# Infections in the Liver Transplant Recipient

# 19

Michele Bartoletti, Matteo Rinaldi, Linda Bussini, Maddalena Giannella, and Pierluigi Viale

**Overview**

In this chapter, several aspects of infections in liver transplant recipients are summarized. Both donor- and recipient-derived infections will be described. In the latter group, an important role is played by hospital-acquired infection that is predominant in the first period after transplant. Additionally, in certain geographical areas, multidrug-resistant pathogens are increasingly isolated in this setting. Beyond bacterial infection, most important viral and fungal infections are summarized in this chapter. After completing this chapter, the reader should be able to: (i) distinguish patients at high risk for invasive fungal infection and select patients at high risk who may require antifungal prophylaxis; (ii) individualize preventive measures for cytomegalovirus disease; (iii) understand epidemiology, screening, and treatment algorithm for latent and active *Mycobacterium tuberculosis* infection.

## 19.1 Introduction

Liver transplantation (LT) is a life-saving treatment for liver cirrhosis and hepatocellular carcinoma. It is estimated that more than 12,000 LTs are performed yearly in Europe and the United States, and a global trend of increasing number of procedures has been observed in the last decade [1, 2]. Consistently, with the progression of surgical technique and availability of more effective immunosuppressive therapies, the overall 10-year survival rate after LT has increased from 45% to 60% in the

M. Bartoletti · M. Rinaldi · L. Bussini · M. Giannella · P. Viale (✉)
Infectious Diseases Unit, Department of Medical and Surgical Sciences, Sant'Orsola-Malpighi Hospital, University of Bologna, Bologna, Italy
e-mail: pierluigi.viale@unibo.it


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last three decades [1]. Infection is the most important complication and cause of death of LT. Several aspects of LT can contribute to increase the risk of infection in this setting. Beyond the aforementioned surgical complexity and intensity of immunosuppression, most of the patients with end-stage liver disease commonly undergo LT in critical condition, with concomitant acute-on-chronic liver failure, and are exposed to multiple antibiotic therapies [3].

The infectious risk of solid organ transplant (SOT) recipients in strictly related to the intensity of immunosuppression and the time period that elapses between the transplant and the onset of symptoms. Typically in the early posttransplant period (<30 days), infections are hospital or intensive care unit (ICU) acquired and are related to surgery or presence of devices [4]. Accordingly, in this period, the prevalence of MDR pathogens is high, especially in certain geographical areas [5]. During the first 6–12 months of transplantation, immunosuppressive effect is more intensive, and therefore, transplantation opportunistic infections are predominant. The occurrence of opportunistic infection may also be related to the kind of preventive strategy adopted, such as antifungal prophylaxis or administration and duration of anticytomegalovirus (CMV) prophylaxis. Beyond 6–12 months posttransplant, infection occurring in patients with acceptable graft function is related to community exposures or, less frequently, reactivation of latent infections. Thus, the majority of infections in this period are community-acquired pneumonia, urinary tract infection, and food-borne infections (gastroenteritis or *Listeria monocytogenes* infection) [6].

▶ Tips
- Occurrence of infection after LT follows typical timeline. Careful evaluation of patient history, exposures, and medication is necessary during patients' assessment.
- Symptoms of infections are atypical, more than one process may be present. Fever could be the expression of both infectious and non-infectious diseases.
- Screening of MDRO colonization should be performed before and after OLT.
- Decision on antifungal prophylaxis should be based on specific risk factors.
- CMV preventive strategies are based on prophylaxis for high-risk patients or preemptive treatment following serum CMV-DNA monitoring.
- In OLT recipients, treatment for LTBI could be started when graft function is completely restored, as TB reactivation is a late complication in the timeline of infections.

## 19.2 Donor-Derived Infections

This group comprises infections transmitted via infected tissue or systemic infection of the donor at the time of organ procurement of donor organs generally in the form of latent infections (usually viruses such as cytomegalovirus—CMV),

unrecognized colonization/infection of biliary or urinary tract, unknown bacteremia, or surgical contamination at procurement or preservation. Infected organ donors have been found to transmit bacteria and fungi carrying resistance to routine surgical antimicrobial prophylaxis [7, 8]. In addition, unexpected clusters of donor-derived infections in transplant recipients have been recognized including those due to West Nile virus, lymphocytic choriomeningitis virus (LCMV), rabies, HIV, hepatitis B and hepatitis C viruses, herpes simplex virus, tuberculosis, endemic fungi, and Chagas disease [9, 10]. As a result of the urgency and time limitations between organ procurement and transplantation, donor infectious work up may be less than ideal. At present, donor testing relies on any history gained from donor caregivers as well as serology, culture, and nucleic acid testing (NAT). Because of donor shortage compared to the number of candidates on wait list, more marginal donors such as those who are actively infected, colonized by MDR pathogens or those at increased infectious risk from HIV, HBV, and HCV are commonly being used, increasing the risk of donor-derived infections [5, 11, 12].

