

INVITED REVIEW SERIES:  
TRANSLATING RESEARCH INTO PRACTICE  
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## Lung transplant infection

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### ABSTRACT

**Lung transplantation has become an accepted therapeutic procedure for the treatment of end-stage pulmonary parenchymal and vascular disease. Despite improved survival rates over the decades, lung transplant recipients have lower survival rates than other solid organ transplant recipients. The morbidity and mortality following lung transplantation is largely due to infection- and rejection-related complications. This article will review the common infections that develop in the lung transplant recipient, including the general risk factors for infection in this population, and the most frequent bacterial, viral, fungal and other less frequent opportunistic infections. The epidemiology, diagnosis, prophylaxis, treatment and outcomes for the different microbial pathogens will be reviewed. The effects of infection on lung transplant rejection will also be discussed.**

**Key words:** *Aspergillus*, bacterial pneumonia, cytomegalovirus, immunosuppression, lung transplantation.

### INTRODUCTION

Significant progress has been made since the first human lung transplant (LT) in 1963, and although survival after transplantation was initially plagued by

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Received 1 February 2012; invited to revise 26 February 2012; revised 1 March 2012; accepted 8 March 2012.

issues of rejection, the advent of immunosuppression ushered in a new era in transplantation science and made long-term survival a possibility. With this success came the dilemma of post-transplant infectious complications, which, to this day, remain a significant contributor to overall morbidity and mortality in the lung transplant recipient (LTR). Of all solid organ transplants, lungs are the most prone to infection, and this is likely due to several factors unique to the lung allograft. Apart from constant exposure to the outside environment, the lungs are exposed to the colonized native airway and have been stripped of their usual mechanisms of defence including the cough reflex, bronchial circulation and lymphatic drainage. These factors, coupled with the induction of an immunosuppressed state collaborate to produce an environment that is ripe for the development of infection.

Apart from direct injury, infection leads to several complications that may then have an effect on overall survival including the development of both acute and chronic rejection with eventual graft failure. The immune modulating effects of some pathogens, such as cytomegalovirus (CMV), can also augment the risk of developing other infections further leading to increased morbidity.<sup>1</sup>

A thorough and comprehensive screening and management approach must be undertaken to optimize the survival of these patients and minimize the risk of infectious complications. We present a review of the major infectious complications following LT as well as recent recommendations for the evaluation and management of these entities.

### EPIDEMIOLOGY

The respiratory tract is the most common area of infection after LT, and bacterial pneumonia is the most common infectious complication. CMV is the second most common complication, and its occurrence is much higher than in other solid organ recipients.<sup>2</sup> It appears that the critical period for infections

after LT is within the first 90 days. In a recent epidemiological study in which 51 LTR were followed for a mean of 38.2 months, 75% of infectious episodes occurred within the first year after transplantation, and nearly half (42%) occurred within the first 3 months.<sup>3</sup> Bacterial disease accounted for the largest proportion of infections (48%) followed by viral, fungal and mycobacterial disease (35%, 13% and 4%, respectively). In the early post-LT period (days to 1 month), nosocomial organisms account for the majority of infections. Following this period and for the next several months, at a time when immunosuppression is at the highest level, opportunistic organisms such as CMV and fungi account for the majority of infections. In the late post-transplant period, community-acquired bacterial and viral infections develop, although infection with health care-associated organisms remains common (Fig. 1).

It is within the first year that infection makes the biggest impact on mortality. According to the Registry of the International Society for Heart and Lung Transplantation, infection is listed as the leading cause of mortality, accounting for 31% of deaths within the first year after transplant.<sup>5</sup> Thereafter, infection is a close second to bronchiolitis obliterans syndrome (BOS) as a cause of death. Recently, it has been increasingly recognized that infection may both predispose the airways to the development of BOS and increase the mortality of those with BOS, thus still contributing significantly to this mortality.<sup>6</sup>

## PREDISPOSING FACTORS FOR INFECTION

The lungs are unique organs in that they are constantly exposed to antigens from both the environment (inhaled antigens) and the bloodstream

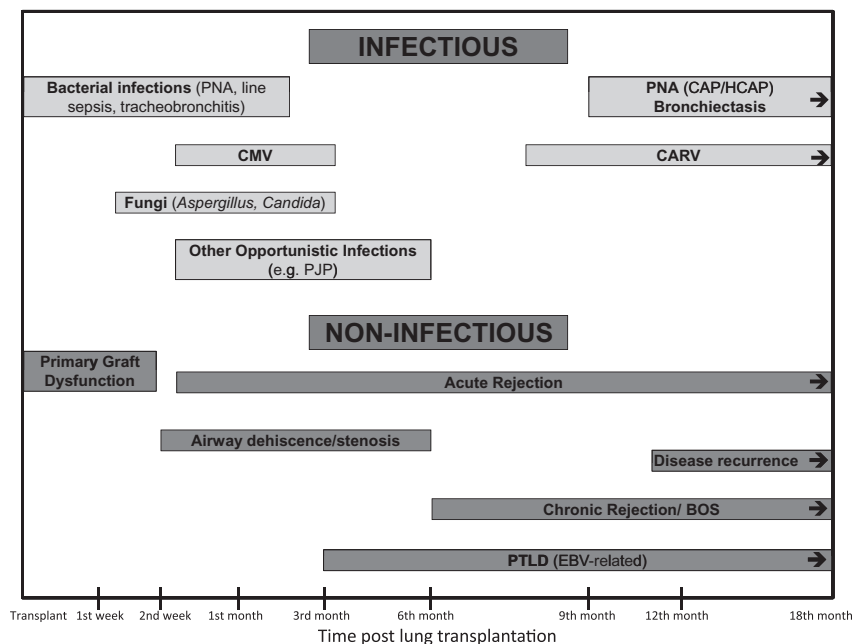
(blood-borne antigens). The upper airways and pulmonary tissue have defence mechanisms composed of physical barriers and cellular components. Physical barriers include hairs in the nasal cavity, mucus secretions, cilia and turbulent airflow generated by the nasal cavity that prevent pathogens from reaching the lower airways. Despite these barriers, pathogens may still reach and infect the pulmonary tissue.

## Anatomical factors

There are several risk factors that make LTR more vulnerable to infection (Table 1). Immediately post-surgery, LTR may have disruption of normal physical barriers and are at risk of aspiration and infection (e.g. use of nasogastric and endotracheal tubes).<sup>7,8</sup> There are also other important changes that happen post-surgery. First, during the surgical procedure of LT, there is a complete disruption of the bronchial circulation, and this may cause a loss of epithelium integrity, ciliary function and mucus production.<sup>9</sup> These effects are transient because of the development of collateral circulation but remain at risk of infection during the initial stages.<sup>9-11</sup> Second, denervation of the allograft may suppress the cough reflex and promote bronchial hyperresponsiveness.<sup>2</sup> Third, the lymphatic drainage of the allograft is also severed promoting stasis and oedema in the bronchial tissues impairing normal healing.<sup>2</sup> Fourth, stenosis or necrosis may occur at the site of the bronchial anastomosis, which may in turn facilitate colonization and invasion by opportunistic pathogens and decrease the clearance of secretions beyond the anastomosis.<sup>12</sup>

## Immunosuppression

At the cellular level, the LTR is vulnerable to infection due to the immunosuppression regimen used to



**Figure 1** Infectious and non-infectious complications after lung transplantation and the typical time frame in which they occur. Modified with permission from Levine.<sup>4</sup> BOS, bronchiolitis obliterans syndrome; CAP, community-acquired pneumonia; CARV, community-acquired respiratory virus; CMV, cytomegalovirus; EBV, Epstein-Barr virus; HCAP, health care-associated pneumonia; PJP, *Pneumocystis jirovecii* pneumonia; PNA, pneumonia; PTLD, post-transplant lymphoproliferative disorder.

