

# 11

## Risks and Epidemiology of Infections After Lung or Heart–Lung Transplantation

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### 11.1 Introduction

Currently, lung transplantation (LT) is an established therapeutic option for patients who have severe respiratory insufficiency [1–5]. Nevertheless, complications do frequently occur, and they can lead to intermediate-term or long-term graft dysfunction and decreased survival. According to the International Society for Heart and Lung Transplantation (ISHLT) registry, survival rates at the first, second, and fifth years are 80%, 65%, and 53%, respectively [6]. The prognosis of lung transplant recipients (LTR) has improved considerably in recent years, thanks to the careful selection of donors and recipients, advances in surgical techniques and postoperative care, and better methods for graft preservation.

LT can be either unilateral or bilateral. Single-lung transplantation is generally used for non-septic lung diseases, whereas double-lung transplantation is mandatory for septic lung diseases, such as cystic fibrosis (CF) and bronchiectasis. Infections and episodes of acute rejection are both significant complications soon after LT. Moreover, the main obstacle to the long-term success of LT remains chronic rejection, characterized histologically as bronchiolitis obliterans. It occurs in up to two thirds of patients [7]. The most relevant risk factor for the development of bronchiolitis obliterans syndrome (BOS) after the number of previous acute rejection episodes and the incidence of persistent rejection is cytomegalovirus (CMV) infection and disease [8]. Recent evidence also suggests a possible role for respiratory viruses (RV) as risk factors for chronic rejection in LTR [9, 10]. Finally, a restrictive allograft syndrome came up as a novel phenotype of chronic rejection with worse prognosis than BOS [11].

Infectious complications are a frequent cause of morbidity and mortality and the most prominent cause of death the first year. More than two thirds of them affect the respiratory tract [6, 12].

This chapter focuses on the epidemiology and prevention of bacterial, viral, and fungal infections in lung or lung–heart transplant recipients. Additionally, it addresses specific aspects of donor, residual, or native lung infection or coloni-

zation, as well as issues involving recipients with CF. One of the main problems with dealing with infection in LT is the paucity of randomized, controlled studies. So more controlled studies are needed to answer the questions regarding infection in LTR.

### 11.2 Risk Factors for Infection

The risk of infection in an LTR is determined by interrelationships among numerous factors related to the recipient, associated with the type of transplant and the surgical procedure, and inherent to the infecting microorganism and the state of permanent therapeutic immunosuppression required to avoid graft rejection. Table 11-1 summarizes these risk factor groups.

#### 11.2.1 Recipient-Related Factors

The recipient's pre-transplantation clinical status is important; patients with renal failure, those on mechanical ventilation, and those with morbid obesity or malnutrition have a higher incidence of infection after LT [12–15]. Advanced age is also associated with an increased risk [16]. In some programs, mechanical ventilation is a major contraindication to LT as airway colonization with bacteria may lead to nosocomial infection and the associated respiratory muscle deconditioning may require prolonged postoperative ventilatory support. However, recent results have shown that pre-transplantation mechanical ventilation is not associated with a higher risk of later bacterial infection [17–19]. In fact, nowadays, most programs accept mechanical ventilation as a bridge for LT for candidates previously included on the waiting list.

Various treatments administered to the candidate before LT as well as underlying diseases (such as diabetes mellitus) may be relevant to the type and severity of infection after LT. Candidates treated with corticoids or antimicrobial agents before transplantation have a higher incidence of

TABLE 11-1. Risk factors for infection in recipients of a lung or heart–lung transplantation

Recipient
Underlying conditions such as diabetes or hepatitis
Older age
Absence of specific immunity to CMV, HSV, VZV, EBV
Colonization of the recipient by bacteria or fungi
Latent infection due to TB, CMV, VZV, HSV, EBV
Previous therapy with antimicrobial agents, corticoids, or other immunosuppressors
Clinical state of the recipient at the time of transplantation:
Renal failure
Malnutrition
Low vitamin D levels
Obesity
Mechanical ventilation
Transplantation
Preservation lesion
Surgical factors:
Duration of procedure, meticulous technique
Surgical complications: suture dehiscence, hemorrhage, arterial ischemia
Repeated surgery required
Postoperative instrumentation:
Duration of mechanical ventilation
Intravascular catheters
Urethral catheter
Continuous exposure to the external environment
Denervation of allograft:
Diminished cough reflex
Abnormal mucociliary clearance
Reactive hyperresponsiveness
Interrupted lymphatic drainage (especially during first weeks)
Anastomosis site:
May enhance colonization
Airway dehiscence and mediastinitis
Bronchial stenosis and postobstructive infection
Donor lung may transmit infections:
From prolonged mechanical ventilation
From latent infections (TB, CMV, VZV, HSV, EBV)
From previous bacterial or fungal colonization
Native lung after single-lung transplantation:
Occult pretransplant infection (TB, <i>Aspergillus</i> spp., <i>Pneumocystis jirovecii</i> , etc. especially with immunosuppression before transplantation)
Sinus infection in cystic fibrosis and ciliary dysfunction syndromes
Bronchiolitis obliterans:
Enhanced immunosuppression
Impaired clearance
Bronchiectasis
Immunosuppression
Immunomodulating viruses
Graft rejection

Abbreviations: CMV cytomegalovirus, HSV herpes simplex virus, VZV varicella-zoster virus, EBV Epstein–Barr virus, TB tuberculosis.

infections due to bacteria and *Candida* spp. [16, 20]. On the other hand, low-dose pre-transplantation corticosteroid treatment has proved to be even beneficial; it allows LT in patients who cannot be completely weaned from such therapy [21]. In cases of single-LT plus pre-transplantation corticosteroid treatment, the remaining native lung may harbor opportunistic microorganisms, including *Aspergillus* spp. (IA), tuberculosis, or *Pneumocystis jirovecii* [22]. Therefore, performing a histopathologic study and culture of the resected lung to rule out these infections and to provide treatment when they are detected is extremely important. Finally, the indiscriminate use of antimicrobial agents before transplantation can lead to the selection of multidrug-resistant (MDR) strains that are difficult to treat. This often occurs in recipients with CF, as discussed below.

The absence of specific immunity in the recipient to some viral infections, especially CMV or Epstein–Barr virus (EBV), implies a higher risk of acquiring these infections when the donor lung harbors latent infection by these viruses. Such primary infection produces disease with greater frequency and more severity than do cases of reactivation.

Vitamin D deficiency is frequent in LT candidates and greater than in general population. Vitamin D plays a role in cell-mediated immunity as well as in innate immune response. A retrospective cohort study showed that 80% of LTR were deficient for vitamin D. Infectious episodes due to bacteria, CMV, fungi, and non-tuberculous mycobacteria (NTM) in this group were more frequent than in the non-deficient group within first year after transplantation (5.41 vs. 3.15;  $p > 0.001$ ) [23].

## 11.2.2 Transplant-Related Factors

Initial dysfunction of the transplanted organ caused by arterial ischemia or severe preservation lesions secondary to a prolonged interval of ischemia influences the frequency and severity of post-transplant infections. Similarly, alloreactivity reactions against the graft make it more prone to infection by certain viruses. The most frequent sites of infection in the immediate postoperative period are the lung, the pleura, and the extrapulmonary chest cavity, since the integrity of the visceral pleura is not restored and the mediastinal space is lost due to communication with the pleural spaces.

