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Review

Advances in Managing Infections in Lung Transplantation: A Review

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Abstract

Transplanted lung allografts are particularly susceptible to infection among SOT due to the constant exposure to the environment, aggressive immunosuppressive strategies, and impaired clearance mechanisms after denervation of the transplanted lung. Though prophylactic antimicrobial, antifungal, and antiviral regimens are used as preventive strategies to mitigate the risk of infection, complications related to allograft infection remain one of the primary causes of morbidity and mortality after lung transplantation. Here we will review the common bacterial, viral, and fungal complications after lung transplantation, and discuss some newer agents and treatment strategies that have been implemented recently.

Keywords

Lung transplantation; bacterial; fungal; viral complications; cytomegalovirus

1. Introduction

Lung transplantation is a surgical option for select patients with life-threatening pulmonary disease. Despite improved survival in post-lung transplant outcomes over recent years, the risk for both early and late post-surgical complications remain high [1]. Among solid organ transplantation recipients, lung transplant recipients are at particularly high risk to develop allograft infections. The higher risk for infectious complications is thought to be related to aggressive immunosuppression, constant exposure of the airways to the outside environment, and poor ciliary clearance of the denervated transplanted lung [2]. After allograft failure, infection represents the most common cause of death within the first 30 days after transplant and represents the most common cause of death within the first year [1]. In the immediate post-transplant period, infections can be related to complications of surgery, donor or recipient pre-existing colonization, or nosocomial infection [3]. Bacterial pneumonia from nosocomial or hospital-acquired organisms is the most common infection in the first 30 days post-transplant. One month post-transplant, there is high risk for cytomegalovirus, pneumocystis jirovecci, and fungal pneumonia, though with prophylaxis, these infections are less commonly seen [3]. The initial risk for infection decreases after the first 6 months post-transplant; however, the likelihood of colonization or infection with multi-drug resistant (MDR) bacteria increases with each hospitalization, especially in patients who have had a prolonged post-surgical intubation time [3, 4]. Therefore, careful postoperative surveillance, timely vaccinations, and appropriate prophylactic anti-bacterial, anti-viral, and anti-fungal medications are essential to limiting major infections after transplant. Here we will review the common bacterial, viral, and fungal complications after lung transplantation, and discuss some newer agents and treatment strategies that have been implemented recently.

2. Bacterial Infections

Bacterial pneumonia is the most common infectious complication after lung transplant, accounting for about 50% of all infectious complications [5]. Transient disruption of bronchial circulation can lead to epithelial dysfunction and poor ciliary function. Similarly, denervation of the allograft can suppress the cough reflex and ciliary elevator, thus allowing for easier colonization with various organisms. Lung transplantation requires particularly aggressive immunosuppression compared to other solid organ transplants, which subsequently results in T and B cell dysfunction and cytokine dysregulation. Patient comorbidities, including the type of underlying pulmonary disease they have, play a major role in determining the risk for bacterial infection. For example, patients with cystic fibrosis (CF), diabetes, obesity, hepatitis, human immunodeficiency virus (HIV), latent tuberculosis (TB), kidney disease, previous colonization by MDR bacteria, prolonged post-surgical intubation times, and aspiration are at higher risk for bacterial infectious complications [6, 7]. Postoperatively, patients are at risk for pneumonia, central line-associated bloodstream infections (CLABSI), and clostridium difficile colitis [7, 8]. In the first month after transplant, *Staphylococcus aureus (including MRSA), Enterococcus (VRE)*, and *Pseudomonas aeruginosa* pneumonia are the most common organisms identified [8-11]. *Acinetobacte*r, *Stenotrophomonas maltophilia* and other gram-negative organisms were previously identified less frequently, but are increasing in incidence as a result of antibiotic suppression therapy [12]. *Clostridium difficile* colitis is common 30 days post-op and is associated with the use of antibiotics, proton pump inhibitors, and steroids in the immediate transplant period [13]. CF patients are more likely to develop

colonization and subsequent infection by *P. aeruginosa*, non-tuberculous mycobacteria (NTM), and *Burkholderia cepacia* complex [14].