**Table 1** Predisposing factors for infection in the transplant host

Interruption of bronchial circulation
Disruption of the integrity of the epithelium
Abnormal ciliary function
Decreased sputum production
Denervation of the allograft
Diminished cough reflex
Bronchial hyperresponsiveness
Interruption of lymphatic drainage
Anastomosis site complications
Ischaemia, necrosis or dehiscence promoting colonization
Stenosis with impairment of secretion clearance
Previous colonizing pathogens
Contralateral lung (i.e. single lung transplant recipient)
Donor-harboured pathogens
Recipient-harboured pathogens
Immunosuppression
T-lymphocyte dysfunction (e.g. calcineurin inhibitors)
B-lymphocyte dysfunction (e.g. mycophenolate mofetil)
Macrophage and cytokine dysregulation (e.g. corticosteroids)

prevent rejection affecting multiple inflammatory cellular lines and cytokines. The regimen consists of induction agents (medications used immediately post-transplant) and maintenance agents for prolonged use. Because immunosuppression is needed indefinitely, LTR has a life-long increased risk for opportunistic pathogens to proliferate and cause significant complications.

### Maintenance agents

The maintenance immunosuppression regimen consists typically of a calcineurin inhibitor, an antimetabolite and corticosteroids.<sup>13,14</sup> The calcineurin inhibitors used in LT are cyclosporine A and tacrolimus. Cyclosporine A binds to cyclophilin preventing the activation of the nuclear factor of activated T-lymphocytes (T cells) by calcineurin. Tacrolimus binds to FK-binding protein 12 inhibiting calcineurin and preventing the activation of the nuclear factor of activated T cells.<sup>13,15</sup> By reducing the activation of nuclear factor of activated T cells, both drugs reduce the production of interleukin-2 limiting the clonal expansion of activated T cells (Fig. 2).<sup>16</sup>

Azathioprine and mycophenolate mofetil (MMF) are the commonly used antimetabolites after LT. Azathioprine, a derivative of 6-mercaptopurine, inhibits both ribonucleic acid and deoxyribonucleic acid production, reducing the proliferation of both T cells and B-lymphocytes. MMF is a prodrug of mycophenolic acid, an inhibitor of the inosine monophosphate dehydrogenase (Fig. 2). This enzyme is responsible for the synthesis of guanine nucleotides, which both T cells and B-lymphocytes are critically dependent of.<sup>17</sup>

Other maintenance agents that have been used less frequently to maintain immunosuppression include

sirolimus and everolimus. Sirolimus binds to the FK-binding protein 12 and through the mammalian target of rapamycin pathway prevents the synthesis of deoxyribonucleic acid and proteins by T cells (Fig. 2).<sup>18</sup> Through an independent mechanism, sirolimus also affects B-lymphocytes and decreases cytokine and antigen production.<sup>19</sup> Everolimus reduces the mammalian target of rapamycin kinase activity, inhibiting the downstream pathways of proliferation and activation of T cells.<sup>20</sup>

Finally, through the alteration of gene transcription factors, corticosteroids can exert a wide variety of immunosuppressive effects: interruption of antigen presentation, changes in the production of cytokines and alteration in the proliferative responses of various cell lines.<sup>21</sup>

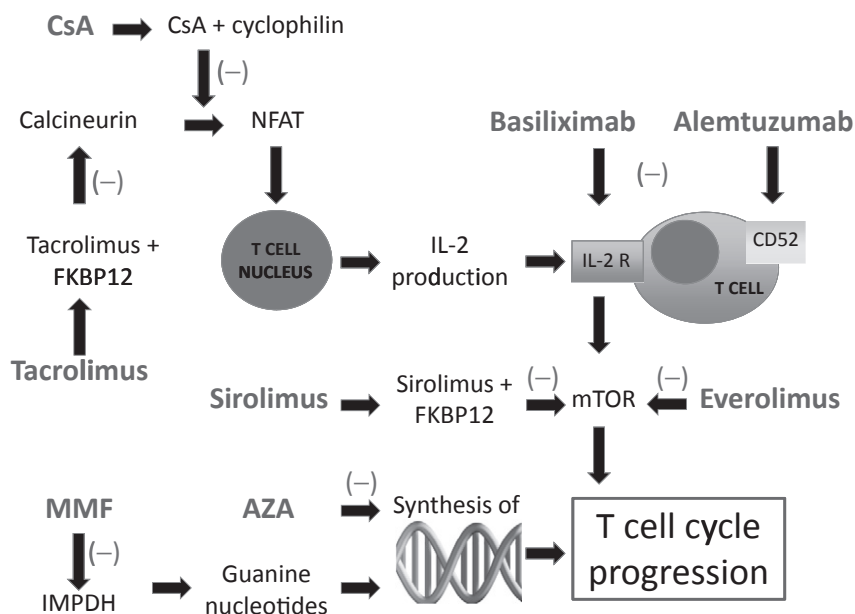
### Induction agents

The use of induction agents after LT varies among centres. These agents include OKT3, antithymocyte globulin (ATG), alemtuzumab and basiliximab. OKT3 is a murine monoclonal antibody that inactivates the T cell receptor-CD3 complex preventing the activation of circulating T cells with a partial sparing of T regulatory cells. ATG is a polyclonal antibody directed against lymphocytes. It depletes circulating lymphocytes through complement-mediated lysis and destruction by the reticuloendothelial system after opsonization.<sup>13</sup> Basiliximab is a chimeric monoclonal antibody that targets the  $\alpha$  subunit of the interleukin-2 receptor inhibiting the differentiation and proliferation of T cells.<sup>22,23</sup> Alemtuzumab is a murine monoclonal antibody that targets CD52. This receptor is present in macrophages, monocytes, B-lymphocytes and T cells among other inflammatory cells. The binding of CD52 causes complement-mediated cytolysis and activation of pathways leading to apoptosis.<sup>13</sup>

The use of OKT3 is now significantly limited due to an increase risk of infection.<sup>24-27</sup> For this reason, most centres have elected to use ATG, basiliximab or alemtuzumab, in combination with corticosteroids for induction of immunosuppression after LT.<sup>28</sup> Evaluation of large series of solid organ recipients has shown that this combination prevents graft rejection and improves survival.<sup>29</sup> ATG does not increase the rate of infections in transplant recipients and has been associated with a survival benefit.<sup>30,31</sup> Basiliximab compared with ATG does not increase the risk of infection and was safer than OKT3 in heart and LTR.<sup>22,23,26,32</sup> Alemtuzumab was recently shown to improve survival compared with ATG.<sup>33</sup> Despite these positive outcomes, the immunosuppression is more profound during induction, and patients should be monitored closely for infection during this period.