With respect to the interval of graft ischemia, Fiser et al. [24] showed that a cold ischemia time longer than 6 h did not increase the risk of reperfusion injury, acute rejection, CMV infection, bacterial or fungal pneumonia, BOS, 1-month mortality, 1-year mortality, or 5-year mortality, after reviewing data from 136 LTR over a 10-year period. These findings have not been supported by results from other groups [16].

The length and the need for repeated surgery are the most important surgery-related risk factors for the development of

bacterial or invasive fungal infection (IFI) during the immediate post-transplantation period [16].

In LT, several special predisposing factors for the appearance of bacterial pneumonia are present. The state of ischemia for several hours after donor lung extraction, and reimplantation without reestablishment of the graft's lymphatic drainage and innervation clearly affect the graft's defense mechanisms. The airway mucosa is damaged, and the mechanism of mucociliary clearance is paralyzed. Anastomosis of the airway also decreases the clearance of respiratory secretions. Graft denervation eliminates the cough reflex, allowing secretions to accumulate. The interruption of lymphatic drainage prevents the immune system effector cells of the regional lymph system from reaching the lung, which in turn alters the immune response against antigens deposited in the lung [25]. Moreover, the graft's microenvironment consists of human leukocyte antigen incompatibility between the host alveolar macrophages and the donor alveolar lymphocytes [26]. Additionally, small inoculum of microorganisms extracted with the graft can produce severe pneumonia in the already immunosuppressed recipient [27]. Finally, the lung is in constant contact with ubiquitous airborne bacteria.

Finally, the most important predisposing condition for post-transplantation infection is BOS. LTR with BOS are usually profoundly immunosuppressed, and their lung function and mucus clearance are often markedly impaired. In fact, the most common cause of death in patients suffering from BOS is infection.

### 11.2.3 Lung Transplant Donor

Almost all donor lungs harbor microorganisms at the time of procurement [28]. Thus, the risk of donor-to-host transmission of infection is inherent; this has repercussions on donor

selection and on the choice of prophylactic regimens administered to the recipient of a lung or heart–LT.

The authors' group has recorded data from donors of lung allografts transplanted to 49 recipients surviving at least 24 h after LT [28]. Overall incidence of donor infection was 73.4%. The types of donor infection included isolated contamination of preservation fluids (17.9%), graft colonization (69.2%), and bacteremia (12.8%). Donor infection rates did not differ statistically between those mechanically ventilated for 48 h or less or more than 48 h. Donor-to-host transmission of bacterial or fungal infection occurred in 15 (7.6%) LTR (Table 11-2). In our experience, 25% of donors with bacteremia and 14.1% of colonized grafts were responsible for transmitting infection. Two patients died because of transmitted infection (Table 11-2). Microorganisms for which it is extremely difficult to design effective prophylactic regimens caused five cases of infection: *A. fumigatus*, *Stenotrophomonas maltophilia* and methicillin-resistant *Staphylococcus aureus* (MRSA). Excluding these cases, prophylaxis failure occurred in 5.6% of procedures (5.6%).

Similarly, Low et al. [29] reported that 28 of 29 bronchial washings taken from donors grew at least one microorganism. The most common microorganisms identified were *Staphylococcus* spp. and *Enterobacter* spp. In 43% of these cases, similar microorganisms were isolated from the recipient tracheobronchial tree, and, of these, 21% had subsequent invasive pulmonary infections. Waller et al. [30] performed a retrospective comparison of the outcome of 123 donors in 125 consecutive, technically successful lung or heart–LT. Microbial contamination of routine donor bronchial lavage was about 60%. Five recipient deaths were due to donor-transmitted pneumonia.

A bronchial washing or aspiration for microbiologic sampling should be routinely performed in the lung donor to guide the choice of adequate recipient prophylaxis. Gram,

TABLE 11-2. Description of infection episodes due to donor-to-host transmission

Microorganism	Type of donor infection	Type of recipient infection	Outcome	Prophylaxis
<i>A. fumigatus</i>	Colonization	Tracheobronchitis	Cured	A–A
<i>A. fumigatus</i>	Colonization	Tracheobronchitis	Cured	A–A
<i>A. fumigatus</i>	Colonization	Mediastinitis	Died	A–A
<i>S. viridans</i>	Colonization	Pneumonia	Cured	A–A
MRSA	Colonization	Pneumonia	Died	A–A
<i>S. aureus</i>	Colonization	Pneumonia	Cured	Cefuroxime
<i>S. aureus</i>	Bacteremia	Tracheobronchitis	Cured	A–A
<i>S. aureus</i>	Colonization	Tracheobronchitis	Cured	Cefuroxime
<i>S. aureus</i>	Colonization	Tracheobronchitis	Cured	A–A
<i>S. aureus</i>	Colonization	Cutaneous lesions	Cured	A–A
<i>S. maltophilia</i>	Colonization	Tracheobronchitis	Cured	A–A
<i>P. aeruginosa</i>	Colonization	Tracheobronchitis	Cured	Cefuroxime
<i>P. aeruginosa</i>	Colonization	Tracheobronchitis	Cured	A–A
<i>P. aeruginosa</i>	Colonization	Tracheobronchitis	Cured	A–A
<i>K. pneumoniae</i> + <i>E. coli</i>	Bacteremia	Pneumonia	Cured	A–A

Abbreviations: MRSA methicillin-resistant *Staphylococcus aureus*, A–A amoxicillin-clavulanate + aztreonam.

methenamine silver, calcofluor (for fungi identification), and Ziehl–Neelsen staining; and specific cultures for bacteria, fungi, and mycobacteria should all be conducted [31]. The main problem is that culture results may not be available soon enough. Nevertheless, the finding of positive Gram stain or scanty purulent secretions should not be contraindications for accepting the lung for transplantation [31] because the outcome of these marginally suitable lungs is similar to that obtained with ideal grafts [32]. However, most groups consider the existence of pneumonia, aspiration of gastric juice, abundant purulent secretions that persist after bronchial washing, or the growth of filamentous fungi on a culture of fiber-optic bronchoscopy samples to be contraindications to transplantation. Since two of the authors' patients who received lungs contaminated with *Aspergillus* spp. developed invasive aspergillosis (IA) and died, the group excludes lungs for which calcofluor stain evidences hyphae. The heavy growth of *Candida* species in the donor bronchus makes these lungs risky because of the potential involvement of the vascular sutures or large vessels, which could lead to mycotic aneurysms and consequent rupture [33]; therefore, this represents a significant obstacle for accepting these organs. This is more important for heart–LTR. So, the graft should be excluded if the culture is pure and highly abundant. If this is not the case, an echinocandin should be initiated immediately after transplantation.