## 19.3 Bacterial Infections

### 19.3.1 Community-Acquired Infections

After the first 6–12 months of transplant, the intensity of immunosuppression may be reduced. Thus, in this period the characteristics of infection may change, and most patients are likely to experience more typical community-acquired infections (CAI). It is worth to be noted that common CAIs are more frequent in SOT recipients than the general population. The prevalence of pneumococcal invasive disease (PID) is 10-fold higher in all SOT patients and 40-fold higher in lung transplant recipients. Similarly, SOT recipients are at higher risk for developing bacterial meningitis and meningococcal invasive disease [13]. Additionally, in a small series of bacterial meningitis in kidney transplant recipients, *Listeria monocytogenes* was one of the most common etiological agents. Another potential pathogen in this population, relatively uncommon in nonimmunocompromised hosts, is *Nocardia* spp. [14]. The incidence of nocardiosis after organ transplantation varies according to the transplanted organ, ranging from <1% after kidney or liver transplantation to 1–3.5% after heart and/or lung transplant. Common risk factors are corticosteroids and high serum levels of calcineurin inhibitors. Commonly, nocardiosis occurs after the first year of transplantation and disseminated disease may be as high as 40% with a reported mortality of 16% of cases [15, 16]. Nocardia is an important pathogen in immunosuppressed patients and is associated with skin and soft tissue, lung, central nervous system, or disseminated disease. A review of 13 studies over the last 5 years dealing with *Nocardia* SSTIs has been recently published in SOT recipients [17]. The most common underlying type of transplant was kidney and the time from transplantation to infection varied from 6 months to 16 years. Misdiagnosis was frequent. Available identified species included *N. brasiliensis* (2), *N. farcinica* (2), *N. flavorosea* (1), *N. abscessus* (1), *N. anaemiae* (1), *N. asteroides* (1), *N. nova* (1), and *N. vinacea* (1).

## 19.4 Hospital-Acquired Infections

Liver transplant patients are particularly prone to develop bacterial infections during the first month after transplant. The surgical complexity of LT is higher if compared with other kinds of solid organ transplant. Additionally, most LT candidates are patients with end-stage liver disease, admitted in intensive care unit and frequently colonized or infected by multidrug-resistant (MDR) pathogens. During the first posttransplantation month, 4.4 episodes of bacterial infection were reported per patient per year. Most infections are related to the surgical procedure or medical complications. Surgical site infections (SSIs), including deep intra-abdominal infections or pneumonia, bacteremia, urinary tract infections, catheter-related and biliary tract infections, are common. In the latter case, biliary leakage and stricture of biliary tract are important risk factors that may require combined surgical and medical management [18].

## 19.5 Epidemiology of MDR Pathogens Among SOT Recipients

In the current era, ruled by an alarming evolution of antimicrobial resistances, the SOT recipients seem one of the patients category most prone to develop infection caused by multidrug-resistant (MDR) pathogens [19–21]. Not surprisingly, infection caused by MDR pathogens are found more frequently in SOT recipients than in non-SOT population [22].

The current major challenges of MDR pathogens are the followings. First, MDR infections in transplanted people are frequently associated with graft complication, while their treatment is often hampered by an ominous lack of effective drugs, resulting in an overall poor outcome. Second, MDR pathogens are frequently associated with outbreaks. This is related to the ability of these pathogens, especially Gram-negative bacilli, to spread among frail population.

The prevalence, risk factors, and mortality of infection caused by MDR pathogens in the setting of organ transplant are summarized in Table 19.1. Significant differences are present between different pathogens. Furthermore, prevalence and incidence of infections may vary among different centers located in different countries and between American and European centers.

### 19.5.1 Methicillin-Resistant *Staphylococcus aureus* and Vancomycin-Resistant Enterococci

*Staphylococcus aureus* is a major cause of invasive infection in the general population, being the second most common bacterial species after *Escherichia coli* [23]. Among all *S. aureus* infections, those due to MRSA represent 21–24% of cases in Europe and 31–39% in the United States [24, 25].

**Table 19.1** Risk factors for invasive fungal infections in liver transplant recipients

| Risk factors for invasive candidiasis (IC) | Risk factors for invasive aspergillosis (IA) |
|---|---|
| *Preoperative variables* | |
| ICU hospitalization in the prior 90 days | Fulminant hepatic failure |
| Perioperative *Candida* spp. colonization | Steroid treatment[a] |
| *Intraoperative variables* | |
| Choledochojejunostomy | Multivisceral transplantation |
| Transfusion of ≥40 units of cellular blood products | |
| *Postoperative variables* | |
| Acute renal failure | Renal replacement therapy |
| Any rejection within 2 weeks after transplant | Rejection requiring treatment with ATG, OKT3, or Alemtuzumab |
| CMV DNAemia >100,000 copies/mL | Retransplant |
| Prolonged or repeat operation | Reoperation |

Abbreviations: ATG Antithymocyte globulin, *CMV* Cytomegalovirus, *ICU* Intensive care unit, *OKT-3* Anti-CD3 monoclonal antibody

[a]Steroid treatment refers to receiving an equivalent of 16 mg/day prednisone for ≥15 days in the last month prior to transplantation

The incidence of MRSA infection appears higher in lung and liver transplant recipients (0.2–5.7 cases per 100 transplant-years for the former, 0.1 cases per 100 transplant-years the latter) with respect to other kinds of transplants. Most MRSA infections occur in the early posttransplant period, after a median of 7–29 days following liver and lung transplantation [26–28]. The most frequent sources of infection are pneumonia, bloodstream infection (BSI), vascular catheters, and the surgical site itself. However, the latter is found mostly in heart and lung transplants. Risk factors for infection found in previous studies are pretransplant and posttransplant nasal colonization, ICU stay, mechanical ventilation for more than 5 days and cytomegalovirus (CMV) primary infection in CMV-seronegative recipients. Mortality for infection caused by MRSA ranges between 14% and 36% [28–30].