Post-transplant empiric antibiotics should be tailored to each patient individually based on recipient and donor cultures. A diagnostic up workup often involves cultures, chest imaging, and a bronchoscopy. Given increasing antibiotic resistance, new agents have come to market, particularly for treatment of difficult to treat (DTR) pseudomonas pneumonia [15]. Cefiderocol is reserved as salvage therapy if other agents are resistant (Table 1). Cefiderocol works by binding free iron, and is stable to all classes of carbapenamase hydrolyzing enzymes (metallo-carbapanemases, porin channel mutations, and efflux pump over producers [16]. MDR gram negative bacteria such as carbapenem resistant Enterobacterales (CRE) are another particularly difficult to treat class of organisms. Agents such as meropenem/vaborbactam (Vabomere) and imipenem/cilastatin/relebactam (Recarbrio) have recently come to market and are indicated for these infections [17]. Ceftazidime/avibacam (Avycaz) and ceftolozan/tazobactam (Zerbaxa) are effective newer agents as well [17]. Lastly, nebulized antibiotics such as inhale colimycin, can be of utility, especially for ventilator associated pneumonia (VAP) related to MDR gram negative organisms. The addition of inhaled antibiotics are typically recommended as add on therapy to systemic antibiotic treatment for patients with VAP due to MDR GNB which are susceptible to aminoglycosides or polymyxins, though the strength behind this recommendation in inconsistent.

Table 1 Common bacterial infections and treatment algorithms.

Bacteria	1st Line Treatment	Alternative Regimens
Staph aureus	Cefazolin 2 g IV q 8 hr Oxacillin 2 g IV q 4 hr Ceftaroline 600 mg IV q 8 hr	Linezolid 600 mg IV q 12 h
Enterococcus spp.	Ampicillin 200 mg/kg/day IV amoxicillin 1 g PO q 8 h + ceftriaxone 2 g IV q 24 h	If VRE:Linezolid 600 mg IV/PO q 12 Tedizolid 200 mg PO q 24 h
Pseudomonas aeruginosa	Ceftazidime 2 g IV q 8 hr cefepime 2 g IV q 8 h + aminoglycosides IV IV/aerosolPiperacillin/tazobactam 4.5 g IV q 6 h + ciprofloxacin 750 mg IV q 12 h	If ESBL:Meropenem 2g IV q 8 hr Imipenem/cilastatin 1 g IV q 6 hr Ceftolozane/tazobactam 3 g IV q 8 hr Ceftazidime/avibactam 2.5 g IV q 8 h or meropenem/vaborbactam 4 g IV q 8 h carbapenemase:Ceftazidime/avibactam 2.5 g IV q 8 h + aztreonam 2 g IV
Acinetobacter spp.	Cefepime 2 g IV q 8 h	Meropenem 2 g IV infusion over 3 h q 8 hr Meropenem 2 g IV LD then 3 g Colistin 9 MIU IV LD then after 12 h 4.5 MIU q 12 h + colistin aerosol
CRE	Ceftazidime/avibactam 2.5 g IV q 8 hr ± colistin 9 MIU IV LD then after 12 h 4.5 MIU q 12 hr Fosfomycin 24 g CI or aminoglycosides IV/aerosol (check local epidemiological data)	Meropenem/vaborbactam 4 g IV q 8 hours Imipenem/relebactam 1.25 g IV q 6 hr Ceftazidime/avibactam 2.5 g IV q 8 hr + aztreonam 2 g IV Cefiderocol 2 g IV q 8 h

Nocardia spp.	Trimethoprim-sulfamethoxazole 160/800 mg PO q 12 h (or 15 mg based on trimethoprim/kg/day IV) + meropenem 2 g IV q 8 h	Linezolid 600 mg IV q 12 hr + meropenem 2 g IV q 8 hr or imipenem/cilastatin 500 mg IV q 6 hr
S. Maltophilia	Trimethoprim-sulfamethoxazole 160/800 mg PO q 12 h (or 15 mg based on trimethoprim/kg/day IV)	Levofloxacin 750 mg IV q 24 h Minocycline 200 mg IV LD then 100 mg q 12 h

3. Viral Infections

Viral complications represent the second most common post-transplant infections. The incidence of viral infections increases with escalating immunosuppression, largely due to the reactivation of latent infections. As a group, lung transplant recipients are at an increased risk of CMV related disease compared to other solid organ transplant recipients [18]. There are many factors that can explain this finding. First, seropositive donors have increased over time by transplant era, increasing from 55.3% between 1992 and 2000 to 61.6% as of 2018 [19, 20]. Second, when compared to kidney, liver, or heart, the lung may carry a higher burden of donor CMV infected cells increasing the risk for reactivation [19, 20]. Third, due to the significant amount of immunosuppression needed for maintenance therapy, lung transplant recipients are at higher risk of recrudescent viral disease. Finally, there is increased risk for CMV reactivation after patients develop acute rejection, requiring high doses of lymphocyte depletion therapies and high dose corticosteroids [21].