### Recipient-harboured infection in patients with suppurative lung disease

Despite the removal of both lungs during bilateral procedures, residual colonization and/or infection



**Figure 2** A schematic overview of the mechanisms of action of medications used for immunosuppression. IL-2 is required for the activation of the mTOR pathway and progression of the T cell cycle. Both CsA and tacrolimus reduce the activation of NFAT, which in turn results in a decreased production of IL-2. Basiliximab is a monoclonal antibody that inhibits the IL-2 receptor. Sirolimus and everolimus inhibit the mTOR pathway through inhibition of specific enzymes. Alemtuzumab targets protein CD52 causing T cell dysfunction. Both MMF and AZA disrupt key elements of the deoxyribonucleic acid synthesis affecting the progression of the T cell cycle. AZA, azathioprine; CsA, cyclosporine A; FKBP12, FK-binding protein 12; IMPDH, inosine-50-monophosphate dehydrogenase; IL-2, interleukin-2; IL-2R, IL-2 receptor; MMF, mycophenolate mofetil; mTOR, mammalian target of rapamycin; NFAT, nuclear factor of activated T-lymphocytes.

can remain in the thoracic cavity, the bloodstream, the upper airways or the sinuses. Those patients with cystic fibrosis (CF) present the highest risk for recipient-harboured infection due to the frequent colonization and infection with multiresistant microorganisms including bacteria (Gram-negative rods and Gram-positive cocci) and fungi. Resistant Gram-negative organisms pose perhaps the greatest risk, and some studies suggest an association between pre-transplant colonizing organisms from patients with suppurative lung disease and pneumonias following LT.<sup>34</sup> The majority of recent data suggests that patients colonized with multi-drug-resistant pseudomonas appear to have acceptable outcomes, including survival following LT, and should not be excluded on that criterion alone.<sup>35,36</sup>

In contrast, a former subspecies of pseudomonas, now subspecies as *Burkholderia cenocepacia* due to its unique resistance patterns, can pose significant problems in transplant recipients. There have now been at least nine distinct genotypic variants (genomovars) identified in the *Burkholderia cenocepacia* complex.<sup>37</sup> Colonization with *Burkholderia cenocepacia* complex (genomovar 3) can result in significant morbidity and mortality post-transplant and should be considered a strong relative contraindication to LT,<sup>38,39</sup> although isolated reports of successful outcomes have been reported.<sup>40</sup> In one study of 75 patients,<sup>38</sup> there was a significant difference in 1-year-

survival between those patients not infected (92%) and those colonized with a non-*Burkholderia cenocepacia* strain (89%) compared with those colonized with *Burkholderia cenocepacia* (29%). Similar results of variable survival rates based on *Burkholderia cenocepacia* species have been found in other studies.<sup>37,39</sup> Because of these overwhelming data, the majority of transplant centres will not transplant colonized or infected patients with this organism.

### Donor-harboured infection

When evaluating the potential LT donor, routine screening is done to prevent transmission of donor-harboured infection to the recipient.<sup>41</sup> Donor screening includes routine serology for viral infection including CMV, Epstein-Barr virus, varicella-zoster, hepatitis B and C, and human immunodeficiency virus, among others. In addition, the potential donor lungs are evaluated radiographically and bronchoscopically.

Despite these measures, infection may still occur. To potentially pre-empt the development of donor-transmitted infection at the time of the transplant procedure, a culture swab or wash, or a portion of the donor bronchus is sent for culture. In contrast with some older studies,<sup>42,43</sup> more recent data suggest that recovery of an organism from the donor lung,

including a positive Gram stain, or subsequent growth in culture does not always translate into infection and/or poor outcomes in the recipient.<sup>34,44,45</sup> In one study of 80 LTR, the investigators noted that organisms were grown from 57% or 89% of donors for a total number of isolates of 149.<sup>44</sup> Of these, most isolates were staphylococci or streptococci. Post-transplant pneumonias were found in 41% of recipients in this study; however, pseudomonas, and not Gram-positive organisms, was the most prevalent causative organism. The results of this study and others<sup>45</sup> suggest that the presence of organisms in the donor does not necessarily predict post-transplant pneumonia, and perhaps this donor criterion should be re-evaluated. Despite these suggestions and because empirical bacterial prophylaxis was used in the majority of these studies, the general practice is to routinely initiate prophylactic, broad-spectrum antibiotics (regimens are discussed later) and then narrow the antibiotic therapy based on donor isolates.<sup>41</sup>

### Native lung infection

Any patient with suppurative lung disease, such as CF or bronchiectasis, being considered for LT will receive a bilateral procedure with attempts at avoiding infection from a remaining native lung. However, in those diagnoses where a single LT may be performed, such as chronic obstructive pulmonary disease or interstitial lung disease, the native lung may harbour infectious organisms that can infect the new graft, particularly when the patient is subjected to immunosuppression. Alternatively, the native lung can develop severe infection leading to sepsis and further compromise. Although attempts at avoiding this risk are undertaken by routine pretransplant screening, examples of infection that can be harboured in the native lung include bacteria, fungi (perhaps contained in a mycetoma) or non-tuberculous mycobacteria (NTM).<sup>46</sup>

### General recipient screening

As part of the initial pretransplant evaluation, all potential transplant recipients should undergo careful screening for infection. Although there may be some variation between transplant centres, routine screening includes serological measurement for CMV, Epstein–Barr virus, varicella-zoster, hepatitis B and C, and human immunodeficiency virus, and screening for latent tuberculous infection. The results obtained from this screening are used to assess the patient's overall candidacy for LT (e.g. human immunodeficiency virus is generally an exclusion) and also to stratify the patient for screening and prophylaxis in the post-LT period (e.g. CMV and Epstein–Barr virus). Recommendations for recipient and donor presolid organ transplant screening are published from the American Society of Transplantation.<sup>41</sup>

## BACTERIAL INFECTION

### Pneumonia

#### Early pneumonia

Pneumonias comprise the most common cause of infection following LT, and bacterial pathogens remain the most common cause of all pneumonias.<sup>34,47</sup> In a multicentre, prospective study from Spain, with a median follow-up of 180 days, 85 episodes of pneumonia were documented in 236 LTR for an incidence of 72 episodes/100 LT years.<sup>47</sup> Of these, bacteria were the most common pathogen accounting for 82.7% of the pneumonias.

Bacterial pneumonia is most common in the early post-transplant period (1–30 days) usually due to infection with health care-associated and nosocomial organisms (Fig. 1). In the Spanish study, 40 of 85 of pneumonias (44%) occurred in the first 30 days following transplant. Nearly 3/4 of all bacterial pneumonias (72%) were due to Gram-negative organisms—most commonly pseudomonas (incidence 118.6 episodes per 1000 LTR/year). *Staphylococcus aureus* and *Acinetobacter* infections were the second most common bacterial isolates (each with an incidence of 67.8 episodes/1000 LTR/year). The median time to development of Gram-negative pneumonia was 31 days with a range of 3–394 days. Gram-positive cocci-related pneumonias also occurred in the early post-transplant period at a median of 35.5 days (range 2–486 days) post-transplant. Other bacterial isolates from this and other studies span the spectrum of health care-acquired infectious organisms. Similarly, *P. aeruginosa* was found to be the most common isolate accounting for 33.3%, *Staphylococcus aureus* comprised 26.8%, and *Aspergillus* 16%.<sup>34</sup>

#### Late pneumonia

Pneumonia is also seen in the late post-transplant period. Throughout the lifespan of the LTR, ongoing contact with hospital settings, both outpatient and inpatient, and frequent antibiotic exposure commonly result in infections with health care-associated, often resistant, pathogens. Community-acquired pneumonias can also develop in the late post-transplant period.<sup>48</sup> In a single-centre study, 14 out of 220 LTR (6.4%) developed invasive pneumococcal infection (pneumonia and/or sepsis) at a median of 1.3 years after transplantation (incidence rate: 22.7 cases per 1000 person-years). Routine vaccination for pneumococcus with the pneumococcal polysaccharide vaccine is recommended both before and every 5 years following LT.<sup>41</sup>

#### Diagnosis

In general, the approach to suspected pneumonia at any time period post-transplant includes sputum, blood cultures and often bronchoscopy with bron-

cholevalveolar lavage (BAL), sterile brush and sometimes biopsy. The role of new biomarkers such as procalcitonin for diagnosis or follow-up has not been well established in the LTR.