*Enterococcus* spp. infection is common after abdominal SOT. Prevalence of *Enterococcus* spp. infection is reported in up to 15% of SOT recipients, mainly liver transplant recipients [31]. *Enterococcus* spp. is the causative pathogen of 6–15% of BSIs in SOT recipients. This rate can reach 20% in hospital acquired BSI [32–34]. Among all enterococcal infections, the impact of vancomycin-resistant Enterococcus (VRE) is extremely variable between countries. Centers in North America reported a prevalence of 2–11% of VRE infection in liver transplant recipients [35–37], whereas nearly no infections were reported in studies conducted in Europe [31, 32]. VRE infections occur mainly in liver transplant recipients, probably as a consequence of high prevalence of colonized or infected patients before transplantation [38, 39]. The main types of infections are bacteremia, peritonitis, surgical site infection (SSI), and urinary and biliary tract infections [38, 40, 41]. Overall, crude mortality for VRE infection represents 9–48% of cases, but can reach 56–80% during the 1 year of follow-up period [36, 37, 40, 41].

### 19.5.2 Enterobacterales and Nonfermenters

#### 19.5.2.1 Extended-Spectrum Beta-Lactamase-Producing Enterobacterales

The prevalence of extended-spectrum beta-lactamase (ESBL)-producing Enterobacterales strains among transplant patients has increased dramatically in recent years. In a study analyzing the etiology of BSI occurring among transplant recipients in a center in Spain in the first year posttransplant, an increasing rate of ESBL-producing strains was found, principally *Klebsiella pneumoniae,* from 7% in 2007–2008 to 34% in 2015–2016 [42].

Most infections in patients receiving LT occur early on in the posttransplant period [43–45]. Mortality associated with infection due to ESBL-producing strains may vary from 8% to 26% of cases. In addition, a significant rate of recurrent infection has been observed (21–41% of cases) [43, 44]. Similarly to other MDR pathogens, ESBL-producing Enterobacteriaceae fecal colonization is frequent in liver and kidney transplant candidates during the pretransplant phase (4–31% of subjects) and it has found to be independently associated with posttransplant infection [45, 46].

#### 19.5.2.2 Carbapenem-Resistant Enterobacteriaceae

Nowadays the global emergence of CRE is a major health challenge. In studies analyzing CRE BSI episodes in the general patient population, SOT patients are involved in 14–37% of cases [47, 48]. In addition, a multicenter study conducted in SOT recipients in Italy shows that the prevalence of carbapenem resistance was 26% among all isolated Enterobacteriaceae and 49% among all isolated *Klebsiella* spp. [49].

Overall, in endemic areas, the incidence of CRE infection following SOT is approximately 5%, CRE infection commonly occurs in the initial posttransplant period (on average 11–36 days) [50–52]. Infection associated with CRE is usually BSI, including catheter-related BSI, pneumonia, UTI, intra-abdominal infection, and SSI. Posttransplantation renal replacement therapy, CRE rectal colonization, HCV recurrence in liver transplant recipients, bile leak, and prolonged mechanical ventilation are risk factors for CRE during the early posttransplant period [50, 53]. CRE-associated crude mortality rates vary from 25% to 71% [52, 54–57].

Similarly, the prevalence of CRE fecal carriers before liver transplantation is reported between 5% and 18% of cases. Studies evaluating the impact of pretransplant colonization on posttransplant infection risk report conflicting results [50, 52]. However, in a recent larger prospective study of 553 LT recipients screened routinely for CRE in the pre- and post-transplant period, colonization was an independent risk factor for posttransplant CRE infection, irrespective of the timing of acquisition [58].

#### 19.5.2.3 Carbapenem-Resistant Acinetobacter baumannii

Carbapenem-resistant *Acinetobacter baumannii* (CR-AB) is commonly reported to affect 9–29% of SOT patients. This variability is primarily related to the distinctive

propensity of CR-AB to generate outbreaks [59–61]. Epidemiological studies of BSI in SOT patients report a rate of CR-AB of 2–6% [32]. Most infections occur in liver and lung transplant recipients, commonly during the ICU stay in the early post-transplant period. The most common infections are SSI, pneumonia, and BSI, with a mortality rate after 30 days of 57–62%.

#### 19.5.2.4 MDR *Pseudomonas aeruginosa*

*Pseudomonas aeruginosa* is involved in 6–13% of BSI after SOT, being a leading pathogen in lung transplant patients [34, 42, 62]. Prevalence of drug resistance among *P. aeruginosa* strains may vary significantly between centers. Outside the lung transplantation setting, the most common sources of MDR/XDR *P. aeruginosa* BSI are the urinary tract, central venous catheters, and the abdomen [63, 64]. New drugs are available to treat *P. aeruginosa* invasive infections, such as ceftolozane-tazobactam [65].