CMV plays a significant role in solid organ transplant recipients. The virus can affect allograft function and increase patient morbidity and mortality through several direct and indirect effects. The spectrum of disease from CMV includes the development of asymptomatic viremia, CMV syndrome, or tissue invasive disease [22]. Late onset CMV disease often complicates allograft rejection, and remains a common complication in this patient population. Prior to initiation of CMV prophylaxis, infection was most common in the three months after transplantation. Late-onset CMV disease is seen in high-risk CMV donor-positive/recipient-negative (D^+/R^-) patients after the completion of antiviral prophylaxis [23]. The incidence of CMV disease among lung transplant recipients who received antiviral prophylaxis for 6 to 12 months was 14.9%, with a higher incidence (26.6%) in the (D^+/R^-) group [24]. The high-risk D^+/R^- patients lack the ability to mount an effective immune response against CMV due to the significant immunosuppression that is needed in lung transplant recipients when compared to other solid organs transplants [25]. Other risks for CMV infection post-transplant are related to the type of induction and maintenance agents that are used, such as anti-thymocyte globulin (ATG), alemtuzumab, or the IgG fusion protein belatacept, lymphocyte depleting agents which increase the risk for CMV infection when compared to the CMV protective agents such as mTOR inhibitors (sirolimus or everolimus [26, 27]).

There is a bidirectional relationship between CMV and allograft rejection. Allograft rejection creates a pro-inflammatory environment that can reactivate CMV, and the treatment for allograft rejection severely impairs the ability to mount an immune response to control the virus. CMV has both direct and indirect effects on lung transplant recipients. Direct effects are CMV disease, such as CMV syndrome and CMV pneumonitis, whereas indirect effects include the increased risk for developing other infections, acute rejection, and the increased risk of developing chronic lung

allograft dysfunction [28]. CMV upregulates antigens as well which results in increased alloreactivity and facilitates allograft rejection. Many studies have shown a significant association between CMV infection and early development of chronic allograft dysfunction (CLAD). Patients who have had at least one episode of CMV were shown to have shorter CLAD-free survival curves. Patients with three or more CMV infections had the shortest CLAD-free survival times and had worst survival generally when compared to those with <3 infections [29].

The concept of CMV blips are important to understand in the context of lung transplant complications as well. The term "viral blips" was initially coined in HIV patients when transient HIV viremia was identified in those treated with anti-retroviral therapy. Similarly, CMV blips are seen in patients with CMV viremia which is thought to be related to immunosuppressive therapy [30]. CMV blips are frequent; particularly when the viral load of the first positive PCR is <910 IU/mL, and the serostatus risk is intermediary/low [31]. Accumulating blips suggest intermittent low-level replication. Blips are usually caught when CMV PCR's are positive, and followed weekly or biweekly for monitoring purposes. CMV blips influence the risk of CMV infection, suggesting that these blips at least partly reflect low-level viremia rather than merely intermittent false positive results. CMV blips should therefore be considered as important markers for subsequent infection [31].

Ganciclovir and valganciclovir are CMV DNA polymerase inhibitors and are first line agents for CMV treatment [32]. Foscarnet and cidofovir are alternative agents that are available for refractory or resistant disease, or for those that cannot tolerate first line treatment [33]. Three are multiple definitions for classifying refractory and resistant CMV. For the purposes of this review, refractory CMV is considered when CMV viremia increases despite two weeks of antiviral therapy, whereas resistant CMV is considered when there has been genetic alteration that decreases the activity of certain antiviral medications. Ganciclovir and valganciclovir can cause myelosuppression, foscarnet and cidofovir can be nephrotoxic, with foscarnet also known to cause significant electrolyte abnormalities [33]. Even with universal prophylaxis, CMV disease is seen due to resistance or breakthrough infections even while on prophylaxis.