### Prophylaxis

Due to the high incidence of early post-transplant pneumonia, whether derived from the recipient, donor or nosocomially acquired, broad-spectrum postoperative prophylaxis is routinely used. Prophylaxis in the post-transplant period varies by centre but typically includes a third generation cephalosporin and vancomycin and is then tailored to the results of donor and recipient cultures, or as clinically indicated for 7–10 days. Prophylactic antibiotic treatment should be extended to 14 days for known pretransplant recipient colonization. For specific prophylactic regimens for viral and fungal pathogens, see later.

### Treatment

Treatment of bacterial pneumonia includes standard regimens as outlined by the American Thoracic Society and Infectious Disease Society of America treatment for health care-acquired pneumonia.<sup>49</sup> In the setting of known prior colonization or infection, initial antibiotic selection may be based on prior culture and sensitivity results. Typical antibiotics used should include coverage for Gram-negative (including pseudomonas) and Gram-positive (including *Staphylococcus aureus*) pathogens. In general, 8–14 days of therapy is recommended. In the case of resistant organisms, inhaled aminoglycosides may also be added to the treatment regimen.

### Outcomes

Pneumonia has significant impact on overall post-transplant survival and the eventual complication of chronic rejection. In the Spanish study, attributable 1-year survival was reduced in those patients developing pneumonia of any aetiology (29.5% mortality) versus those without pneumonia (14% mortality), although bacterial pneumonia alone was not separated out in this analysis. These authors also found that the probability of survival during the first year of follow-up was significantly higher in the multivariate analysis in LT recipients who did not have a pneumonia episode compared with those that had at least one episode of pneumonia.<sup>47</sup> In the Bonde *et al.* study, pneumonia was found to be an independent predictor of overall mortality.<sup>44</sup>

## VIRAL INFECTION

Viral infection after LT is common and classified into disease caused by CMV or caused by other community-acquired respiratory viruses (CARV). A recent study showed that a viral pathogen was

responsible for 25 of 71 infectious episodes in a cohort of LTR, with CMV accounting for 68% of those cases. Additionally, the majority of CMV episodes occurred within the first 3 months following LT, while the majority of the later infections were due to influenza and occurred after 1 year (Fig. 1).<sup>3</sup>

### CMV

Among the opportunistic infections following LT, CMV is the most prevalent and most important despite significant advances in both diagnosis and management. As well as contributing directly to both morbidity and mortality, mounting evidence suggests a relationship between CMV pneumonitis and chronic rejection in the form of BOS and decreased survival despite treatment.<sup>50</sup> CMV seropositivity can range from 30% to 97% in the general population, and after infection, the patient will harbour the virus for life. Of all solid organ transplants, LTR has the highest risk of developing CMV disease.<sup>51</sup> The incidence of CMV infection has been reported to range from 30% to 86% in post-LTR, with a mortality of 2–12%.<sup>52</sup> This increased incidence is thought to be due partly to the high viral load of CMV transmitted in the lymphatics of the lung compared with other solid organs, as well as the high level of immunosuppression required for lung allograft.

The most important risk factor for the development of CMV infection is the donor-positive/recipient-negative serostatus of a transplant patient, as these patients will lack immunity to CMV. The lowest risk occurs in donor-negative/recipient-negative patients.<sup>51</sup> Other important risk factors include type and intensity of both induction and maintenance immunosuppression, concurrent infections, rejection and host factors such as age or comorbidities.<sup>51,52</sup>

There is almost a symbiotic relationship between rejection and CMV infection. Both of these individual processes induce a cytokine cascade that in essence promotes the development of the other. Tumour necrosis factor- $\alpha$ , a key signal in the reactivation of CMV from latency, is released during allograft rejection, thereby facilitating the onset of viral replication and subsequent infection. Conversely, infection of the vascular endothelium and smooth muscle by CMV leads to an upregulation of adhesion molecules promoting an increase in the quantity of inflammatory cells in the graft and subsequent development of rejection. Additionally, molecular mimicry and the production of anti-endothelial antibodies with CMV may also play a role in the development of rejection.<sup>52</sup> CMV serology of both donor and recipient must be checked prior to transplant.<sup>53</sup>

### Diagnosis

There is an important distinction between CMV infection and disease. Infection is defined as 'CMV replication regardless of symptoms', while disease is defined as 'evidence of CMV infection with attributable

symptoms', such as 'a viral syndrome with fever and/or malaise, leukopenia, thrombocytopenia or as tissue invasive disease'.<sup>51,54</sup>

Recent technologies have effected a shift in the diagnosis of CMV infection and disease. The previous method of diagnosis, pp65 antigen detection, has been replaced by quantitative nucleic acid-based amplification testing via polymerase chain reaction (PCR) for the recognition of viraemia by most centres, with 85% of institutions using this method for monitoring and diagnosis.<sup>55</sup> There are no universally accepted viral load cut-offs for positive and negative results, and that reported values may be dissimilar between different laboratories. Despite this, current guidelines on the management of CMV in solid organ transplant patients do not clearly favour one test over the other and cite both as acceptable options for diagnosis. Additionally, viral culture of blood or urine has a limited role for diagnosis and is not routinely recommended.<sup>53</sup>

Most recently, tests for cell-mediated immunity against CMV have shown promise for predicting risk of developing disease. Lisboa and colleagues demonstrated that cell-mediated immunity to CMV, as shown by a CD8+ T cell response assay, was associated with decreased risk of developing disease in patients with detectable low-level viraemia. Twenty four of 26 patients (92.3%) with a positive interferon-gamma release assay were able to clear their viraemia without disease compared with 5 of 11 (45.5%) in patients with a negative cell-mediated immunity at onset ( $P = 0.004$ ).<sup>56</sup> In a similar study, the same group was able to show that a negative assay was associated with a higher chance of developing late-onset CMV after prophylaxis. In their study, CMV disease occurred in 2/38 (5.3%) patients with a detectable interferon-gamma response versus 16/70 (22.9%) patients with a negative response ( $P = 0.038$ ).<sup>57</sup>

### Prophylaxis

There are two accepted approaches to the prevention of disease from CMV, universal prophylaxis and pre-emptive therapy, and although there are no randomized trials comparing one strategy versus the other in LTR, most centres favour the former or may sometimes employ both.<sup>55</sup> The first, universal prophylaxis, involves administration of antivirals to all transplant patients deemed to be at high risk by serostatus. The second, pre-emptive therapy, is comprised of monitoring at-risk patients for viral replication and administering antivirals at a predetermined level of replication in the hopes of treating patients prior to the onset of disease. A Cochrane Review comparing prophylaxis in different groups of solid organ transplant patients with antivirals versus placebo or no treatment showed a significant reduction in disease (relative risk 0.42), infection (relative risk 0.61), mortality from CMV disease (relative risk 0.26) and all-cause mortality (relative risk 0.63). Interestingly, the review also found a decrease in the risk of developing herpes-simplex virus, varicella-zoster virus and bacterial infections.<sup>58</sup>

Prophylaxis may not only be beneficial in decreasing direct morbidity and mortality from CMV disease but may also have secondary effects by decreasing the morbidity and mortality of both acute and chronic rejection. The Cochrane Review mentioned earlier failed to show a difference in acute rejection episodes, but other small studies have shown statistically significant differences in LTR specifically and it is generally believed that prevention of CMV decreases the risk for acute rejection.<sup>58-60</sup> The data for BOS are more encouraging. A recent study by Chmiel and colleagues was able to show a 23% absolute risk reduction of developing BOS in a group of LTR on CMV prophylaxis as compared with a historical cohort that was not prophylaxed and a 35% absolute risk reduction compared with data in the literature ( $P = 0.002$ ).<sup>1</sup>