## 19.6 Invasive Fungal Infections

Invasive fungal infections (IFI) represent a major life-threatening disease among infections occurring after SOT [1]. In orthotopic liver transplant (OLT) recipients, due to the complexity of intraperitoneal surgical procedures, invasive candidiasis (IC) is the most common IFI, followed by invasive aspergillosis (IA) accounting for 49–76% and 5–14% of IFI, respectively [2, 3]. Other IFI rates may range from local epidemiology, however, data from the Transplant-Associated Infection Surveillance Network (TRANSNET) suggest that after IC and IA, cryptococcosis (8%), non-*Aspergillus* molds (8%), and endemic fungi (5%) are the most frequent IFI [4].

The occurrence of IC is commonly earlier than other IFIs, with a peak of incidence within the first month after OLT [66]. Risk factors for IC have been evaluated in several studies more than a decade ago [67]. Some preexisting conditions (perioperative *Candida* spp. colonization, previous hospitalization in intensive care unit), kind of biliary anastomosis (choledochojejunostomy), or post-OLT complications (acute renal failure, rejection, or CMV infection) could lead to IC development [67, 68]. Approximately 50% of isolates involves *C. albicans*, whereas *C. glabrata* is the most common *non-albicans* species [68]. However, epidemiologic data show a change in the spectrum of IC toward an increase of *non-albicans* species, probably coinciding with a massive use of fluconazole [69, 70]. In addition to this shift in the spectrum of *Candida* species, an emergence of novel species has been reported, such as *C. auris*, especially in the United States [71].

In OLT recipients, due to the intraperitoneal surgical procedures, the primary sites of infection are the bloodstream and the intra-abdominal cavity.

The diagnosis of IC may be challenging. In fact, blood cultures have an overall sensitivity of about 50–70% [68]. To improve the accuracy of diagnosis of IC, several noncultural tests are available. The (1-3)-β-D-glucan (BDG) is a cell wall polysaccharide found in most fungi, with the exception of the cryptococci, the zygomycetes, and *Blastomyces dermatitidis*. A recent study conducted on OLT

recipients showed that combining two subsequent samples positive for BDG (with a cut-off of 146 pg/mL), sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were 83%, 89%, 50%, and 97.6%, respectively [72].

New techniques have been introduced: polymerase chain reaction detecting *Candida* DNA was found to be more sensitive (89%) than both BDG and blood cultures among SOT recipients, although there is still a heterogeneity in the available results as well as the lack of reference standards [73]. Of interest, sensitivity decrease significantly for candidemia at 59% [74].

Another emerging diagnostic tool is T2 *Candida* test that allows the detection of the five most frequent *Candida* species within 3–5 h from blood collection. The advantage of this test is the greater sensitivity (96.4%) compared to blood cultures. However, the disadvantages rely on the high costs and the inability of providing any information about antifungal susceptibility [75].

Regarding treatment, echinocandins are recommended as primary and empirical therapy, eventually an accurate de-escalation to fluconazole according to pattern of susceptibility could be performed [68]. All patients with candidemia should exclude secondary localization, such as endophthalmitis and endocarditis. In case of candidemia without metastatic complications, treatment could be stopped after 14 days from the first documented negative blood culture [68, 76].

In general, IA onset recognize two different moments in the infection timeline after SOT [77]. Risk factors for early onset of IA, occurring within the first 3 months post-OLT, are retransplantation, urgent transplantation for fulminant hepatic failure, whereas donor CMV seropositivity is a risk factor for late onset of IA [77, 78].

Although IA is commonly localized in lungs and could disseminate in SNC and in other organs, no specific symptoms exist, the typical presentation is fever and presence of mucopurulent secretion in lungs. Bilateral nodular involvement on CT scan is often present, whereas the presence of cavitation or the halo sign is reported in 33% and 25% of patients, respectively [79]. As proven, demonstration of IA is not always feasible, diagnosis is based on clinical, radiological, and microbiological characteristics of the patient, according to revised EORTC/MSG criteria [80].

Although *Aspergillus* spp. is rarely isolated from respiratory tract samples in OLT recipients, its detection is related to a relatively high PPV (40–70%) [77]. Noncultural tests such as galactomannan (GM) from the serum may be considered, but its use may be limited by low sensibility despite the high specificity (30% and 98.5%, respectively) [77, 81, 82]. Conversely, GM testing on bronchoalveolar lavage fluid provides a higher sensitivity, as high as 67–80% in SOT recipients [77]. Regarding treatment, voriconazole is recommended as first-line therapy. However, voriconazole may be associated with transient visual disorders in 30% of patients, as elevation of liver enzymes is a common side effect. Due to major interaction with other drugs, especially immunosuppressive agents, monitoring of serum concentration of voriconazole is recommended by IDSA guidelines [83, 84]. Additionally tacrolimus dosage should be lowered to a 30% of initial dosing when concomitant voriconazole is administered. Second-line therapy could be LamB 3–5 mg/kg daily or isavuconazole 200 mg/day [77, 85]. Compared to voriconazole, isavuconazole shows similar efficacy but displays both less liver adverse events and drug-drug

interactions [85]. However, clinical data of isavuconazole use in LT are lacking with exception of small case series.