Oral valganciclovir achieves comparable blood levels to IV ganciclovir and is recommended for the treatment of mild to moderate CMV disease in SOT recipients. IV ganciclovir is preferred drug for treatment of severe (CMV infection requiring hospitalization and/or thought to be life threatening) or in those with issues with medication absorption [34]. IV ganciclovir is also recommended for those with very high viral loads [34]. CMV-specific immunoglobulin (CMVIG) is a hyperimmune globulin obtained from plasma donors with high titers of CMV-specific antibodies, which is a consideration for prophylaxis and treatment for refractory disease.

Immune globulin obtained from plasma donors with high titers of CMV-specific antibodies. CMV infections often occur as a result of an immunocompromised state. Often when infected, immunosuppression regiments are decreased to allow for recovery of CMV immunity [35]. Though uncommon, ganciclovir resistance has been increasing recently, with rising morbidity and mortality in the SOT community, particularly in lung transplant recipients [36]. The major sources of drug resistance in CMV are mutations in UL97, a phosphotransferase, and UL54, a DNA polymerase [37]. Mutations in UL54 are less common, and usually develop after a UL97 mutation. Combined mutations have the highest resistance to ganciclovir. D^+/R^- serostatus is most consistent risk factor for subsequent drug resistant CMV. Other risk factors include high pre-treatment CMV viral load, intensity of immunosuppression, prolonged subclinical viremia, and exposure to sub-therapeutic levels of antiviral agents.

Maribavir has a multimodal mechanism of action, does not require intracellular processing by UL97 protein kinase and targets a different location on UL97 from valganciclovir/ganciclovir [38-41]. An oral drug that inhibits UL phosphotransferase and stops viral maturation. It has trialed for refractory CMV and has been shown to be superior in achieving viremia clearance and symptom control in transplant patients when compared to standard of care [39-41]. Management of resistance and cross-resistance to anti-CMV therapies is challenging (Figure 1). Maribavir remains active against CMV strains resistant to ganciclovir, foscarnet, or cidofovir due to UL54 or UL97 viral kinase mutations [42].