An experimental study in canine LT has provided evidence that antibiotic treatment of donors showing bacterial contamination prevents the development of pneumonia in recipients [34]; nevertheless, no consensus has been reached on whether antimicrobial treatment should be used in all human lung donors. Although this measure might decrease the risk of early bacterial pneumonia, it might also induce false negative results in cultures and thus may make recipient management after transplantation more difficult.

#### 11.2.4 Cystic Fibrosis

Chronic infection of the respiratory tract before transplantation distinguishes patients with CF from patients with other diseases. Nonetheless, several studies report that recipients with CF receiving bilateral lung transplants do not have a higher risk of infection after the procedure despite the common presence of airway pathogens (*Pseudomonas* spp., *S. aureus*, and molds). Many patients show the same strains of *P. aeruginosa*, as demonstrated by electrophoretic DNA analysis, after transplantation, probably due to contamination during surgical graft placement or from the chronic sinusitis occurring in these patients [35]. Although the efficacy of surgical sinus drainage has not been established, some recommend this procedure [2–4, 36].

Some centers exclude patients with certain respiratory pathogens, such as *P. aeruginosa* resistant to all antibiotics, or those with other MDR bacteria, including *B. cepacia*, *S.*

*maltophilia*, or *Alcaligenes xylosoxidans*. However, data demonstrating post-transplantation infection and survival rates that are similar to those of patients with sensitive strains suggest that this policy is unwarranted [2, 37–39]. The presence of *B. cepacia* is considered an absolute contraindication to LT in some centers because of its high associated risk of severe and often lethal postoperative pneumonia and sepsis and because transmission between patients is well documented [40]. Recent reports have documented lower survival in recipients previously colonized by *B. cepacia*, and specifically, by *B. cepacia* genomovar III strains [41, 42].

*Aspergillus* spp. is recovered from respiratory tract cultures in up to 50% of patients with CF. Its presence is not, however, predictive of subsequent allograft infection, and it should not be considered a contraindication to transplantation unless evidence shows mycetomas adhering to the chest wall.

An increase incidence of NTM has been observed [43]. All patients with CF should be evaluated for NTM pulmonary disease before LT. Patients with NTM disease should begin treatment before transplant listing. In case of progressive pulmonary or extrapulmonary disease despite optimal therapy or an inability to tolerate it, LT is a contraindication [44].

#### 11.2.5 Native Lung

In single-LTR, the residual native lung can give rise to a large number of post-transplantation complications. In addition to bacterial or fungal pneumonia and bronchial anastomosis infections leading to dehiscence, the native lung can have noninfectious problems such as severe overinflation, perfusion mismatch, or pneumothorax. The incidence of native lung infectious complications in single-LTR ranges from 20 to 50% [15]. In patients with idiopathic pulmonary fibrosis treated with high-dose steroids, infection of the native lung by *M. tuberculosis*, *P. jirovecii*, and *A. fumigatus* may go unnoticed in the evaluation of the candidate and may result in a serious exacerbation of infection after transplantation. Pathologic and histologic analyses of the resected lung are essential. Native pulmonary aspergillosis is the most feared complication because it is difficult to diagnose and practically impossible to treat unless a pneumonectomy can be performed. Moreover, primary prophylaxis for IA is complex because of the problems in reaching acceptable concentrations of therapeutic drugs and the fact that nebulized amphotericin B (AFB) is not properly distributed in a lung with significant ventilation and perfusion defects.

#### 11.2.6 Immunosuppression

LTR have a permanent deficit of immunity due to the immunosuppressive treatment required indefinitely to avoid rejection.



The use of OKT3 as an induction agent is now very limited due to an increase risk of infection [45]. In contrast, antithymocyte globulin (ATG) and basiliximab do not increase the rate of infections and have been associated with a survival benefit [46].

In patients treated with cyclosporine (CsA) or tacrolimus, the incidence of infection is quite similar [47]. The University of Pittsburgh performed a study that compared the effects of tacrolimus and CsA. The prevalence of bacterial infection was 1.5 episodes per 100 patient days in the CsA group and 0.6 episodes per 100 patient days in the tacrolimus group, although with no statistical significant difference. The prevalence of CMV and fungal infection were also similar in both groups [48].

The role of antimetabolites such as mycophenolate mofetil (MMF) and inhibitors of the mammalian target of rapamycin (mTOR) such as sirolimus or everolimus is discussed below when assessing CMV infection.

The incidence of serum immunoglobulin deficiencies can be as high as 44% in LTR and has been associated with community-acquired respiratory viral infections, IFI and BOS [49, 50]. However, a randomized, double-blind, placebo-controlled trial of immune globulin intravenous administration in LTR with hypogammaglobulinemia failed to demonstrate a reduction in the short-term risk of bacterial infection [51].

Infection by immunomodulating viruses, such as CMV, increases the net state of immunosuppression favoring the development of opportunistic infections [52]. An extensive study performed at the University of Pittsburgh assessed the risk factors for infection other than CMV in 250 transplantations (99 single lung, 102 bilateral lung, and 49 heart–lung) [16]. Early post-transplantation risk factors for infection included CMV mismatch (donor is CMV-positive, recipient is CMV-negative [D<sup>+</sup>/R<sup>-</sup>]), among others. Risk factors for late infection included again CMV mismatch, the absence of CMV prophylaxis, and CMV disease, among others [16].

## 11.3 Bacterial Infection

### 11.3.1 Epidemiology

Bacterial infection is the most frequent infectious complication for lung and heart–LTR. The rate of bacterial infections (mainly respiratory) is much higher than that observed in other SOTR. Of the total infections observed in different series, 35–66% were bacterial, and 50–85% of recipients presented a bacterial complication after transplantation. Frequently, patients experienced more than one bacterial infection and bacterial respiratory infection occurred most frequently [1, 5, 6, 12, 13, 16, 53, 54]. Beginning with persistent colonization, lung and heart–LTR can present with any of the clinical forms of this process (tracheobronchitis, sinusitis, pneumonia).

TABLE 11-3. Factors related to bacterial infections in LTR

Immediate post-transplant period	Late post-transplant period
Pre-transplantation colonization [55]	Increased immunosuppression due to rejection
The surgical procedure itself and technical complications (e.g., bronchial anastomosis dehiscence) [13]	Invasive diagnostic procedures
Intubation and/or prolonged hospitalization [16]	Development of BOS [16, 56]

Factors related to bacterial infections presenting in the immediate and late post-transplantation are depicted in Table 11-3.