Mortality rates of IFI in LT recipients are really high: the 1-year survival after IC is about 66%, IA mortality rates may range from 22% up to 80% in lung transplant recipients [77, 86]. Considering the high mortality rate of IFI, an antifungal prophylaxis strategy is commonly employed at the majority of transplant centers in order to reduce the incidence of IFI and the IFI-related mortality after OLT [87]. Nevertheless, even today there is discrepancy between universal antifungal prophylaxis and targeted antifungal prophylaxis, in the latter case addressed to LT recipients with more than one risk factor for IFI (Table 19.1). According to recent studies [88–90] and as recommended by AST guidelines [91], a targeted approach seems to be preferred to universal strategy in order to avoid overexposure with consequent toxicity and resistance selection.

For IC prevention, fluconazole could be an optimal option according to local epidemiology, although the prophylactic agent should have anti-*Aspergillus* activity if there is also an augmented risk for IA [68].

Generally, in high-risk patients, echinocandins have been shown to be safe with a low rate of drug-drug interactions. In addition, several studies have examined the role of echinocandins versus both liposomal amphotericin B and fluconazole without finding significant differences in terms of mortality rates [92–94]. However, high rates of breakthrough infections have been reported with these agents [95, 96]. Alternatively, as suggested both by American guidelines and a recent review [77, 97], liposomal amphotericin B could be given at a daily dose of 3 mg/kg. However, a weekly high dose of LamB has been reported to be safe and associated with a low rate of IFI [98].

With the common use of antifungal prophylaxis, latest studies report a decrease in cumulative IFI incidence ranging from 1.3% to 11.6% in SOT, reaching 4.7% in OLT [86].

As previously stated, *Cryptococcus* spp. represents the third most common fungal infection, accounting approximately for 8% of the IFIs in SOT. Cryptococcosis usually presents as disseminated fungemia with central nervous system (CNS) infection (55–68% of cases) and it is associated with higher mortality compared to pulmonary or cutaneous cryptococcosis [99, 100]. Thus, literature reports mortality rates ranging from 14% up to 40% [99, 101]. In this particular setting, the type of immunosuppressive regimen significantly impacts on the clinical manifestation of cryptococcosis. Tacrolimus is associated with a lower risk of disseminated infection, particularly in CNS [99], as well as a calcineurin inhibitor-based regimen reflects on a decrease in terms of mortality [101], probably due to a direct inhibition of cryptococcal protein CB1 in SNC. Curiously, OLT recipients are at higher risk of cryptococcosis compared to other SOT, probably due to immune defects related to liver cirrhosis [101]. In addition, early onset of cryptococcosis before SOT is associated with OLT recipients [99]. When pulmonary cryptococcosis is suspected, evaluation for extrapulmonary localizations is mandatory by performing blood cultures and lumbar puncture. Cryptococcal antigen testing is more sensitive compared to cultures or India ink staining in cerebrospinal fluid, nevertheless its sensitivity decreases for isolated pulmonary disease [100].

Once cryptococcosis has been diagnosed, treatment of choice is based on LamB 3 mg/kg daily for at least 2 weeks as induction therapy, followed by fluconazole 400–800 mg daily for 8 weeks as consolidation therapy. Generally, 6–12 months of suppression therapy after treatment is recommended. Antifungal prophylaxis is not recommended, as in literature a high-risk group has not been identified [100].

Histoplasmosis as well as coccidioidomycosis and blastomycosis belong to thermally dimorphic fungi, and they are endemic in some regions, mainly in Middle West, Central, and South America and in some parts of Africa. They are an environmental, soil-based fungi usually acquired through inhalation of conidia [102]. In SOT recipients, incidence of invasive infections due to these microorganisms is about 0.2%, as attested by TRANSNET data during a study period of 5 years [103]. As often happens in this particular setting, the virulence of these pathogens depends on a balance between the burden of disease and the state of immunosuppression of the host. Classically, histoplasmosis is first localized in lungs, whereas could become disseminated when immunosuppression causes a loss of containment of a previously controlled infection, such as that occurs from antirejection medication [104, 105]. Establishing a diagnosis could be difficult, as disseminated histoplasmosis could present itself with constitutional symptoms, enteritis, enlarged lymph nodes, and arthralgia [106]. Typically, from symptoms onset to diagnosis, there is a median of 2 weeks [107, 108].

In histoplasmosis, the median time to diagnosis is 27 months from transplant, but up to one third of patients are diagnosed with histoplasmosis within the first year posttransplant [109]. Diagnosis could be advantaged by biopsy and tissue culture of cutaneous lesions [106], however, antigenuria has the highest sensitivity for histoplasmosis, being positive in 93% of patients, whereas antigenemia is positive in 86% of cases [109]. Treatment for disseminated histoplasmosis is comprehensive of LamB for 1–2 weeks, followed by oral azoles for at least 1 year [106]; antigen concentration could be used as stopping rule when it is <2 ng/mL, as recommended by IDSA guidelines [110].