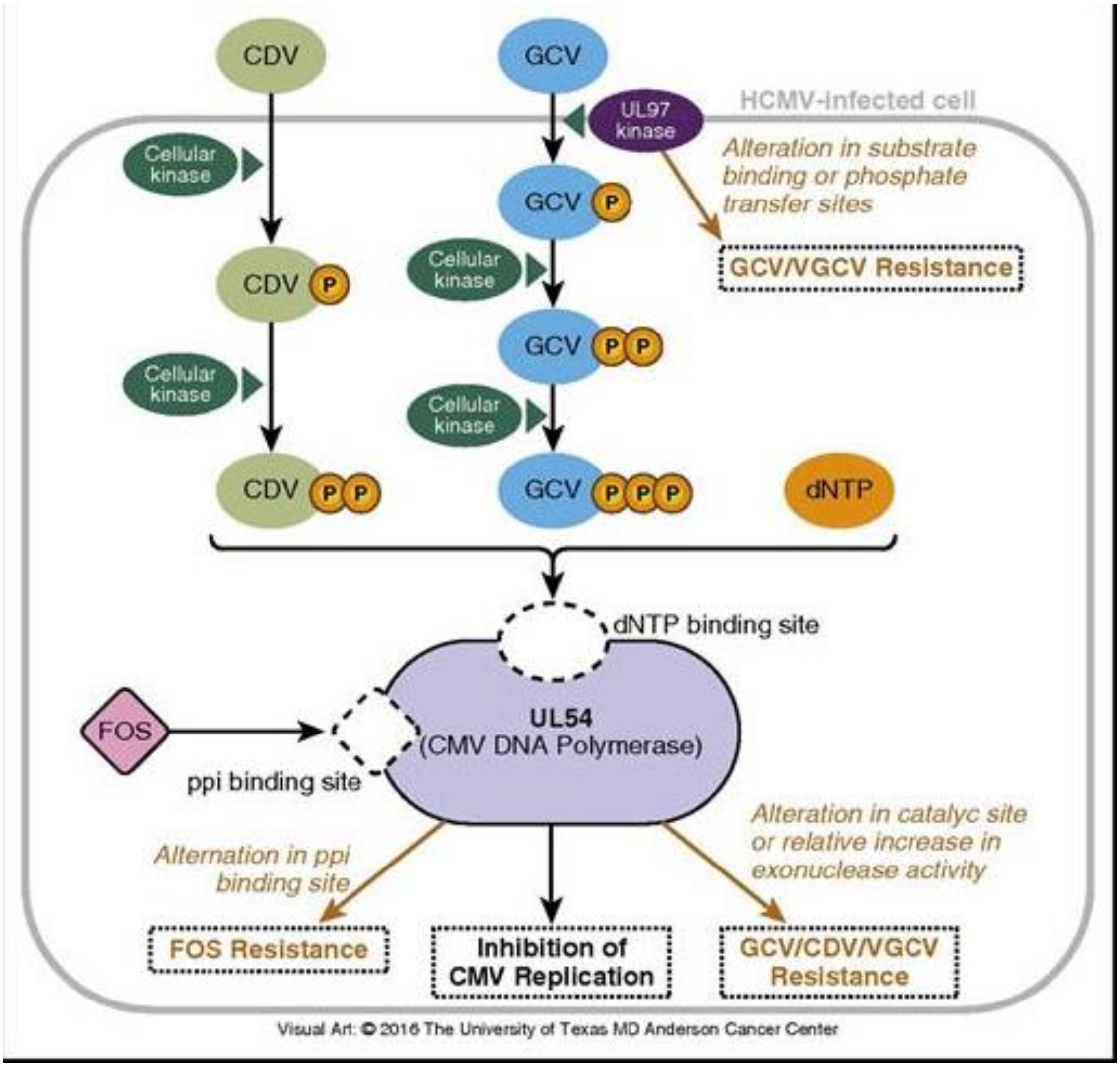

Figure 1 Mechanisms of CMV Resistance [43].

Recently, the antiviral letermovir has gained traction as a non-inferior alternative to valganciclovir as seen in recent studies comparing the two in high risk CMV seronegative kidney transplant recipients who received organs from CMV seropositive donors [44]. Letermovir is an antiviral active against CMV without associated myelotoxicity, does not require dose adjustment for kidney impairment, has a unique mechanism of action as an inhibitor of the CMV DNA terminase complex, and is not associated with cross-resistance to other anti-CMV agents [45]. Letermovir resistance has also previously not been observed, though breakthrough infections are not uncommon [46].

Epstein Bar virus (EBV) is a herpes virus can cause a wide spectrum of clinical conditions in SOTr from uncomplicated infectious mononucleosis to true malignancies. This phenomenon becomes clinically relevant when T-cell immunity is blunted by immunosuppressive medications after transplant, as the infected latent B cells can lead to post-transplant lymphoproliferative disorders (PTLD) [47]. PTLD comprise a heterogeneous group of lymphoid or plasmacytic proliferations/neoplasms which can occur after SOT or hematopoietic stem cell transplantation [48]. Seronegative EBV patients are at particularly higher risk for developing PTLD prior to transplant. Though PTLD can develop any time after SOT, 60-80% of patients are diagnosed within the first year after transplant [49, 50]. The incidence of PTLD increases again within 10 years post SOT (late onset PTLD), and very late onset PTLD occurring more than 10 years after SOT. Risk factors for the development of PTLD includes EBV status of the donor and recipient, with highest risk in cases of D^+/R^-, type of organ transplanted, age of transplant, and type of immunosuppression, with higher rates seen in patients on calcineurin inhibitors, and ATG [50]. Compared with the standardized immunosuppressants calcineurin such as cyclosporine A and tacrolimus, mTOR inhibitors such as sirolimus and everolimus has the potential to decrease the risk of PTLD [50, 51].

Studies have previously suggested that early-onset PTLD portends a better prognosis, better response to reduced immunosuppression, and improved overall survival compared to late-onset PTLD [52]. The advent of the CD20 inhibitor, rituximab, has led to significantly improved remission rates in SOT recipients, with complete remission seen at 87% in patients treated with rituximab in kidney transplant recipients. The incidences of PTLD are approximately 1-3%, 1.2-7.5%, and 20% in renal and hepatic transplant recipients, thoracic transplant recipients, and small bowel transplant recipients [53].