Most centres provide prophylaxis for a period of 3–6 months after transplantation; however, the optimal duration of prophylaxis has not been well established and is currently under debate.<sup>55</sup> The guidelines recommend a minimum of 6 months for LTR.<sup>53</sup> Recent data suggest that this window of prophylaxis should possibly be extended, especially for donor-positive/recipient-negative patients. Palmer and colleagues report the first randomized, placebo-controlled trial showing a decrease in the risk of CMV disease with extended prophylaxis. In this study, 136 LTR who completed 3 months of valganciclovir prophylaxis were randomized to an additional 9 months of valganciclovir versus placebo. The risk of CMV disease was reduced (32% vs 4%;  $P < 0.001$ ) in the extended-course group versus the short-course group. There were also statistically significant reductions in CMV infection (64% vs 10%;  $P < 0.001$ ) and disease severity as measured by viral load with extended treatment. Acute rejection episodes, opportunistic infections, adverse events and CMV UL97 ganciclovir-resistance mutations were similar between both groups.<sup>61</sup> The international consensus guidelines list valganciclovir and ganciclovir (oral or intravenous (IV)) as the antivirals of choice for the prevention of CMV disease and state that CMV immunoglobulin may also be used in combination with these two, but there are limited data to support its use.<sup>53</sup>

### Treatment

Although foscarnet was commonly used in the past for CMV disease, the significant risk of nephrotoxicity with concomitant calcineurin-inhibitor use has made it fall out of favour for the relatively safer agents ganciclovir and valganciclovir.<sup>55</sup> And, although the recommendation for treatment of severe disease is still IV ganciclovir, the results of the Valcyte in CMV disease Treatment of Solid Organ Recipients trial have made valganciclovir a viable choice in the treatment of less severe CMV.<sup>53</sup> The in CMV disease Treatment of Solid Organ Recipients trial randomized 321 solid organ transplant recipients with non-life-threatening CMV disease to either oral valganciclovir or IV ganciclovir. Valganciclovir demonstrated non-inferiority in regard to clinical resolution of disease as well as eradication of viraemia in both the intent-to-treat and the

per-protocol arms of the study.<sup>62</sup> The current guidelines recommend oral valganciclovir at twice-daily dosing or IV ganciclovir for the treatment of non-severe CMV disease. As there are no efficacy data for valganciclovir in severe or life-threatening disease, IV ganciclovir is still the 'gold standard' for those patients. In both groups, serial monitoring of viraemia should occur optimally at 1-week intervals, and treatment should be continued for a minimum of 2 weeks and until viral eradication has been documented with two consecutive tests. The use of secondary prophylaxis is generally recommended for 1–3 months after treatment of disease.<sup>53</sup>

## CARV

Infection with a CARV is common after LT, and with the development of new diagnostic techniques, the incidence quoted in older literature is likely underestimated. A study of LTR undergoing serial surveillance and diagnostic BAL over a 3-year period showed that a respiratory virus was isolated in 51.6% of patients on at least one BAL sample. Rhinovirus was the most common pathogen isolated, followed by parainfluenza, coronavirus, influenza, metapneumovirus and respiratory syncytial virus (RSV).<sup>63,64</sup> CARV is being increasingly recognized as contributors to significant morbidity in immunocompromised hosts and can cause severe and life-threatening pneumonitis. Additionally, there appears to be evidence that infection with these organisms can also lead to a decrease in graft survival. A retrospective cohort study of 259 LTR followed over 5 years showed a significantly increased risk of developing BOS or death from BOS in the group that was diagnosed with a CARV infection.<sup>65</sup>

Given the paucity of effective antiviral treatment for most of these viruses, early diagnosis is essential for both treatment and to minimize spread among other immunocompromised patients. With the exception of influenza and RSV, for which treatments exist, supportive care and a reduction in immunosuppression remain the cornerstones of care for the treatment of CARV. A complete listing of all the viruses that commonly affect LTR would be beyond the scope of this article so we will focus on those that have the most clinical bearing, namely influenza, RSV, human metapneumovirus and parainfluenza. As it typically does not cause respiratory tract disease, we will not discuss Epstein–Barr virus, except to mention its known association with post-transplant lymphoproliferative disorder after LT.

## Influenza

Infection of normal hosts with influenza most commonly causes a self-limited disease with upper respiratory symptoms, myalgias and fever; however, infection in LTR appears to be associated with increased risk of lower respiratory tract involvement by either a primary viral or a concomitant bacterial superinfection. This was illustrated in a small series of LTR admitted for influenza where all appeared to have

pulmonary parenchymal involvement on imaging and by BAL as well as in another series by Vilchez and colleagues, where 7 of 15 patients with influenza were found to have pulmonary infiltrates, 5 of which were attributed to a primary viral pneumonia after BAL.<sup>66,67</sup> Novel H1N1 influenza appears to have similar clinical features, although there appears to be an increased rate of gastrointestinal symptoms such as nausea and diarrhoea; which may be prominent.<sup>68</sup> Due to the increased severity of disease, all LTR and their household contacts should receive annual influenza vaccination for prevention of disease.<sup>69</sup>

Diagnosis is essential, and efforts should be made to establish the type, as specific therapy will depend on resistance patterns.<sup>69</sup> Diagnosis of seasonal influenza is made by rapid antigen detection of nasopharyngeal swabs, but this method appears to be unsatisfactory for detection of novel H1N1 and molecular real-time PCR methods are currently approved for use when swine flu is suspected.<sup>70</sup> In addition to supportive care and isolation, treatment involves the use of the antiviral agents amantadine and rimantidine for susceptible influenza A strains, and zanamavir and oseltamivir for both influenza A and B strains. Due to the variation in circulating strains from year to year, it is important to stay abreast of the current recommendations from the Centers for Disease Control and Prevention<sup>71</sup> for appropriate treatment.<sup>72</sup> In addition, given the prolonged viral shedding, the typical treatment course of 5 days may be insufficient in LTR, and prolonged therapy may be required. Some experts advocate treating influenza even if symptom onset is greater than 48 h and treating until viral replication ceases.<sup>73</sup> Treatment of novel H1N1 is limited by the resistance of the strain to the M2 inhibitors: amantadine and rimantidine. As such, current guidelines recommend treatment with oseltamivir or perhaps even zanamavir if resistance is suspected to this agent. IV or higher dose therapy is recommended for critically ill patients, and immunosuppression should be decreased.<sup>63,64</sup>

## RSV

By the age of 2, virtually, all children have been infected with RSV, although reinfection can occur throughout life, and early acquisition after transplant or with augmented immunosuppression is a risk factor for severe disease.<sup>72</sup> As with influenza, infection can vary from a self-limited upper respiratory illness to severe pneumonia and occurs through inhalation of infectious droplets and contact with fomites, making isolation precautions paramount for prevention.

There are currently no available vaccines for RSV and no recommended therapies for prevention. Due to a lack of data for effective antiviral treatment, the only universally accepted recommendations for therapy are supportive care and a reduction of immunosuppression.<sup>72</sup> Ribavirin, which has shown *in vitro* activity against RSV, is approved for treatment of lower tract disease by showing benefit in stem cell recipients.<sup>74,75</sup> There are otherwise no controlled



studies showing efficacy with the use of inhaled ribavirin in transplant patients. Despite this, inhaled ribavirin remains the most commonly used treatment for RSV with one report showing a multidrug regimen of ribavirin, steroids, RSV-IV immunoglobulin and palivizumab to be safe, effective and associated with stability of lung function.<sup>76</sup> Two small case series have shown promise for parenteral and oral ribavirin in LTR.<sup>77,78</sup> An optimal treatment strategy for disease due to RSV is yet to be determined, and further studies are needed to better delineate effective agents that can safely be used in the LT setting.