The most frequent causal agents of nosocomial pneumonia are *P. aeruginosa*, Enterobacteriaceae and *S. aureus* [57, 58]. Other prevalent Gram-negative nosocomial bacteria include *Acinetobacter* spp. and *Stenotrophomonas maltophilia*. The period of maximum risk spans the first 3 weeks after transplantation. Nevertheless, its incidence during this interval has markedly decreased with the implementation of antibiotic prophylaxis; most cases of bacterial pneumonia now occur in the intermediate and late postoperative period. In fact, health care-associated pneumonia is more frequent than hospital-acquired pneumonia [58]. Stable, ambulatory transplant recipients after the postoperative phase can develop pneumonia from infection with microorganisms prevalent in the community (e.g., *Mycoplasma pneumoniae*, *Haemophilus influenzae*, or *Streptococcus pneumoniae*). Infection due to MDR bacteria is a widespread problem, especially early after the procedure in the setting of hospital-acquired/ventilator-associated pneumonia (VAP). Its appearance is associated with high rates of morbidity and mortality [59]. These bacteria (e.g., MRSA, MDR *P. aeruginosa* or *B. cepacia*) may colonize the recipient before transplantation (e.g., patients with CF) or can also be acquired after surgery (e.g., MDR *Acinetobacter baumannii*). Our group reviewed VAP incidence, etiology, and outcome in our cohort of LTR. VAP was diagnosed in 20% of LTR. *P. aeruginosa* was the most frequent microorganism isolated (60% MDR), followed by Enterobacteriaceae. Mortality was significantly higher in those patients diagnosed with VAP (OR 9, CI 3.2–25.1,  $p < 0.01$ ) [60]. In another study performed in RESITRA (Spanish Research Network for the Study of Infection in Transplantation), evaluating 85 pneumonia episodes in 236 LTR (with an incidence of 72 episodes per 100 patients-per-year), bacterial pneumonia (82.7%) was more common than fungal (14%) or viral (10.4%). Gram-negative bacilli were the etiology in 34 cases (*P. aeruginosa* in 14 and *A. baumannii* in 8). The absence of pneumonia caused by *Legionella pneumophila* was noteworthy and likely due to the effect of cotrimoxazole prophylaxis [61].

The physician must remember that even the growth of normal oral flora in a respiratory sample in the early transplantation period is considered a risk factor for bacterial

pneumonia. Therefore, laboratory workups should identify and perform susceptibility study of all strains isolated. In addition, the clinician should determine whether the anastomosis shows signs of ischemia. If these are present, they imply a greater risk of both infections to the anastomosis and suture dehiscence, and they might be an indication for the use of nebulized antibiotics to treat respiratory colonization or infection.

Deep surgical site infections (SSI) are an uncommon complication in LTR. In a retrospective study at a single center, 5% of LTR developed SSI [62]. Empyema was the most common (42%), followed by wound infection (29%) and mediastinitis (16%). However, the term “thoracitis,” rather than mediastinitis, is more accurate because the mediastinal space does not exist as such; during lung implantation, the visceral pleura are not joined to create separate mediastinal space. Therefore, when infection occurs in this extraparenchymal thoracic space, the entire thoracic cavity becomes infected with purulent collections in several locations. Interestingly, 23% of SSI was due to pathogens colonizing recipients’ native lungs at the time of transplantation suggesting surgical seeding [62]. One-year mortality associated with SSI was 35% [62].

Bacteremia in LTR is an early complication after transplantation almost related to catheter. The etiology is equally distributed between Gram-negative and Gram-positive bacteria. Nearly half the isolates correspond to MDR microorganisms [63].

Infections caused by *Mycobacterium tuberculosis* are reported because of reactivation, occult disease in the remaining native lung after single-lung transplantation, or transmission by the graft [64]. Within the authors’ transplant program, pulmonary tuberculosis is diagnosed in about 6% of LTR. The mean post-transplantation interval at which *M. tuberculosis* is detected is 115 days. In 40% of the cases, the diagnosis was obtained from the explanted lungs. Despite immunosuppression, an adequate response to antituberculous treatment and a low incidence of adverse side effects is observed [65].

Episodic isolation of NTM is common in LTR with an incidence rate of 9/100 person-years [66]. Previous NTM colonization and treated acute rejection are risk factors for NTM disease [67]. The most common NTM isolated is *Mycobacterium avium complex* (69.8%), followed by *Mycobacterium abscessus* (9.4%), and *Mycobacterium goodii* (7.5%). Most isolates occur among asymptomatic patients and are transient. Nevertheless, NTM disease rate is higher among LTR than in the other SOTR [68]. Moreover, infection due to *Mycobacterium abscessus* is a difficult-to-treat infection. The ISHLT published a study including 5200 LTR. Seventeen patients (0.33%) were identified with *M. abscessus* infection affecting the pulmonary allograft in 12, the skin/soft tissue in 3, or both in 2. Therapies included multiple antibiotics in 16, surgical debridement in 2, interferon-gamma in 1, or no therapy owing to presumed colonization

TABLE 11-4. Specific risk factors for *Nocardia* spp. infection in LTR

Frequent episodes of rejection
High-dose corticosteroid treatment
Renal impairment
Prolonged respiratory support

in 1. Ten of 17 patients were considered cured while 2 patients died due to infection [69]. More recently, NTM infection has been associated with increased risk of mortality independent of BOS [67].

*Nocardia* spp. infections are uncommon in lung, or heart–LTR. Specific risk factors are shown in Table 11-4. One retrospective review of 540 heart, lung, or heart–LTR examined 10 patients (1.9%) with nocardia infection. It occurred at a median of 13 months after transplantation. All the patients had pulmonary disease and no evidence of extrapulmonary involvement. *Nocardia* infection did not contribute to patient deaths directly. Coinfection with other pathogens was present in six patients, and two had sequential infections [70]. A chart review from 1990 to 2007 revealed *Nocardia* spp. infections in 4 of 410 LTR despite prophylaxis [71]. All infections were confined to lung and occurred at a median of 315 days after transplantation. *Nocardia nova* was isolated in two patients, *Nocardia farcinica* in one, and unspecified *Nocardia* spp. in one. All isolates were susceptible to cotrimoxazole [71].

The incidence of *Clostridium difficile* infection (CDI) is rising in recent years up to 22.5% in LTR [72] and is higher than in other SOTR with the exception of pancreas [73]. Half the cases presents within the first month after transplantation. Previous administration of cephalosporins and corticosteroid use before transplantation has been considered as risk factors for CDI which, in turn, is not predictive of mortality [72, 73].

### 11.3.2 Specific Features of Antibiotic Treatment

The forthcoming treatment recommendations, as well as many of the other found in this chapter, are based mainly on the authors’ experience in managing these patients and not only on scientific data.

No standardized regimen or guidelines exist regarding the choice of perioperative antibiotic therapy. Antibiotic prophylaxis in LTR should be initiated with broad-spectrum antimicrobials to cover *P. aeruginosa*, and *S. aureus*. For initial prophylaxis, the authors’ group uses combined amoxicillin-clavulanate, 2 g, plus aztreonam, 2 g, every 3 h during surgery, and every 8 h thereafter. Recipients with septic lung disease (e.g., CF or bronchiectasis) should receive antimicrobial agents tailored according to their pre-transplantation sputum cultures. In this case, the authors also recommend nebulized tobramycin from the patient’s arrival to the ICU

after surgery. The duration of prophylaxis depends on the results of donor and recipient respiratory sample cultures at the time of LT. When cultures are negative, prophylactic agents are withdrawn on the third to fifth days. When cultures are positive or in recipients with septic lung disease, antibiotic treatment is adjusted and maintained for 2 weeks or until cultures are negative. With this approach, the incidence of bacterial pneumonia in the early post-transplantation period (first 3 months) in the authors' lung transplant population is approximately 10%.