Varicella Zoster virus (VZV) is a herpes virus that is acquired via direct contact with skin lesions or through airborne spread. Most adults are seropositive for VZV having been infected during childhood, or after gaining immunity from vaccination. Acute varicella typically presents with fever, malaise, and diffuse pruritic vesicles which eventually crust over, a syndrome commonly known as chicken pox [54]. After the initial infection, VZV lies dormant in a dorsal root ganglion. Patients may present years later with reactivated herpes zoster, a flare of vesicular lesions in a dermatomal pattern often associated with severe neuropathic pain. Lung transplant recipients are at risk for severe disseminated VZV, thus pre-transplant screening is essential. Those seronegative prior to transplant should get vaccinated prior to surgery [55]. After the transplant, live-attenuated vaccines like Varivax are not routinely recommended, but patients can still safely be administered Shingrex. Treatment for VZV is with acyclovir, valacyclovir, or famciclovir.

Community-acquired viruses can cause detrimental infections after lung transplantation as well. These include influenza, parainfluenza, human rhinovirus, adenovirus, respiratory syncytial virus, and various coronaviruses, including the novel SARS-COV-2 virus [56]. Transplant recipients and their close contacts should be counseled on the importance of prevention, with emphasis on hand washing, mask-wearing, and staying up to date with available vaccines, such as for RSV. Figure 2 shown common antiviral regimens for CMV. Rhinovirus, coronavirus, and influenza are the most frequently isolated viruses in both upper and lower respiratory specimens in this population [57, 58]. In fact, studies have shown that influenza and paramyxoviruses related infections account for about half of emergency room visits and hospitalizations for lung transplant patients in a given year [58]. Another important consideration with lower respiratory tract infections in transplant

recipients is the immunomodulatory effect of these infections have on allograft survival. Lower respiratory tract infections such as RSV to lead to CLAD [59].

Preferred Drugs	**Antiviral prophylaxis**	**Treatment**	**Side effects/Remarks**
Valganciclovir	900 mg PO once daily	900 mg PO twice daily	Bone marrow suppression - Leucopenia
Ganciclovir IV	5 mg/kg once daily	5 mg/kg twice daily	Bone marrow suppression - Leucopenia
Alternative drugs	**Antiviral prophylaxis**	**Treatment**	**Side effects/Remarks**
Oral ganciclovir	1 g PO thrice daily	Not recommended	Leucopenia, high pill burden Induction of resistance
Valaciclovir	2 g PO four times daily	Not recommended	Only in kidney recipients Second line even in kidney SOT High pill burden
Foscarnet	Not recommended	60 mg/kg IV every 8 h or 90 mg/kg every 12 h	Used in high level UL97 mutant ganciclovir resistance Nephrotoxic
Cidofovir	Not recommended	5 mg/kg once weekly × 2, followed by q 2 weeks thereafter.	Used as alternative drug in UL97 mutant ganciclovir resistance Nephrotoxic

Figure 2 Common antiviral regimens for CMV [20].

4. Fungal Infections

Lung transplant recipients are at greater risk for invasive fungal infections among all SOTs because of direct exposure of the allograft to fungi in the environment, intense immunosuppression, and impaired lung host defenses [60]. Invasive fungal infections occur withi one year of transplant in 3-19% of cases, and are associated with high morbidity and mortality, as well as significant healthcare cost [60]. Fungal infections may clinically present as ulcerative tracheobronchitis, invasive pneumonia, systemic fungemia, or disseminated disease [61]. Fungal infections after lung transplant have high mortality rates, particularly in the context of disseminated disease, thus optimizing the right prevention strategy is critical. Fungal infections have also been associated with the development of bronchiolitis obliterans and chronic rejection. The current 3-month mortality rate of all lung transplant recipients with invasive fungal infections is about 22%, whereas the 1-year mortality rate is around 44% [62].