### Other paramyxoviruses

Like RSV, human metapneumovirus and parainfluenza are members of the paramyxovirus family and present similarly to RSV. Although typically they are milder than RSV, they have been shown to cause severe disease and have also been associated with both acute rejection and BOS.<sup>67,79,80</sup> real-time PCR is the diagnostic modality of choice, and a diagnosis should be pursued, as clinical features alone are not specific enough to distinguish between the CARV. Supportive care remains the mainstay of treatment although inhaled ribavirin appears to be increasingly used for the treatment of these pathogens in patients with lower respiratory tract involvement despite a lack of controlled trials. Furthermore, some experts also consider the use of IV immunoglobulin with significant disease for both parainfluenza and human metapneumovirus.<sup>72,80</sup>

## FUNGAL INFECTIONS

Fungal infections are a common complication after LT with an estimated incidence of 15–35% and an overall mortality of 80%.<sup>81</sup> Complications at the site of the anastomosis (i.e. stenosis or necrosis) create the ideal environment for these infections to thrive. Other risk factors include the immunomodulatory effect of coexistent infections (i.e. viral) and neutropenia.<sup>82–84</sup> As previously mentioned, transmission of infection from donor to host after LT can occur, or the native lung may serve as a reservoir of fungal organisms during single LT.<sup>85</sup> This is particularly important in chronic obstructive pulmonary disease patients in whom the lung surfaces are irregular and may have colonized bullae.<sup>84</sup> Pretransplant fungal colonization is common, especially in patients with CF and chronic obstructive pulmonary disease, and it has been associated with post-transplant fungal infection and BOS,<sup>86</sup> although not all colonized patients develop active/invasive infection.<sup>83</sup>

The most common fungal pathogens in LTR are *Candida* and *Aspergillus* species, while *Zygomycetes*, *Scedosporium*, *Fusarium*, *Cryptococcus* species, histoplasmosis and coccidiomycosis occur less commonly. In general, these infections are more prevalent during the first few months after transplantation and, in some cases such as with *Cryptococcus* species, histoplasmosis or coccidiomycosis, can present as a reac-

tivation of a latent infection. Fungal infections can manifest as invasive disease with a reported 1-year cumulative incidence of 8.6% in LTR.<sup>87</sup> Similarly, disseminated disease, post-transplant empyema, and airway and anastomotic infection have been reported.

### Aspergillus

*Aspergillus* species are the most common cause of invasive fungal infection after LT with an incidence of 32%.<sup>84</sup> More than half the cases occur within the first six months following LT,<sup>84</sup> (Fig. 1) and more often involve LTR than other solid organ recipients.<sup>88</sup> Several species have been described as pathogenic: *Aspergillus terreus*, *Aspergillus flavus*, *Aspergillus fumigatus* and *Aspergillus niger*. Among these species, *Aspergillus fumigatus* remains the most common cause of invasive disease.<sup>89</sup>

The majority of *Aspergillus* isolates in sputum or BAL represent colonization (23%), and only a fraction of these will develop invasive disease (<10%), which carries a high mortality.<sup>69,90,91</sup> In LTR, the risk of invasive pulmonary aspergillosis rises with airway colonization by *Aspergillus* species.<sup>84,89,92</sup> Colonization is found in up to 50% of patients with CF. Despite higher colonization compared with other populations, these patients have lower risk of invasive aspergillosis, but a higher risk for aspergillus tracheobronchitis.<sup>93</sup> In addition to colonization, airway ischaemia and BOS have also been implicated as risk factors for invasive aspergillosis.<sup>84,89,92</sup> Disseminated disease has been reported with an incidence of 22%, occurring as reactivation from an occult focus and/or as a new post-transplant infection.<sup>84</sup> Other less common manifestations, such as mediastinal masses, skin, soft-tissue, sinus, orbit, central nervous system, sternal wound and chest wall infections, have also been described.<sup>89,91</sup>

### Diagnosis

There are limited data on the role of minimally invasive tests such galactomannan, PCR and 1,3-β-D-glucan assay for the diagnosis of invasive aspergillosis in LTR.<sup>94,95</sup> 1,3-β-D-glucan, a cell component of all fungi, has been used in the diagnosis of multiple invasive fungal infections, but unfortunately, the role in LTR has limitations.<sup>96</sup> Diagnosis of invasive aspergillosis may require aggressive procedures (i.e. biopsy) to verify tissue involvement; however, this is not always possible, and often, the diagnosis is reached on evaluation of computed tomography chest findings and fungal staining/culture from bronchoscopy (i.e. BAL). The radiological findings of invasive aspergillosis include consolidations, nodules, cavitary lesions and mass-like opacities, often with a 'halo sign'.<sup>84</sup> In cases where the diagnosis is not possible with a less invasive approach, a biopsy with fungal stain/culture and histopathology may be required. Once the diagnosis of invasive pulmonary aspergillosis is made, computed

tomography or magnetic resonance of the central nervous system is suggested to rule out disseminated disease.

### Treatment

Over the years, the use of antifungal prophylaxis has decreased the overall risk of aspergillosis. Despite this, the risk of late infection after discontinuation of prophylaxis or even while using it is still present.<sup>97</sup> The treatment of pretransplant colonization has not been shown to reduce the incidence of post-transplant aspergillosis, but invasive disease in the pretransplant setting should be treated.<sup>90</sup>

Recent data has shown the superiority of voriconazole compared with amphotericin B deoxycholate in patients with invasive pulmonary aspergillosis, but solid organ transplant patients were poorly represented in the study.<sup>98</sup> A major concern with the use of voriconazole in LTR is the interaction with most of the immunosuppressants used in this population. Tacrolimus, sirolimus and cyclosporine can potentially increase the serum concentrations of voriconazole. For this reason, close monitoring of drug levels is needed. Other options for the treatment of invasive aspergillosis are posaconazole and itraconazole, but their roles as first-line agents are not well established. The echinocandins (caspofungin, micafungin and anidulafungin) have shown some *in vitro* activity against *Aspergillus* species, but their utility as first-line antifungals for this infection has not been studied either. The evidence for combined therapy with two or more agents as initial therapy is limited and not recommended.

Despite several alternatives, voriconazole remains the standard therapy for invasive aspergillosis along with reduction of immunosuppression.<sup>99</sup> Voriconazole levels should be monitored carefully, especially in CF patients where serum concentrations can be variable.<sup>99,100</sup> In general, target trough levels should range between 1 and 5 µg/µL. Duration is typically recommended for a minimum of 12 months and depends on clinical and radiographical improvement. Finally, surgical resection might be indicated when there is progression of disease despite optimal antifungal therapy, life-threatening haemoptysis, sinus infection or lesions in the proximity of great vessels, pericardium or in the brain.<sup>82</sup>

### Candida

Severe candidal infections can appear within weeks to months after transplant, especially in the presence of heavier donor or recipient colonization.<sup>91</sup> Typically candida infections occur within the first 30 days after LT and appear to be the second most common cause of invasive fungal infection in LTR.<sup>69</sup> Candidaemia usually occurs during the first 4 weeks and is often related to the intensive care unit stay and the surgical procedure; however, parenchymal lung infection is rare.<sup>101</sup> Mortality for invasive candidal infections, excluding anastomotic infections, has been estimated at more than 50%.<sup>102</sup>

Cultures are essential for the diagnosis of candidal infection in LTR. Identification of species and susceptibilities need to be obtained as intrinsic resistance and dose-dependent susceptibility has been reported in different *Candida* species.<sup>103</sup> Other methods such as β-D-glucan have not reached significant accuracy for clinical use,<sup>104</sup> while others such as PCR are still experimental. *Candida* species are commonly found in the oropharynx and can potentially colonize the airway. Their presence in respiratory secretions may make it difficult to differentiate between invasive infection and colonization. Invasive lung infection with *Candida* is very infrequent even in the LT recipient colonized with *Candida*.<sup>97</sup> Clinical suspicion, culture results and direct bronchoscopic findings should guide any decision for treatment of candidal infections.