Whenever a clinically significant microorganism is isolated in a respiratory sample within the first 3 months, specific intravenous antibiotic therapy is started, even if the patient is asymptomatic. The only situations in which treatment should not be started are colonization with oral streptococci or plasmococagulase-negative staphylococci. Combined and aminoglycoside treatment should be used for pneumonia. In the case of tracheobronchitis due *P. aeruginosa*, the authors combine a  $\beta$ -lactam with nebulized tobramycin at a dose of 100 mg every 12 h. Other indications in the authors' hospital for nebulized tobramycin or colistin include colonization with MDR Gram-negative bacilli, particularly *Acinetobacter* spp., *Pseudomonas* spp., and *S. maltophilia*; and episodes of tracheobronchitis in which signs of anastomotic ischemia are found.

From the third to sixth month after transplantation, only symptomatic episodes of infection are treated. Colonization is only treated when the microorganism is demonstrated in two respiratory samples taken at 1-week interval.

## 11.4 Fungal Infections

### 11.4.1 Epidemiology

Among SOTR, the lung and heart–lung have the highest associated incidence of fungal infection. The etiology is characteristically *Aspergillus* spp., in contrast to others in which infection by *Candida* spp. is the most common. A large study observed a 12-month cumulative incidence of 5.5% of IFI with *Aspergillus* spp. as the leading etiology (72.7%) [74]. *Aspergillus* infection in LTR is manifested in several ways, including airway colonization and various forms of tracheobronchitis (simple or ulcerative, with or without pseudo-membrane formation). Colonization with *Aspergillus* spp. occurs in 22–85% of LTR at some time after transplantation [36, 75]. Without prophylaxis, the incidence of IA ranges from 13 to 26%, and the related mortality is high (41–100%). With prophylaxis, the incidence of IA is 2–8% [75–77]. The incidence of tracheobronchitis is about 4–12% [75]. In our center, the incidence of IA and tracheobronchitis in 104 LTR given nebulized liposomal amphotericin B (n-LAB) prophylaxis was 0.9% and 1.9%, respectively. IA was classically considered a complication of the immediate post-transplant period, but a RESITRA study demon-

TABLE 11-5. Risk factors for *Aspergillus* spp. infection in LTR

Previous colonization with <i>Aspergillus</i> spp. [73]
CMV pneumonitis [22, 78, 79]
Airway ischemia
Single-lung procedure [13, 22]
Single-nucleotide polymorphisms in the genes encoding interleukin-1 $\beta$ and $\beta$ -defensin-1 [80]
<i>Bronchiolitis obliterans</i> syndrome

strated that its incidence remains high after this period [76]. However, about two thirds of the episodes of ulcerative tracheobronchitis and IA occur at 6–9 months after transplantation. Mortality for tracheobronchitis is around 25%, but for IA rises to 67–82% [78].

Significant risk factors for the development of IA in LTR are listed in Table 11-5. Surprisingly, no relationship with rejection or augmented immunosuppression has been recognized, but this possibility cannot be ruled out. BOS is a risk factor for IA but, on the other hand, LTR colonized with small conidia *Aspergillus* spp. (*A. fumigatus*, *A. nidulans*, and *A. terreus*) are prone to developing BOS [81]. Patients in whom *Aspergillus fumigatus* was isolated from airway samples during the first 6 months were 11 times more likely to develop IA than were those not colonized [79]. The relationship between colonization and invasive disease at 6 months to 1 year after transplantation is not so evident. No difference in the frequency of postoperative colonization is established between recipients with CF and recipients without [75]. The authors' transplant group does not consider previous colonization by *Aspergillus* spp. to be a transplant contraindication; however, in these patients, bilateral lung transplant is mandatory, and chest computed tomography (CT) scanning must be performed to rule out the adherence of mycetomas to the chest wall.

Tracheobronchitis is a characteristic type of aspergillosis almost exclusive to LTR [75, 82]. A spectrum of disease occurs, from simple bronchitis to pseudomembranous, nodular, and finally ulcerative tracheobronchial aspergillosis that is considered a form of IA. The anastomotic site is often affected, and this can lead to suture dehiscence, severe hemorrhage, or disseminated disease, invariably being fatal. Distinguishing between asymptomatic colonization and tracheobronchitis can be difficult as clinical symptoms may be absent or attributed to a concurrent clinical process (e.g., bacterial infection, rejection). When *Aspergillus* spp. is isolated from respiratory samples in the first 6–9 months, the authors perform a bronchoscopic study to rule out pseudomembranous or ulcerative tracheobronchitis. Likewise, early isolation of *Aspergillus* spp. from the airways identifies LTR at increased risk for the development of endobronchial abnormalities such as exuberant granulation tissue or stricture formation [83]. The authors believe that initiating treatment is mandatory whenever this microorganism is isolated from respiratory samples.



The diagnosis of IA is problematic because of the risk of colonization and contamination and the low predictive value of respiratory sample cultures (mainly sputum). For LTR, the presence of a new or progressive infiltrate or consolidation can be taken into consideration for diagnosis, although classical radiological criteria include the appearance of dense, well-circumscribed lesions, cavitations, or endobronchial lesions [84]. Galactomannan (GMN) detection in bronchoalveolar lavage (BAL) is useful in diagnosing IA. The role of GMN quantification was assessed in a study of BAL samples in 116 LTR. The authors found a sensitivity of 60% and a specificity of 95%, based on a cutoff of 0.5, that raised to 98% when the cutoff was 1.0 [85]. Another study reported sensitivity and specificity of GMN in BAL of 100% and almost 91%, respectively, using an index >1.0 as cutoff [86]. Finally, the ISHLT includes pan-*Aspergillus* PCR in BAL together with compatible symptoms and radiological imaging for the diagnosis of probable IFD in LTR based on a study that reported a sensitivity and specificity for diagnosing IA of 100% and 88%, respectively [87]. Nevertheless, the authors consider that PCR techniques warrant further studies and should not be used for routine daily diagnosis or treatment monitoring until standardization is performed.

Another distinctive issue is IA of the native lung in single-LTR. This may develop immediately after transplantation because of preexisting disease that was not detected, or it may represent de novo infection in patients with destroyed native lungs [13, 22, 88]. At times, IA is extremely difficult to diagnose. It occurs in patients with unilateral grafts who are diagnosed with *Aspergillus* tracheobronchitis; because of the unstructured nature of the native lung parenchyma, alterations are difficult to visualize on CT until the process is well advanced. This type of disease has poor prognosis, since achieving therapeutic concentrations of antifungal agents in the residual lung parenchyma is virtually impossible. In cases of tracheobronchitis in single-LTR, the authors employ BAL of each lung and initiate the same treatment used for IA when selective BAL of the native lung culture is positive. It is advisable to perform a native lung pneumonectomy if possible because it probably represents the only way to cure an established process.

Most cases of candidiasis occur during the first months after surgery. The main portal of entry is the gastrointestinal tract, followed by endovascular catheters and the urinary tract. Candida infections can manifest as peritonitis, empyema, candidemia [89], urinary tract infection, necrotizing bronchial anastomotic infection [90], mediastinitis, or esophagitis. Graft-transmitted candidiasis, which ends most often in fungal arteritis, has been described in heart and so can be in heart–lung transplantation [33].