The most common invasive pathogen is Aspergillus. Mucor, non-aspergillus molds, Cryptococcus neoformans, Pneumocystis jirovecii, and the endemic mycoses are less common [63]. Manifestations of fungal disease include colonization, tracheobronchial infections, invasive fungal infection, and anastomotic fungal infections. The mortality rate of tracheobronchitis is typically low, but local complications such as tracheobronchomalacia, stenosis, and dehiscence may occur [64]. Fungal colonization is also risk factor for chronic rejection and subsequent allograft failure [65]. Azoles are frontline agents for treatment of invasive infections, with local debridement as needed for tracheobronchial disease. Antifungal prophylaxis is commonly administered, but benefits and optimal regimens are not well defined. Prophylaxis regimens involve azole therapy, typically with posaconazole, voriconazole, or isavuconazole. Studies have shown isavuconazole as non-inferior to voriconazole for the primary treatment of suspected invasive mold disease, and is typically better tolerated than voriconazole with less drug related adverse effects [66]. Inhaled agents such as amphotericin B are usually reserved for severe tracheobronchitis or anastomotic infections [67].

Pneumocystis jiroveci prevention is usually done with trimethoprim-sulfamethoxazole, atovaquone, or pentamidine.

Fungal pneumonias in lung transplant recipients are typically suspected based on chest imaging, change in spirometry, and positive cultures. Patients may be asymptomatic, or present with productive cough and dyspnea. Imaging may show infiltrates or nodules. A bronchoalveolar lavage (BAL) is often done to obtain deep respiratory cultures. Invasive aspergillosis is the most common fungal pneumonia, for which first line treatment is typically voriconazole [68]. Amphotericin B is an alternative if unable to tolerate voriconazole. Echinocandins are often reserved only as salvage therapy for invasive aspergillosis [69]. Aspergillomas are often treated with surgical resection, often with systemic antifungal therapy. Often treatment for invasive aspergillosis is based on probable disease, as histopathology for definite disease is not always obtainable [70]. Probable invasive aspergillosis is based on the presence of a combination of host factors, clinical features, and positive mycology. A diagnosis of possible disease is made in the presence of host factors and clinical features but in the absence of or with negative mycological criteria [71].

Fungal infection is often suspected when pseudomembranes are seen on bronchoscopy, there is irregularity of the airways on inspection, or there is extraluminal air on chest imaging. Diagnosis requires fungal cultures, stain and biopsy Positive cultures for aspergillus in sputum has been linked with subsequent anastomotic complications. These patients are typically treated with prolonged antifungal prophylaxis. The reported incidence of anastomotic fungal infections ranges from 4.9% to 24.6% [72, 73].

Galactomannan is a polysaccharide present in the cell wall of Aspergillu*s* species. Serum galactomannan antigen titers can be tested for to help aid diagnosis [74]. In patients with impaired immunity, antigen testing is more specific because there are many cases with no Aspergillus galactomannan antibody response, even if in the presence of invasive disease. BAL can also be used to test for galactomannan, and is more sensitive and specific than serum assays. Another marker for detecting fungal infection is 1,3-beta-D-glucan. This is a cell wall in many fungal species, except Cryptococcus spp*.,* zygomycetes, *and* Blastomyces dermatitidis*,* which either lack glucan entirely or produce it at a minimal level. A key advantage of using 1,3-beta-D-glucan analyses is that only serum is required [75].

Resistance to azole antifungals has been shown via both acquired resistance and intrinsic resistance. Azole resistance is increasing over time, especially for organisms like Scedosporiuum or Mucor [76]. Isavuconazole is FDA-approved to treat invasive forms of aspergillosis and mucormycosis as well as voriconazole resistant candidiasis [77]. Ibrexafungerp is an oral glucan synthase inhibitor which is a promising agent for treatment of invasive candidiasis, including azole resistant candida [78]. Other agents that are currently on the market include rezafungin, oteseconazole, olofim, fosmanogepix, and opelconazole (Table 2) [79].

Table 2 Review of available Azoles.

Azole	Brand name	Common Indication
butoconazole	Gynazole-1, Mycelex-3	uncomplicated and recurrent vaginal candidiasis
clotrimazole	Lotrimin	oral and vaginal candidiasis, and tinea versicolor, cruris and pedis
isoconazole	Icaden, Travogen	tinea pedis and vaginal candidiasis

ketoconazole	Nizoral	seborrhoeic dermatitis, dandruff, tinea and cutaneous candidiasis
miconazole	Monistat, Desenex	dermatophytosis and cutaneous, oral and vaginal candidiasis
oxiconazole	Oxistat, Oxizole	dermatophytoses and cutaneous candidiasis
fluconazole	Diflucan	dermatophytoses and cutaneous candidiasis
fosfluconazole	Prodif	prophylaxis in the immunocompromised
fosravuconazole	Nailin	onychomycosis
isavuconazonium	Cresemba	mucormycosis and invasive aspergillosis
itraconazole	Sporanox, Orungal	aspergillosis, histoplasmosis, coccidioidomycosis and blastomycosis
posaconazole	Noxafil, Posanol	invasive candidiasis, aspergilosis, mucormycosis and scedosporiosis
voriconazole	Vfend	aspergillosis, candidiasis, penicilliosis, histoplasmosis and fusariosis