## 19.7 Cytomegalovirus

Human cytomegalovirus (CMV) is a double-stranded DNA virus and member of the herpes virus family and of β-herpes virus subfamily. Approximately 60–100% of the adult population has had exposure to the virus and are potential carriers of infection, with primary infection mostly occurring within the first two decades of life. It is the most common opportunistic infection following solid organ transplant and may occur as primary or secondary infection or as a reactivation form of a reservoir where the virus commonly remains latent following primary infection. In fact, during the first infection CMV disseminates from the respiratory tract, most commonly via mononuclear cells and polymorphonuclear cells to endothelial, epithelial, and fibroblast of tissues and organs [111]. Commonly, in an immunocompetent individual both innate and adaptative immunity allow a complete control of the infection. After this phase, CMV establishes lifelong latency in endothelium, epithelium, smooth muscle, and fibroblasts by evading immune detection [111].

**Table 19.2** Risk stratification for cytomegalovirus disease in solid organ transplant recipients

| | High risk | Intermediate risk | Low risk |
|---|---|---|---|
| CMV serostatus | D+/R- | D+/R+<br>D−/R+ | D−/R− |
| Immunosuppression | ATC, Alemtuzumab<br>OKT3 | MMF, FK, AZA, CoA<br>HD-steroids | mTOR inhibitors |
| Organ transplanted | Lung<br>Pancreas<br>Bowel | Heart | Liver<br>Kidney |
| CMV-specific cell-mediated immunity | Low | Intermediate | High |

In solid organ transplantation, CMV may occur in up to 50% of allograft recipients, usually between 2 months and 1 year after transplantation. Several factors may be involved in the occurrence of the infection (Table 19.2). These include type of organ transplanted, donor and recipients serostatus, immunosuppressive regimen, and preventive strategy [112].

In liver transplant recipients, the prevalence of CMV disease is lower than recipients of other organs. In the absence of any prevention strategy, the incidence of CMV in this setting is around 20% of patients within 6 months from transplant [113].

CMV may be responsible for several direct and indirect effects in this population. The direct effects may be summarized into the following definitions:

- CMV infection: Evidence of CMV replication regardless of symptoms (differs from latent CMV).
- CMV disease: Evidence of CMV infection with attributable symptoms. CMV disease can be further categorized as a viral syndrome with fever, malaise, leukopenia, and thrombocytopenia or as a tissue-invasive disease (or "end-organ" disease).

The indirect effects attributable to CMV may be divided into short-term effects such as acute rejection, new-onset posttransplant diabetes, and opportunistic bacterial, fungal, and protozoal infections. Long-term effects may include transplant vasculopathy, bronchiolitis obliterans, vanishing bile duct syndrome, and coronary artery disease [114].

Several risk factors are related to CMV infection or disease (Table 19.2). First, the donor/recipients serostatus is one of the most important factors. In fact, having the ability to remain latent into organ and tissues, CMV may be transmitted during transplant. Recipients that are CMV IgG negative and receive an organ from a CMV IgG-positive donor (D+/R− status) are at greatest risk of primary infection. In this case, the infection occurs early and may become symptomatic in the first weeks after transplant, in absence of antiviral therapy. Second, the type and intensity of immunosuppression are related to CMV infection, being this less common among patients treated with mTOR inhibitors and higher among those receiving a higher degree of immunosuppression such as heart, lung, bowel, and combined kidney-pancreas transplantation [115–117].

Prevention of CMV infection and disease among SOT patients may be summarized into two core strategies: prophylaxis and preemptive treatment. Prophylaxis consists of administration of low dosage of antiviral treatment in the first 3–6 months after transplant. Prophylaxis is commonly recommended in high-risk recipients (D+/R− status). It is generally well tolerated and effective, but only for a limited period. In fact, several studies demonstrated that after discontinuation of CMV prophylaxis most of patients with D+/R− serostatus experience late primary infection. Thus, the effect of prophylaxis in this group of patients may be only transitory [117].

Preemptive strategy consists of administration of antiviral therapy only in case of detection of significant CMV blood replication. The basic principle of this strategy is to detect the presence of early CMV replication prior to the onset of clinical symptoms, so that antiviral therapy is administered early in order to prevent the progression of asymptomatic infection to clinical relevant disease. This strategy has the potential advantages of reducing drug use and related adverse events. On the other hand, it requires frequent laboratory monitoring and increased difficulties and need for correct logistic in order to obtain results and start the correct treatment timely [118].

Recent studies has shown that monitoring of CMV-specific T-cell responses with interferon-γ release assay (IGRA) tests can predict the risk of CMV disease post-transplant and may be useful in guiding prophylaxis and preemptive therapies. In fact, in patients with sufficient immune response, the number of CMV recurrences is significantly lower than those with scarce interferon-γ production [119]. Additionally, in a study of SOT patients with detectable CMV DNAemia, those with higher IGRA response had antiviral treatment discontinued without a significant increase in disease recurrence [120].

## 19.8 *Mycobacterium tuberculosis*

SOT recipients are at increased risk of mycobacterial infections. Classically, mycobacterial diseases can be divided into *Mycobacterium tuberculosis* infection and nontuberculous mycobacterial infection.