The incidence of *P. jirovecii* pneumonia varies greatly among centers [13]. A prevalence of up to 88% has been described in patients without prophylaxis. Cotrimoxazole prophylaxis is effective in nearly 100% of patients, so its administration is mandatory. About one-third of *P. jirovecii*

infections occur after the first postoperative year. Then, since recipients maintain steroid treatment, the authors recommend lifelong prophylaxis [91]. Dapsone may be an alternative for patients with contraindications or intolerance to trimethoprim-sulfamethoxazole.

The incidence of cryptococcosis ranges between 0 and 1.5% in American and European series of SOTR, and it is the third most common infection after candidiasis and IA [92]. The antifungal activity of calcineurin inhibitors may explain this low incidence [93] which, in turn, is higher in heart than in lung transplantation. *Cryptococcus neoformans* var. *grubii* has no particular geographical predilection and causes the most infections. *C. neoformans* var. *neoformans* is prevalent in northwestern Europe, and *C. gattii*, has emerged in the Pacific Northwest [94] and in Europe [95]. Patients who receive high doses of corticosteroids or monoclonal antibodies such as alemtuzumab and infliximab have the highest risk [96]. Cryptococcosis is typically a late-occurring infection; the time to onset usually ranges from 16 to 21 months post-transplantation. More than half of SOTR have disseminated disease or CNS involvement and as many as 33% have fungemia [97]. The mortality of cryptococcosis ranges from 14 to 27% [92, 93].

The incidence of infections by molds other than *Aspergillus* spp. has increased in recent years [98]. Most are caused by Mucorales (mucormycosis or zygomycosis), although infections by *Fusarium* spp. [99] and *Scedosporium* spp. are also recorded. Recent American and European series reported a frequency of mucormycosis lower than 3% among all SOTR with fungal infection [92, 100]. Renal insufficiency, diabetes, and previous administration of voriconazole or caspofungin have been described as independent risk factors for mucormycosis [101]. The most common site of mucormycosis is the lung, with a mortality of 45–50% [101]. Mortality can reach 73% in cerebral forms [102]. Infections by *Scedosporium apiospermum* account for 25% of IFI caused by molds other than *Aspergillus* spp., especially in single LTR and CF [103].

Endemic mycoses can potentially cause infection in LTR. These are especially important in endemic areas of the United States such as the Midwest for histoplasmosis. The first year is the period of highest risk for histoplasmosis as a consequence of reactivation of a latent infection, new exposure or donor-derived infection [104]. Urinary antigen appears to be a better diagnostic tool than the fungal antibody serology in LTR [105]. In patients whose explanted lung is found to have histoplasmosis, antifungal prophylaxis seems effective at preventing reactivation [105]. Coccidioidomycosis is typically acquired when patients are exposed to the desert soil of the Southwestern United States and Northern Mexico. The most common mechanism of infection in LTR is reactivation, but donor-derived transmission has also been reported. Patients, in whom there is evidence of prior coccidioidomycosis, either radiographically or serologically, may require lifelong antifungal prophylaxis [106].



TABLE 11-6. Prophylaxis for *Aspergillus* spp. in the lung and heart–lung transplant recipient [107]

Target population	Antifungal drug	Duration
All recipients	Nebulized liposomal amphotericin B 25 mg <sup>a</sup>	Indefinite or for a minimum of 12 months
Recommended strategy	Three times a week until resolution of bronchial suture Once a week from 2 to 6 months Once every 2 weeks thereafter	
or <i>Guided prophylaxis</i> in case of the presence of risk factors		
Induction with alemtuzumab or thymoglobulin	Nebulized liposomal amphotericin B 25 mg	Determined by the presence of risk factors
Acute rejection	Three times a week for 2 weeks then once a week	
Single-lung transplant <i>Aspergillus</i> spp. colonization Acquired hypogammaglobulinemia (IgG <400 mg/dL)		

<sup>a</sup>Considered also nebulized amphotericin B lipid complex 50 mg.

#### 11.4.2 Specific Features of Antifungal Treatment

The first point to remember regarding fungal infection is that the risk period—a minimum of 1-year post-transplantation—for developing IA is quite long. This fact makes the parenteral administration of antifungal treatment unfeasible. Thus, two alternatives, nebulized AFB and oral voriconazole, remain.

Universal prophylaxis against *Aspergillus* spp. is generally accepted in lung and heart–LTR (Table 11-6) [107]. Since most *Aspergillus* infections in LTR affect the respiratory tree and airway colonization by the conidia precedes the infection, nebulized AFB appears to be an attractive approach. The authors' group conducted a study to evaluate the pharmacokinetics and distribution of nebulized AFB in LTR [108]. Airway concentrations of AFB after nebulization with 6 mg of AFB deoxycholate theoretically offer adequate protection. Concentrations in the alveolar lining were higher than those found in the proximal bronchial tree, but the latter were still sufficient to protect anastomoses. Additionally, distribution studies using ventilation and perfusion gammagraphy imaging with technetium-99 m-labeled AFB deoxycholate were performed. All demonstrated acceptable delivery of the agent to native lungs and allografts in amounts proportionate to their degree of ventilation. Prophylaxis with

nebulized AFB decreased the incidence of IA below 3% [108]. In the authors' experience, the incidence of any kind of *Aspergillus* spp. infection in 226 consecutive LTR was 7.5%. However, administration of nebulized AFB every 8 h day after day is a considerable drawback. With the aim of prolonging the dosing interval, our group determined the airway concentrations of the drug after nebulization of 24 mg of the liposomal formulation (Ambisome<sup>®</sup>) [109]. We could demonstrate that AFB concentrations after n-LAB remained high enough for prophylaxis of *Aspergillus* spp. infection over 14 days. There was no significant systemic absorption of the drug and no effect was observed on respiratory function. Thus, the main advantages of nebulized prophylaxis are the lack of drug–drug interactions, the cost-effectiveness relationship, and the ability to achieve high levels of lung antifungal concentrations without systemic side effects [109]. One disadvantage is local irritation that leads to cough or bronchospasm. These effects occur in fewer than 10% of patients. The use of salbutamol or halving the drug concentration can improve the symptoms. Other disadvantages are the need for appropriate equipment and for the patient or family members to know how to administer it. The possibility of irregular distribution of the drug in the lung is another potential limitation [110]. Voriconazole is an alternative although there is also a lack of randomized studies [111]. Moreover, an increase in liver enzymes has been observed in up to 60% of LTR receiving voriconazole leading to discontinuation of the drug in 14% of them [112]. Skin cancer has also been reported in LTR with its prolonged use [113].

Colonization with *Aspergillus* spp. must be treated to prevent IA. The authors recommend n-LAB 25 mg/24 h for 7 days, then 25 mg/72 h, or nebulized AFB lipid complex 50 mg/24 h once every 2 days. In the case of intolerance, voriconazole should be considered (loading dose 400 mg/12 h PO, then 200 mg/12 h PO).

