techniques. The mechanisms associated with the increased risk of infections in LC are complex and include genetic predisposition, fecal dysbiosis, disruption of the intestinal barrier causing intestinal hyperpermeability, and multiple immunological deficits (Figure 1). In LTR, immunosuppression and risk factors associated with surgery and prolonged hospital stay represent the main causes for bacterial and fungal infections.

Research into the mechanisms favoring infections in cirrhosis is key to find potential areas of intervention. New strategies to modulate the gut-liver interaction are urgently needed since factors such as systemic inflammation and endotoxemia, that may cause life-threatening complications in LC (e.g., SBP and hepatic encephalopathy), are related to the gut environment^[165,166]. Studies on the preservation of microbiome composition and function appeared promising in hematological patients undergoing hematopoietic stem cell transplantation^[167]. Preliminary studies on gut microbiota-based therapeutics (e.g., probiotics, prebiotics, rifaximin, etc.) in cirrhosis are ongoing^[166], but the impact of targeted intervention on gut dysbiosis, bacterial function, or metabolic state is still unclear.

Studies on cirrhosis-associated immune dysfunction appear also important to understand the patterns of pro-inflammatory or immunodeficient phenotypes that can lead to infection susceptibility and/or organ failure in different phases of liver disease, in order to identify potential markers or specific targets of disease progression^[168,169].

Bacterial and fungal infections in LT candidates and recipients are often peculiar and may be characterized by confounding factors that favor delayed diagnosis and poor outcomes. For this reason, research dedicated to the development of rapid and accurate diagnostic tools is urgently needed. This is particularly relevant, considering the exponential increase in MDRO, in order to promote the correct use of antibiotics based on the results of microbiological cultures. Specifically, novel instruments of rapid diagnostics (e.g., matrix assisted laser desorption/ionization time-of-flight mass spectrometry, multiplex polymerase chain reaction platforms, etc.) may allow for prompt identification of pathogens, giving direction to clinicians dealing with severe infections in terms of broadening, discontinuation, and de-escalation of empiric regimens^[170,171].

Furthermore, despite the availability of novel antibiotics in recent years, there is currently no consensus on optimal antimicrobial regimens that can safely and effectively treat infections caused by MDR Gram-negative bacteria in immunocompromised hosts. Results from pathogen-directed clinical trials employing novel antibiotics with broad activity are largely awaited. Limitations in the use of new molecules, however, include the scarce clinical experience from real-world studies, the lack of knowledge of their pharmacokinetics principles in

CONCLUSION

The impact of bacterial and fungal infections on the

immunocompromised patients, and an increased risk of toxicity, especially for combination therapies^[172].

Finally, the optimization of current strategies directed towards the prevention and treatment of infections in patients with liver disease and LTR remain a key point for their successful management. Examples are represented by the implementation of dedicated antimicrobial stewardship programs and specific bundled interventions based on transplant centers' local needs and epidemiology^[171,172]. Studies evaluating antimicrobial stewardship programs in transplant recipients, for example, are limited but have shown promising results^[173,174]. All these efforts, however, cannot be successful without the constant involvement of multidisciplinary teams, including transplant surgeons, hepatologists, specialists in infectious diseases and infection control, microbiologists, and pharmacologists^[175-180].

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