



# Bacterial infections in lung transplantation

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*Contributions:* (I) Conception and design: D Pitrak; (II) Administrative support: None; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: None; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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**Abstract:** Lung transplantation has lower survival rates compared to other than other solid organ transplants (SOT) due to higher rates of infection and rejection-related complications, and bacterial infections (BI) are the most frequent infectious complications. Excess morbidity and mortality are not only a direct consequence of these BI, but so are subsequent loss of allograft tolerance, rejection, and chronic lung allograft dysfunction due to bronchiolitis obliterans syndrome (BOS). A wide variety of pathogens can cause infections in lung transplant recipients (LTRs), including a number of nosocomial pathogens and other multidrug-resistant (MDR) pathogens. Although pneumonia and intrathoracic infections predominate, LTRs are at risk of a number of types of infections. Risk factors include altered anatomy and function of airways, impaired immunity, the microbial flora of the donor and recipient, underlying medical conditions, and genetic factors. Further work on immune monitoring has the potential to improve outcomes. The infecting agents can be derived from the donor lung, pre-existing recipient flora, or acquired from the environment over time. Certain infections may preclude lung transplantation, but this varies from center to center, and more recent studies suggest fewer patients should be disqualified. New molecular methods allow microbiome studies of the lung, gut, and other sites that may further our knowledge of how airway colonization can result in infection and allograft loss. Surveillance, early diagnosis, and aggressive antimicrobial therapy of BI is critical in LTRs. Antibiotic resistance is a major barrier to successful management of these infections. The availability of new agents for MDR Gram-negatives may improve outcomes. Other new therapies, such as bacteriophage therapy, show promise for the future. Finally, it is important to prevent infections through peri-transplant prophylaxis, vaccination, and infection control measures.

**Keywords:** Bacterial infections (BI); lung transplantation

Submitted Jun 23, 2020. Accepted for publication Feb 18, 2021.

doi: 10.21037/jtd-2021-12

View this article at: <http://dx.doi.org/10.21037/jtd-2021-12>

## Introduction

Lung transplantation has lower survival rates compared to other solid organ transplants (SOT) as a result of higher rates of infections and rejection (1-4). Infectious complications cause significant morbidity and mortality at all time points post-transplantation and the cause of death in a majority of lung transplant recipients (LTRs) (5). Bacterial infections (BIs) are the most frequent

infectious complications. Despite modern approaches to immunosuppression and antimicrobial prophylaxis, opportunistic pathogens can still cause infection, but BIs predominate, most frequently in the first year for all SOT, including lung transplants (3). In the Swiss Transplant Cohort Study, 55% of all LTRs developed infections in the first year, and 63% of these infections were bacterial (5). Another study reported 69% of LTRs were diagnosed with BIs, most often with Gram-negative isolates (6). There was

reduced survival with *A. baumannii* infections, and overall 43% developed bronchiolitis obliterans syndrome (BOS). Overall 50–85% of LTRs have at least one episode of BI (7). Most BIs occur in the early post-transplant period and upwards of 80% affect the lung, mediastinum, and pleural space (2,5). While BIs are common, they have lower mortality compared to viral or fungal infections (8,9). In absolute numbers, however, bacterial pneumonias are responsible for most of early infectious deaths (10,11). Other serious life-threatening BIs also occur. BIs are a problem for pediatric LTRs as well as adult LTRs (12).

Infections also play a role in rejection and chronic allograft dysfunction (13). Chronic rejection characterized as obliterative bronchiolitis on pathological examination is a major barrier to lung allograft survival. Infections increase the risk of BOS, and BOS is subsequently the major predisposing factor for increased risk of infections (14). Each class of infection (bacterial, viral, and fungal) has been associated with chronic allograft dysfunction (15).

### Risk factors

The risk of BIs is the sum of exposures to infectious agents and effects of immunosuppression on host defense to these agents. LTRs are at risk for infection with common nosocomial pathogens, as well organisms with which they colonized or infected pre-transplant. Twenty-three percent of LTRs with deep surgical site infections were infected with organisms colonizing the patient's native lungs pre-transplant (16). In particular, cystic fibrosis (CF) patients are frequently affected by infections with MDR organisms pre-transplant, and this leads to recurrent infections with these organisms and poor outcomes.

### Time after transplant

Similar to other SOT, the risk of infection, including BIs, following lung transplantation varies according to time from transplant (17,18). The vast majority of infections occur in the first year following transplant, with most BIs occurring in the first 3 months post-transplant (19). Pneumonia is common, but deep surgical site infections, empyema, wound infections, mediastinitis, sternal osteomyelitis, and pericarditis also occur, and are associated with decreased survival at 1 year (19,20).

Risk factors for late infections in different SOT, occurring >6 months post-transplant, include acute rejection occurring in the early post-transplant period, relapsing

CMV infection, and previous BIs (21). Lung transplantation itself is a risk factor compared to other SOT.