*Mycobacterium tuberculosis* infection (TB) is a serious complication of SOT. SOT candidates and recipients are at greater risk for developing active TB with a rate of occurrence up to 74 times higher than that of the general population.

In LT patients, rates of active TB range between 0.47% and 2.3%. However, the burden of disease seems to be underestimated as its deceitful onset can make diagnosis challenging. In addition, prevalence of TB in LT patients varies across geographic areas, being higher in low-income countries of Africa and Asia. Even median time from LT to TB diagnosis varies geographically ranging from 189 days in Spanish RESITRA cohort to 20 months in a recent Chinese retrospective study. Few risk factors have been identified for active TB onset after LT, that is, living in an endemic country, previous TB infection, known contacts with TB cases, use of mTOR inhibitors, poor social and physical status, presence of findings on chest imaging consistent with healed TB [121].

TB in LT patients can have peculiar clinical features, such as a more frequent involvement of extrapulmonary organs and atypical symptoms and signs leading to a delayed diagnosis and, consequently, to a worse outcome. Thus, TB-related mortality may reach 20–30% in this setting.

In LT recipients, TB may be represented by four different scenarios, some of which can be prevented with a specific strategy [122]:

(a) *Endogenous reactivation due to latent infection with M. tuberculosis (LTBI) in the candidate recipient*. This is the commonest pattern of TB infection. Candidates to OLT should be evaluated and screened in order to rule out active TB with a careful assessment of patient history, including previous exposure to *M. tuberculosis* (MTB), sign/symptoms, previous and recent chest imaging. Patients with lung imaging abnormalities, history, or physical examination consistent with active TB should be assessed with acid-fast bacilli smear, MTB polymerase chain reaction testing, and acid-fast bacilli culture on at least three sputum samples or other appropriate microbiological work up based on suspected infection site. In the absence of clinical or radiological suspicion, OLT candidates should be tested with methods measuring immune response to MBT in order to detect LTBI. These include tuberculin skin tests (TSTs) and INF-γ release assays (IGRAs). When compared to TST, IGRAs have some operational advantages that are particularly relevant in immunocompromised patients. Unlike the TST, antigen-specific stimulation in vitro is carried out along with negative and positive controls. Since the positive control allows assessment of general T-cell responsiveness, IGRA tests may be able to discriminate true negative responses from anergy and/or overt immunosuppression. Further advantages of IGRAs may result from an increase in specificity in the face of increased, or at least similar, sensitivity.

Treatment of LTBI in LT candidates provides major concern due to the risk of drug-induced liver injury. Indeed, in patients with end-stage liver disease, LTBI treatment can be deferred to the postsurgical period. Conversely, patients with stable liver function can be treated pretransplant, even before starting therapy, and continuing after OLT. Generally, first-line regimens used for LTBI therapy in solid organ recipients include: (a) isoniazid for 9 months (9H); (b) rifampin for 4 months (4R), and (c) isoniazid + rifapentine for 3 months (3RH) given weekly via directly observed therapy (DOT). For LT candidates, some authors proposed an algorithm based on transplant timing, drug interaction, and hepatotoxicity risk (Fig. 19.1) [123]. Patients ineligible for rifampin-based regimen due to drug interactions or impending LT could be treated with 9 months of isoniazid (9H) with only slightly increased risk of transaminase elevation. Rifabutin could be another option, being less hepatotoxic than H and weaker inductor of cytochrome P450 than rifampin. Fluoroquinolones (FQ) have been recently investigated as LTBI treatment option owing to their low hepatotoxicity and minor drug interactions. However, strong evidences of reduction of TB reactivation with FQ monotherapy have not emerged yet. Furthermore, an open-label randomized clinical trial comparing levofloxacin with H among LT

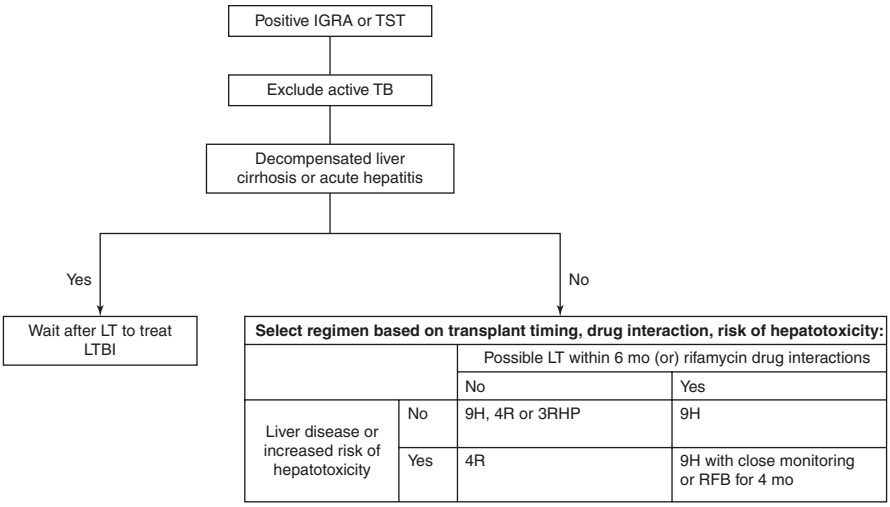


**Fig. 19.1** Algorithm for LTBI treatment in liver transplant candidates

candidates was early interrupted owing to high rates of tenosynovitis arisen in FQ arm [124].