In the case of nodular or ulcerative tracheobronchitis, voriconazole plus nebulized lipid formulations at the doses above mentioned are recommended. A bronchoscopy should be performed every week or every 2 weeks to evaluate the extension of disease and to clear necrotic debris and fungus balls. A high-resolution CT scan should also be performed to rule out parenchymal extension.

In LTR with anastomotic tracheobronchitis due to *Candida* spp. the recommended treatment is n-LAB 25 mg three times a week, or nebulized AFB lipid complex every other day plus removal of the debris by repeated bronchoscopies. Echinocandins may be more effective than azoles for *Candida* spp. growing in the biofilms of the anastomoses.

When dehiscence of the bronchial anastomosis occurs, both surgical resection and stent placement may be necessary in addition to antifungal therapy, although the prognosis is poor. Other indications of surgery are shown in Table 11-7.

TABLE 11-7. Indications for surgery in IA

Massive hemoptysis
Hemoptysis due to lesions located near large vessels
Isolated or cavitated pulmonary lesions that progress despite the administration of appropriate antifungal treatment
Sinus disease
Infiltration of the pericardium, large vessels, bone, or subcutaneous thoracic tissue while receiving treatment

## 11.5 Viral Infections

### 11.5.1 Epidemiology

The second most frequent cause of infection after LT is CMV. The overall incidence of replication and disease without prophylaxis ranges from 53 to 75% [114], a much higher rate than those associated with other SOTR with the exception of small bowel transplantation. In patients without prophylaxis, the incidence of pneumonitis approaches 100% in CMV D<sup>+</sup>/R<sup>-</sup> cases, but, in contrast to other types of transplant, CMV-positive recipients also have a high incidence, estimated at 60–75%.

The risk factors for CMV disease (Table 11-8) have not been extensively studied in LT, but knowledge obtained in other SOTR can be applied. The most important risk factor for the development of CMV disease is CMV mismatch, which confers more than 50% risk in the absence of antiviral prophylaxis or preemptive treatment strategies [119]. However, cell-mediated immunity is known to be more important than humoral immunity in controlling CMV. CMV infection elicits a strong virus-specific CD4<sup>+</sup> and CD8<sup>+</sup> T-cell response that, currently, can be measured [120, 121]. As an example, those LTR considered negative or indeterminate to Quantiferon-CMV are at risk of developing CMV disease [115, 116]. In a trial comparing sirolimus to azathioprine, the overall incidence of any CMV event was lower in the sirolimus arm at 1 year (RR=0.67, CI 0.55–0.82, *p*>0.01) [122]. The relationship between CMV disease and other risk factors such as co-infection with Human Herpesvirus 6 (HHV-6) [123], hypogammaglobulinemia [124], polymorphisms in toll-like receptors (TLR2 and TLR4) [125], or low levels of mannose-binding lectin [126] has been demonstrated in other types of SOTR rather than lung. Thus, HHV-6 was not detected in 145 samples from 26 LTR, even though 30% of the samples were from 9 CMV DNA-positive patients in whom 13 episodes of CMV pneumonitis were recorded [127].

Transplantation of organs containing a large number of certain cells that can harbor latent or replicating CMV (e.g., macrophages and lymphoid cells) may provide the recipient with a higher initial CMV viral load, which then undergoes reactivation. Similarly, recipients with active CMV infection at the time of transplantation have a higher risk of post-transplantation CMV disease [128]. CMV viral load is an

TABLE 11-8. Risk factors related to CMV replication and disease in LTR

CMV serology mismatch: positive donor and negative recipient
Absence of specific cell-mediated immunity [115, 116]
Cytolytic agents such as OKT3 [117] or antithymocyte globulin [118]
Acute rejection and its subsequent treatment with corticosteroids
MMF when the dose exceeds 2 g/day
mTOR inhibitors is associated with a lower risk

important and clinically useful correlate of CMV pneumonitis in LTR [129–131].

CMV pneumonitis is the second leading cause of pneumonia [15] and the most frequent disease in LTR without prophylaxis. The use of prolonged valganciclovir prophylaxis has changed the incidence of pneumonitis that has decreased in contrast with the viral syndrome that has increased. In addition, the time at which the disease appears is from 2 to 4 weeks after stopping prophylaxis. In the authors' experience, approximately 10% of episodes has a late onset, appearing during the second year. Encountering CMV disease after the second year is exceptional. CMV pneumonitis has an insidious onset, which is manifested by constitutional symptoms and fever, with a later progression to dyspnea and tachypnea. The only relevant sign in an otherwise normal respiratory auscultation is tachypnea. Arterial hypoxemia is almost always present. The clinician should remember that, when a sudden deterioration of respiratory function is observed during treatment for CMV pneumonitis, superinfection by Gram-negative bacilli or fungi must be investigated. The radiologic manifestations of CMV pneumonia are diverse. Bilateral, symmetric, interstitial, and/or alveolar infiltrates predominating in both lung bases are the most common radiologic features.

The diagnosis of CMV disease is based on the definitions that were established by Ljungman et al. [132]. Several studies have shown that quantification of the CMV load in the plasma or blood can be helpful in making the diagnosis and that it can even be used to anticipate the development of CMV disease [129–131, 133].

Ganciclovir-resistant CMV infection, an emerging problem in the transplantation setting, has been associated with CMV D<sup>+</sup>/R<sup>-</sup> status, a high CMV load, and prolonged exposure to ganciclovir. Limaye et al. described a nearly 10% rate of ganciclovir-resistant CMV infection, as defined by a UL97 mutation, and this was more frequent among D<sup>+</sup>/R<sup>-</sup> patients despite preemptive antiviral therapy or prophylaxis. Compared with other SOTR, ganciclovir-resistant CMV in LTR include an earlier onset (median of 4.4 vs. 10 months) and less-prolonged exposure to ganciclovir (median of 100 vs. 194 days) [134]. A trend toward more frequent detection of MDR and co-circulation of multiple resistant strains has been also shown in LTR [135].

CMV infection has also an indirect effect on the patient's immune state. The immunomodulation exerted by CMV has

two demonstrated effects. CMV infection induces a transient state of additional immunosuppression that makes the host more susceptible to the development of infection by opportunistic microorganisms [136], and it seems to play a role in the pathogenesis of graft rejection [114, 137]. The detection of CMV DNA in the BAL is associated with the development of BOS irrespective of the magnitude of viral replication, the presence of tissue invasive disease or whether viral replication is symptomatic or asymptomatic [138]. The association between augmented antiviral prophylaxis and reduced cellular rejection has been also identified in LTR [139, 140]. Although antiviral drugs adequately suppress CMV replication, LTR remain vulnerable to both clinical and subclinical CMV replication on cessation of prophylaxis that is associated with BOS. However, other studies [141] reported no increased risk of BOS in a cohort of patients with beta herpesvirus (CMV, HHV-6, and HHV-7) replication within the lung allograft.