Echinocandins and liposomal amphotericin B are the first-line agents for empirical therapy of suspected candidal infection.<sup>69</sup> This is especially true in LTR who are at risk of developing severe candidal disease. Fluconazole has been put forward as an empirical agent as well but is frequently reserved for patients with mild-to-moderate disease, non-neutropenic and at low risk for *Candida glabrata* and *Candida krusei*, for which it has less activity. Empirical therapy should then be adjusted based on susceptibilities. For *Candida albicans* infections, fluconazole and echinocandins have been effective, but in widespread disease, amphotericin B might be considered. Finally, the duration of therapy varies among patients and with the degree and severity of infection. In candidaemia, treatment can extend up to 2 weeks but may be even longer in cases of more invasive disease.<sup>69</sup>

### Endemic mycoses

Histoplasmosis, coccidioidomycosis and rarely, blastomycosis are endemic mycoses that can potentially cause infection in transplant recipients. When present in this population, pulmonary and disseminated disease can occur with a high mortality.<sup>105</sup> These are especially important in endemic areas of the United States such as the Midwest for histoplasmosis and the Southwest for coccidioidomycosis.<sup>106</sup>

Histoplasmosis can present in the early or late post-transplant period as a consequence of reactivation of a latent infection, new exposure or donor-derived infection.<sup>106</sup> The diagnosis can be delayed, but in LTR, urinary antigen appears to be a better diagnostic tool than the fungal antibody serologies.<sup>106</sup> The presence of fever without a clear source should raise clinical suspicion for disseminated histoplasmosis in any transplant patient, especially when pancytopenia and absence of pulmonary manifestations are present. In patients whose explanted lung is found to have histoplasmosis, antifungal prophylaxis after transplant seems effective at preventing reactivation of this infection.<sup>106</sup> There is no clear consensus about the duration of prophylaxis, and 18 months has been reported to be effective.<sup>106</sup>

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 LT recipients is reactivation, but donor-derived transmission has also been reported.<sup>107</sup> Patients in whom there is evidence of prior coccidioidomycosis, either radiographically or serologically, may require lifelong antifungal prophylaxis after transplant.<sup>91</sup>

### Miscellaneous fungi

*Cryptococcus* infections can present in solid organ transplant recipients as a pulmonary or extrapulmonary process.<sup>108</sup> The incidence of *Cryptococcus* infection in LTR has been estimated around 2% and has been commonly associated with exposure to pigeons and other birds.<sup>90</sup> Interestingly, LTR may be less likely to have a positive cryptococcal antigen test in the setting of isolated pulmonary cryptococcosis.<sup>38,108</sup> An immunosuppressive regimen containing a calcineurin inhibitor has been associated with decreased mortality possibly due to synergistic effects between calcineurin inhibitors and antifungal agents used to treat *Cryptococcus*.<sup>109</sup> However, a recent study has reported the occurrence of an immune reconstitution syndrome-like illness in some transplant patients after the initiation of antifungal therapy for cryptococcal infection.<sup>110</sup>

Zygomycotic infections appear to be escalating in frequency in immunosuppressed patients, and this trend has been partially attributed to the increasing use of voriconazole for therapy and prophylaxis.<sup>111</sup> This infection is characterized by vascular invasion of affected tissues with subsequent infarction and necrosis. In LTR, it can manifest as bronchial anastomotic or parenchymal infection with a mortality of 87% in the latter.<sup>112,113</sup> Its management includes the combination of surgical debridement and antifungal agents.

### Fungal prophylaxis

In the United States, 80% of transplant centres use antifungal prophylaxis,<sup>114</sup> and approximately 81% perform pretransplant surveillance for fungal colonization.<sup>115</sup> Despite this, there is still no general consensus regarding the most appropriate prophylactic strategy in the peritransplant window.

Although there are no randomized trials evaluating their efficacy, several antifungal agents have been used for prophylaxis in LTR. For universal prophylaxis, voriconazole, itraconazole and amphotericin B are commonly used, while targeted prophylaxis with fluconazole (*Candida*), voriconazole and itraconazole (*Aspergillus*) are used based on the results of surveillance bronchoscopy.<sup>114</sup> In general, the choice for antifungal prophylaxis depends, in part, on the presence of specific risk factors such as colonization with *Aspergillus*, presence of airway stents or ischaemia, single lung transplantation, CMV infection, hypogammaglobulinaemia or treatment of acute rejection.<sup>69</sup>

Despite a lack of controlled trials, several studies suggest potential prevention of invasive aspergillosis with the use of either compound of amphotericin B.<sup>116,117</sup> Inhaled amphotericin B has lower systemic toxicity, better delivery to the site of fungal exposure and a lower likelihood of resistance when compared with systemic antifungal therapy.<sup>116,118,119</sup> The data regarding voriconazole for prophylaxis in LTR is promising, especially given the excellent bioavailability, broad antifungal coverage and good drug levels achieved in lung tissue.<sup>120,121</sup> Unfortunately, the numerous drug interactions with some of the immunosuppressants, and its potential adverse effects may preclude its use as a first-line prophylactic agent. Itraconazole has clinical effectiveness similar to the combination of voriconazole and inhaled amphotericin B and may have lower hepatotoxicity when compared with voriconazole.<sup>114</sup>

Duration of antifungal prophylaxis varies from centre to centre. The use of voriconazole or itraconazole for 3–6 months with or without amphotericin B has been shown to decrease the incidence of *Aspergillus* infection after transplantation.<sup>88</sup> The use of inhaled amphotericin B is typically for 2 weeks or is discontinued at the moment of discharge. In cases where pretransplant fungal colonization is present, patients may be treated for several weeks before LT and continued for up to 3 months after transplantation. Because LTR is at high risk for fungal infections, antifungal prophylaxis should be started in most patients after LT with careful consideration of side-effects and interactions to improve outcomes and be guided by cultures from donor, graft and recipient.

## MYCOBACTERIAL INFECTIONS

Mycobacterial infection after LT is rare. Previously, most of these infections were secondary to *Mycobacterium tuberculosis*.<sup>122</sup> More recently, data have shown an increase in the incidence of NTM, particularly *Mycobacterium abscessus*, ranging between 3% and 9%.<sup>123,124</sup> Chalermkulrat *et al.*, reported higher isolation of NTM in end-stage CF patients undergoing pre-LT evaluation (19.7%) than in post-LT CF patients (13.7%).<sup>124</sup> Colonization, especially when *M. abscessus* was isolated, was associated with an increased risk for invasive mycobacterial infection in CF patients.<sup>124</sup>

Over the last 10 years, multiple cases of *M. abscessus* in LT recipients have been reported with pleuropulmonary and disseminated disease.<sup>125–127</sup> In addition, there is an increase in both mortality and disseminated disease associated with *M. abscessus* in solid organ transplant recipients.<sup>128</sup> On the other hand, *M. avium complex* and other NTM infections are less common, and their impact on morbidity and mortality is less severe compared with *M. abscessus*.<sup>129</sup> If during the pretransplant evaluation, the clinical presentation and radiographical findings are suggestive of NTM infection, diagnostic testing and therapy should be considered before transplantation. In the CF population, the presence of NTM should not preclude LT, but careful monitoring for recurrence after transplant should be performed.<sup>124</sup>

The diagnostic criteria of the American Thoracic Society and Infectious Disease Society of America apply to pre- and post-LTR (symptoms, radiological findings and microbiology).<sup>130</sup> Similarly, the antimicrobial therapy recommended in the NTM guidelines is applicable to LTR.<sup>130</sup> Therapy for mycobacterial infection in the immunosuppressed patient can be problematic particularly due to drug interactions and increased toxicity. Nevertheless, these infections can be controlled, and some patients achieve an appropriate response and cure.