If LT occurs during LTBI treatment, therapy can be safely interrupted in the peritransplant and resumed when clinical conditions and liver function recover without having to start over.

3HP: 3 months of weekly isoniazid and rifapentine via directly observed therapy; 4R: rifampin for 4 months; 9H: isoniazid for 9 months; RFB, rifabutin

(a) *Donor-derived reactivation due to LTBI in a living or deceased donor* is rare in OLT. However, cases of TB transmission with LT and KT with high fatality rate have been reported. Donors, similarly to recipients, should be evaluated and screened for active or LTBI. A suspicion of active TB should contraindicate for donation. In case of deceased donor, history of LTBI or prior TB exposure should be investigated. Radiological signs consistent with latent TB or diagnosis of LTBI in deceased donor do not preclude transplantation unless the recent contact was with MDR TB. In these cases, LTBI treatment should be started after LT.

(b) *De novo exposure and infection posttransplantation*. In LT patients, the risk of rapid progression of TB is high in the case of a de novo infection with a frequent extrapulmonary involvement and/or disseminated infection.

(c) *Urgent transplantation in a patient with active tuberculosis (i.e., urgent liver transplantation).* Even though TB is considered a contraindication for organ transplantation, in specific cases of fulminant hepatic failure (FHF) LT has been successfully performed. We recently reviewed the literature and found 31 cases of LT reported in patients with active tuberculosis. The indication for LT was

fulminant hepatic failure (FHF) in 22/31 (70%) of cases, secondary to antitubercular treatment (ATT), hepatitis B virus, or idiopathic in 86%, 9%, and 4% of cases, respectively. At the end of follow-up, which lasted a median of 12 (12–24) months, 27/31 (87%) patients were alive and none of them experienced a relapse of TB after LT. A recent Brazilian case series described eight patients undergoing transplantation for acute liver failure attributed to antitubercular drugs. MELD score at LT was high (median 38, IQR 33–47) and 1-year mortality of 50%. Three of the eight patients had liver rejection. After 5-year follow-up, surviving patients were considered healed from TB [125].

Treatment of TB after LT remains a challenge [122]. First-line ATT including isoniazid, rifampin, pyrazinamide, and ethambutol is recommended in susceptible strains. However, the potential for drug interaction between rifaximins and immunosuppressant agents and hepatotoxicity of antitubercular drugs make strict monitoring of immunosuppressant serum levels and liver function tests mandatory while administering rifampin and isoniazid. In this setting, in fact, hepatotoxicity requiring isoniazid discontinuation was documented in 41% of recipients. Adequate immunosuppressant drug serum levels can be easier to maintain with the use of rifabutin instead of rifampin, for the lesser potential of cytochrome P3A4 induction of rifabutin. Second-line drugs such as fluoroquinolones and aminoglycosides have been successfully used and are preferred by some authors for the absence of potential hepatotoxicity and low risk of drug interaction. A rifamycin-free regimen (H, Z, E, fluoroquinolone) is an option in nonsevere TB cases (noncavitated pulmonary and nondisseminated disease) in order to avoid interaction with immunosuppressive drugs.

**Key Points**

- Occurrence of infection in LT follows a typical timeline: in the early post-transplant period (<30 days), infections are hospital or ICU acquired and are related to surgery with higher prevalence of MDR pathogens; during the first 6–12 months after OLT, opportunistic infections are predominant as immunosuppressive effect is more intensive; beyond 6–12 months, post-transplant infections are mainly related to community exposures.
- MDR infections in LT recipients are frequently associated with graft complication and treatment is often challenging due to lack of effective drugs. Rates of colonization and infection due to ESBL-producing and carbapenem-resistant Enterobacterales among transplant recipients have increased dramatically in recent years.
- Invasive candidiasis (IC) is the most common IFI after OLT, followed by invasive aspergillosis (IA); echinocandins are the primary and empirical therapy for IC, while voriconazole is first-line therapy for IA. High mortality rates attributed to IFI justify use of antifungal prophylaxis in LT recipients.

- CMV is the most common opportunistic infection after SOT and may occur as primary/secondary infection or as a reactivation. Recipients that are CMV IgG negative and receive an organ from a CMV IgG-positive donor (D+/R− status) are at greatest risk of primary infection. Two prevention strategies for CMV infection are feasible: prophylaxis and preemptive treatment.
- LT candidates and donors should be screened in order to rule out active or latent TB. Based on patient residual liver function and risk of drug-induced liver injury, treatment of LTBI could be administered pre-, post-OLT, or starting before and continuing after transplant. First-line ATT in OLT includes isoniazid, rifampin, pyrazinamide, and ethambutol, even if potential drug interaction between rifaximins and immunosuppressant agents and hepatotoxicity of antitubercular drugs require strict monitoring of immunosuppressant serum levels and liver function tests.

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