Respiratory viruses have been increasingly recognized as common pathogens in LT. Previous cohorts have reported an incidence of RV infections in LT in the range of 7.7–64% [142, 143]. Our group conducted a 5-year prospective study including 98 LTR that demonstrated an overall incidence of RV of 0.85 per patient-year. Our results are similar to data recently published in another large prospective study [144]. Seasonal patterns of RV circulating in LT are comparable to those observed in the community. Picornaviruses (mainly rhinovirus), coronaviruses, and influenza virus were the most common etiological agents, accounting for 76.5% of microbiologically confirmed symptomatic infections. Rhinoviruses are the leading cause of RV infections. Rhinovirus were associated not only with mild self-limiting upper respiratory tract infection but also with lower respiratory tract infection, mainly in form of tracheobronchitis. Patients with paramyxovirus (especially respiratory syncytial virus) and influenza infection had a higher incidence of pneumonia and hospitalization rate [145–147]. The relationship between RV infections and acute rejection has not been clearly established in previous studies [144, 148, 149]. Our data showed a trend toward a significant clinical link between RV and biopsy-proven acute lung rejection including the acute phase of the viral infection (with no relation to clinical presentation) and a follow-up period of 3 months. It has also been advocated that patients with documented community respiratory viral pneumonitis are predisposed to high-grade BOS development [150]. Finally, RV infections have been described as a risk factor for developing bacterial and fungal superinfection [151].

The incidence of pneumonitis due to HSV type 1 ranges from 5 to 10% in LTR without prophylaxis [12]. Most of them are reactivations that appear in the first 2 months, but they can occur as early as 5–10 days after transplantation. HSV pneumonitis is often associated with bacterial or CMV pneumonia. In contrast to CMV pneumonitis, pulmonary involvement by HSV type 1 provokes respiratory insuffi-

ciency and bilateral alveolar infiltrates in the majority of patients affected. Valganciclovir prophylaxis for CMV disease also protects against HSV infection.

The incidence of EBV-related post-transplant lymphoproliferative disorders (PTLD) varies greatly, ranging from 2 to 33% [152, 153]. These differences are probably due to variations in immunosuppression regimens, the number of EBV seronegative recipients, and the percentage of pediatric patients included in the series. The risk for developing PTLD is higher in EBV seronegative LTR. However, late onset PTLD tends to present in seropositive recipients. Early onset PTLD involves predominantly the transplanted lung, whereas late onset PTLD does not [154]. Possible enhancement of EBV activity by the  $\beta$ -herpesviruses, such as CMV, HHV-6, or HHV-7, has not been conclusively established. Monitoring EBV DNAemia does not predict PTLD [153].

The incidence of pneumonitis due to adenovirus is quite low, affecting about 1% of all adult LTR. It tends to appear in the first 3 months after transplantation. It induces severe disease with progressive respiratory failure; in most cases, the clinical course is fatal. In contrast, adenovirus infection is a widespread problem in the pediatric LTR. The attack rate is almost 50%, and at least half of the patients die of respiratory failure because of diffuse alveolar damage. BOS develops uniformly in the survivors.

Recently, the experiences of 239 LTR with herpes zoster infection have been published. The calculated incidence was 55.1 cases per 1000 person-years of follow-up. The cumulative probability of herpes zoster was 5.8% at 1 year, 18.1% at 3 years, and 20.2% at 5 years' post-transplantation. Only 5.7% of the patients had disseminated cutaneous infection and none had visceral involvement. Recurrence of herpes zoster was observed in 13.8% of patients. Postherpetic neuralgia was detected in 20% of cases [155].

### 11.5.2 Specific Features of Antiviral Treatment

Two strategies exist for the prevention of CMV disease in SOTR. The first is prophylaxis, in which an antiviral agent is administered immediately after transplantation to those recipients at high risk for CMV disease (e.g., D<sup>+</sup>/R<sup>-</sup> cases or patients who require the administration of conventional T-cell receptor antibodies). The second strategy, preemptive therapy, consists of the administration of an antiviral agent when nucleic acid testing (NAT) evidences a level of viral replication highly predictive of CMV disease. An international survey showed the lack of uniformity when managing with CMV infection in LT. Although prophylaxis is the most commonly used preventive strategy, its duration is extremely variable (from 3 months to indefinite). Half the centers routinely decreased immunosuppression at the time of viremia while the other half did not take any measure [156]. In an attempt to avoid this issue, guidelines have been published [157].

The authors believe that prophylaxis plus preemptive therapy is the best strategy for the prevention of CMV disease in LTR. The authors' recommendation is intravenous ganciclovir at a dose of 5 mg/kg every 24 h until oral intake is tolerated, followed by a switch to valganciclovir at a dose of 900 mg once a day until 180 days after transplantation for seropositive recipients and 360 days for CMV mismatch. Valganciclovir at reduced doses to avoid toxicity should not be administered due to its association with CMV disease and increased risk of emergence of resistance [158]. During prophylaxis, we do recommend monitoring of viral load by NAT due to the possibility of breakthrough disease, particularly in seronegative recipients [158]. Once prophylaxis ends, surveillance should continue at every medical visit until the second year after transplantation and preemptive therapy with valganciclovir should be initiated. Treatment is initiated in the following situations: (1) in D<sup>+</sup>/R<sup>-</sup> transplant recipients, whenever evidence of viral replication is found, and (2) in CMV-seropositive recipients, when viral load is high (e.g., >5000 UI/mL in plasma) or when an increase is registered in two consecutive analyses. When the viral load is under the established cutoff for initiation of preemptive therapy, the analyses should be repeated within 1 week. The duration of preemptive therapy has not been established, but the authors prefer a minimum of 7–10 days when viral replication is negative.

When CMV disease is diagnosed, treatment is started with ganciclovir at 5 mg/kg every 12 h. Generally, tacrolimus and prednisone doses are not reduced, except in cases of pneumonitis, in which they are progressively tapered. MMF is withdrawn or the dose is halved. If ganciclovir-associated leukopenia develops and the polymorphonuclear count drops below 500 cells/mL, the patient is treated with granulocyte-stimulating factor until the polymorphonuclear count increases to more than 1000 cells/mL. In patients with pneumonitis, gammaglobulins at a dose of 200 mg/kg every 48 h are added during the first week of treatment. The viral load should be monitored, and a significant increase after the fourth or fifth day of treatment should raise the suspicion of ganciclovir-resistant CMV infection. However, an increase in viral load during the first 2 or 3 days of treatment is not infrequent. The duration of therapy is usually 15 days, except in cases of pneumonitis, in which therapy is prolonged to 21 days. Generally, viral replication is negative at the end of treatment.

Current evidence, although not based on high-quality studies, suggests that some benefit is derived from the use of oral ribavirin in LTR with non-influenza RV infections [159], especially respiratory syncytial virus [160].

## 11.6 Conclusion

Despite several advances in surgical technique, immunosuppression and prophylaxis, infection continues to be an important cause of disease and death in LTR. Avoidance of these

infectious complications may not only lead to a decrease in the direct consequences of infection but also to a reduction in the subsequent causes of ultimate graft failure including both acute and chronic rejection. There is a need to explore new fields such as the relationship between microbiome and BOS, or to find new and better antivirals, especially for RV infections. But, without forgetting that there are current concerns that must be addressed such as the growing problem of antimicrobial resistance for which careful antibiotic stewardship is mandatory.

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