## TRACHEOBRONCHITIS AND OTHER INFECTIONS

Anastomotic tracheobronchitis is a unique form of pulmonary infection<sup>131</sup> that usually develops in the first 6 weeks to 3 months following LT. During the transplant procedure, the bronchial circulation is not reanastomosed, and thus, the bronchial anastomosis must receive collateral blood flow from the pulmonary circulation, is subject to ischaemia and may be susceptible to infection. This diagnosis is easily confirmed with bronchoscopic examination revealing purulence, ulcerations, pseudomembranes, necrotic material, dehiscence and sometimes narrowing at the site of the anastomoses, and histological and culture results. The organisms most commonly causing tracheobronchitis in this setting are bacteria (*Pseudomonas*, *Staphylococcus*) and fungi *Aspergillus* (an incidence of 32% and 20%, respectively) and *Candida*.<sup>84,132,133</sup>

Treatment includes appropriate antibacterial and/or antifungal antimicrobials. The treatment of airway anastomotic infections with fungi is with a combination of both systemic and sometimes inhaled antifungal agents.<sup>134,135</sup> For aspergillosis, the combination of voriconazole and nebulized amphotericin B along with reduction of immunosuppression has been advocated.<sup>99,134</sup> Duration of therapy for tracheobronchitis is usually determined by resolution under bronchoscopic surveillance. Late sequelae may include stenosis and or stricture requiring intervention with balloon dilation or occasionally endobronchial stent placement. A study demonstrated a decrease in 5-year survival in single LTR who developed bronchial anastomosis fungal infections.<sup>132</sup>

Other types of bacterial infection described in LTR include those of the pleural space, blood stream and wounds, with organisms often isolated in the nosocomial setting, and *Clostridium difficile*.

### *Pneumocystis jiroveci*

*Pneumocystis jiroveci* pneumonia (PJP) occurs exclusively in immunosuppressed states. The risk of infection is higher during the first 6 months after LT due to the degree of immunosuppression during this period.<sup>136</sup> CMV infection is also an independent risk factor for PJP.<sup>137</sup> Despite this, PJP remains a rare complication after LT.<sup>138</sup> The low rate of infection is due

to the use of prophylaxis with trimethoprim-sulfamethoxazole as a first-line agent, and dapsone, pentamidine and atovaquone as alternatives.<sup>139,140</sup> Trimethoprim-sulfamethoxazole has been shown to have better tolerance, potentially treat a wider range of infections, and has fewer side-effects.<sup>139</sup> There is controversy regarding the duration of prophylaxis after transplant. A study revealed that the rate of PJP did not decline after 1 year of transplantation, suggesting that prophylaxis should be continued beyond this period.<sup>141</sup> LTR should receive at least 6 months of prophylaxis post-transplant, and if tolerated, adequately, it should be continued indefinitely. In those patients in whom prophylaxis has been discontinued, it should be resumed if the patient develops acute or chronic rejection requiring augmented immunosuppression. The standard therapy for PJP is trimethoprim-sulfamethoxazole in combination with corticosteroids.

As previously noted, MMF is used frequently as part of the immunosuppression regimen after LT. Interestingly, this medication has shown antimicrobial properties against several pathogens including *Pneumocystis* spp.<sup>142,143</sup> In three comparative studies, none of a total of 1152 transplant patients who received MMF developed PJP compared with an infection rate of 1.8% in a similar group that did not receive MMF.<sup>144–146</sup> The mechanism for these effects remains unknown, but it is likely that MMF may benefit LTR by two different mechanisms.

### *Nocardia* species

In LT, *Nocardia* remains an important pathogen with a frequency of 0.6–2.1% and a directly attributable mortality of up to 30%.<sup>147</sup> It is important to note that some of these patients (60–100%) were on treatment with prophylactic trimethoprim-sulfamethoxazole, a medication to which *Nocardia* is classically susceptible to, underscoring the resistance of some strains to prophylaxis therapy.<sup>147</sup> The treatment for *Nocardia* is trimethoprim-sulfamethoxazole, but resistance has been documented and other alternatives have been used successfully: imipenem, amikacin, third generation cephalosporins, minocycline, moxifloxacin, linezolid and dapsone.<sup>148</sup> Despite the relatively low frequency of *Nocardia* in LT, because of the high risk of mortality and the ability to mimic other infections, clinicians must have awareness of this pathogen to improve an early diagnosis to initiate appropriate therapy.

## BRONCHIOLITIS OBLITERANS SYNDROME

Chronic rejection following LT is manifested pathologically by bronchiolitis obliterans and clinically by worsening obstructive dysfunction on pulmonary function, the BOS. BOS is the rate-limiting factor in long-term survival following LT, and up to 50% of LTR will develop BOS.<sup>5,149</sup> The aetiology remains unclear,

although acute rejection is one of the identified risk factors. Emerging evidence continues to point towards infectious aetiologies as important factors in the pathogenesis of BOS. Several different viral, bacterial and fungal pathogens have been implicated in this process.<sup>150,151</sup> These findings are critical regarding the understanding the mechanisms of rejection and possible therapies to prevent it.

CMV was the first pathogen linked to the development of BOS. CMV pneumonitis is associated not only with BOS but also with decreased survival despite treatment.<sup>50</sup> Furthermore, there has been an absolute risk reduction in the development of BOS with the use of CMV prophylaxis, supporting the evidence that this virus may play an important role in the pathogenesis of rejection.<sup>1</sup> CARV infections, including RSV, human metapneumovirus and parainfluenza virus, were also identified as a significant risk factor for developing BOS.<sup>65,67,79,80</sup>

Bacterial colonization and infection may be a contributing risk factor to the development of BOS.<sup>152–155</sup> Because macrolides are felt to slow the progression of BOS, it has been postulated that this response is due to the potential treatment of a chronic infection with *Mycoplasma pneumoniae* or *Chlamydia pneumoniae*,<sup>154,156</sup> although macrolide immunomodulation also plays an important role. It has been shown that a positive serology and PCR testing for *Chlamydia pneumoniae* on BAL samples increases the rate of BOS and early mortality.<sup>157,158</sup> Supporting this theory further, a study recently demonstrated that macrolides can prevent the development of BOS.<sup>153</sup>

Fungal pathogens have been also associated with the development of BOS.<sup>159</sup> Fungal pneumonitis and aspergillus colonization have been identified as independent risk factors for BOS and mortality related to rejection.<sup>151,159,160</sup> Moreover, the combination of late-onset aspergillosis and chronic allograft dysfunction was a risk factor for poorer survival.<sup>132</sup>

## CONCLUSION

Despite several advances in surgical technique, immunosuppression and prophylaxis, infection continues to remain an important cause of death and disease in the LTR. Although there are non-modifiable factors that are innate to the patient or to the nature of the procedure, there are several modifiable factors that can be recognized and changed so as to optimize the patient's chances for survival and further extend life. Prompt recognition and treatment of these factors is paramount for appropriate management. Prophylaxis strategies continue to evolve and show promise for several of the infectious agents. 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. Antimicrobial resistance is a growing problem, and although newer antimicrobials will likely be of benefit, especially against viral and fungal pathogens, prevention of these diseases remains the best approach. Careful consideration and

further research are needed regarding the mechanisms by which infection and subsequent inflammation alters the immunoregulatory machinery of the host and subsequently leads to the development failure of the allograft. Factors that are important in evaluating an infectious episode include time after transplant, immunosuppression, CMV serostatus, prophylaxis regimen and treatment for acute rejection.<sup>3</sup> Given that outcomes appear to be improved with early recognition and treatment of disease, all practitioners must always maintain a high index of suspicion caring for these patients.

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