5. Mycobacteria

Mycobacterial infections should also be in the differential when a lung transplant recipient presents with new nodules on chest imaging [80]. This risk is highest in the subgroup of patients undergoing lung transplantation, with reported incidence rates ranging from 6.4% to 10% [81]. TB remains a diagnostic and time-consuming challenge, though the introduction of nucleic amplification tests has been beneficial in obtaining more rapid results. Patients are typically tested for latent TB and if positive, then tested for active TB. The cornerstone of treatment involves a multidrug regimen with a prolonged treatment course to achieve complete eradication. Complicating TB in lung transplantation further is the considerable risk for drug-drug interactions between antitubercular agents and common immunosuppressive medications. Rifampin for example induces hepatic enzymatic activity that promotes rapid metabolism of immunosuppressive drugs and is possibly associated with acute rejection.

6. Non-Tuberculous Mycobacteria

Non-tuberculous mycobacteria (NTM) are saprophytic organisms ubiquitous in the environment, commonly found in soil, dust, and water supplies. Infection typically occurs on average 2 years after transplantation, as most infections are acquired after transplant. In SOTr, the disease can be limited to soft tissues/skin, musculoskeletal, catheter-related infections, pulmonary disease, or present as disseminated disease. Lung transplant recipients in particular may develop surgical wound and bronchial vascular anastomotic NTM infections in the early perioperative period, often due to M. abscessus [82]. The pulmonary disease often presents as nodules, infiltrates, or cavity nodules/abscesses. Like the treatment for TB, a multidrug regimen is required for NTM infections for complete eradication and to limit the risk of developing drug resistance (Table 3).

Table 3 Common NTMs and treatment algorithms.

NTM Species	Drug Regimen	Duration of Therapy
Mycobacterium avium complex	Non-cavitary nodular: clarithromycin 1,000 mg or azithromycin 500 mg TIW + ethambutol 25 mg/kg TIW + rifampin 600 mg TIW	12 mon of negative sputum conversion
	Cavitary: clarithromycin 1,000 mg or azithromycin 250 mg daily + ethambutol 15 mg/kg daily + rifampin 450-600 mg daily + and/or streptomycin 10-15 mg/kg IM TIW or amikacin 10-15 mg/kg IV TIW	12 mon of negative sputum conversion
Mycobacterium abscessus complex	amikacin 10-15 mg/kg IV daily + cefoxitin up to 12 g IV or imipenem 1,000-2,000 mg IV daily + clarithromycin 1,000 mg or azithromycin 250 mg daily	12 mon of negative sputum conversion
Mycobacterium kansasii	isoniazid 5 mg/kg daily up to 300 mg daily + rifampin 10 mg/kg daily up to 600 mg daily + ethambutol 15 mg/kg daily OR clarithromycin 1,000 mg or azithromycin 250 mg daily + rifampin 10 mg/kg daily up to 600 mg daily + ethambutol 15 mg/kg daily	12 mon of negative sputum conversion

7. Conclusion

Transplanted lung allografts are particularly susceptible to infection among SOT due to the constant exposure to the environment, aggressive immunosuppressive strategies, and impaired clearance mechanisms after denervation of the transplanted lung. Though prophylactic antimicrobial, antifungal, and antiviral regimens are used as preventive strategies to mitigate the risk of infection, complications related to allograft infection remain one of the primary causes of morbidity and mortality after lung transplantation. Recent advances particularly with novel antifungals, and novel antivirals for treating resistant CMV infections, have been especially promising.

Author Contributions

Dr. Chakravorty did the literature review and manuscript write up. Dr. Patel did the editing.

Competing Interests

The authors have declared that no competing interests exist.

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