### Etiologic agents

In the first month post-transplant, infections with hospital-acquired multidrug-resistant (MDR) pathogens such as vancomycin-resistant *Enterococcus* (VRE), methicillin resistant *Staphylococcus aureus* (MRSA), and MDR *Pseudomonas aeruginosa* (PsAR) and other gram-negative rods (GNRs) predominate (22–27). There are a number of sources of these infections, including both donor and recipient lungs, central and peripheral intravenous catheters, arterial catheters, urinary catheters, wounds, and leaks at the anastomoses. *Corynebacterium spp.* have been associated with infections of the anastomosis and stents (28). *Mycoplasma hominis* can cause intra-thoracic infections (29,30). *Clostridium difficile* infection (CDI) is also a frequent complication (31,32). Some LTRs have a particularly difficult time with pathogens unique to their underlying pulmonary disease, for example, pneumonia with *Burkholderia spp.* in CF patients (33).

Between one and six months post-transplant, anastomotic leaks and CDI continue to be prevalent. Most patients in this period receive routine *Pneumocystis jirovecii* pneumonia (PCP) prophylaxis with trimethoprim-sulfamethoxazole (TMP/SMX), which may also prevent BIs. Despite this, breakthrough infections with *Nocardia* are occasionally seen. *Mycobacterium tuberculosis* (MTB) and other mycobacterial may arise.

Greater than six months post-transplant, common community-acquired pathogens causing pneumonia and urinary tract infections (UTIs) are encountered. *Strep. pneumoniae* becomes a significant pathogen. *Nocardia spp.* and *Rhodococcus equi* infections have also been reported.

### Pathogenesis

The factors leading to BIs after lung transplantation include anatomic abnormalities, potent immunosuppression, the recipient's own colonizing flora, the flora of the donor and the allograft, and changes in flora post-transplant with constant exposure to the environment, as well the patient's own genetic makeup.

### Anatomic factors

LTRs have altered anatomy that predisposes them to

infection, most specific for pneumonia. There is impaired cough reflex, decreased mucociliary clearance, disruption of bronchial circulation lymphatic drainage, all of which contribute to risk of pneumonia (34,35). Bronchial stenosis is associated with higher rates of tracheobronchitis, pneumonia, and more inpatient days (36).

### *Immune factors*

Lung transplantation has been described as “an immune state characterized by an increase in infections and an alloreactive state” (37). Intensification of immunosuppression to manage rejection and BOS dramatically raises the risk of infection.

Immune suppression reduces Th1 cytokines and decreases macrophage function, impairing host defense against BIs. Patients who have infections have decreased T cell intracellular cytokine production by cells collected by BAL compared to patients without infection (38).

Investigators have studied measures of immunosuppression to determine infection risk (39). The Cylex ImmuKnow assay assesses the function of lymphocytes by measuring production of ATP in response to mitogen stimulation. In 175 LTRs who had 129 infectious episodes, the ATP values for patients developing CMV disease or BIs were significantly lower compared to stable patients (40).

Humoral immune defects also occur, even if patients have not received induction therapy or anti-rejection therapy targeting B cells. Goldfarb reported that 70% of LTRs developed hypogammaglobulinemia (HGG), and in 37% it was severe (IgG <400 mg/dL) (41). Severe HGG was associated with an increased risk for bacterial and fungal infections and increased mortality. Pediatric LTRs also develop significant HGG associated with increased risk of infection and length of hospital stay (42). HGG is not unique to lung transplantation, occurring with other SOT, with severe HGG occurring in 15% (43). A meta-analysis of HGG in SOT calculated a 21.9 times higher relative risk of death for patients with severe HGG in the first year post-transplant (44). Some authorities have recommended routine monitoring for HGG in SOT and replacement therapy when appropriate (45). Other measures of humoral immunity (IgG subsets, IgA, complement levels, pathogen-specific titers, etc.) may also predict BIs (46,47). Pre-transplant levels of IgG and IgA may also be predictive (48,49). Despite the potential benefit of assessing immune markers to determine the risk for BIs, there is no test or set of tests that are currently recognized as a standard of care (50).

### *Microbial flora*

The microbiome of LTRs plays an important role in the pathogenesis of BIs. Although donor graft, blood, and preservation fluids may be infected with MDR bacteria, these usually do not cause infection in the recipient if appropriate prophylaxis directed against the donor isolates (51). The recipient's pre-transplant flora is very important. Patients with high bacterial burden, i.e., those with CF and bronchiectasis, are especially problematic (52,53). Antibiotic resistance due to previous antibiotic exposure contributes to poor outcomes (23-28,52,54). Even though native lungs are removed, rapid colonization of the allograft with pre-transplant strains occurs, perhaps from a focus in the sinuses (55-57). Infections with certain pathogens, including PsAR, *Stenotrophomonas*, *Burkholderia spp.*, and mycobacteria adversely affect outcomes in LTRs and are carefully considered during recipient selection. Colonization or infection with MDR bacteria may be a contraindication to lung transplantation (58). Infection with *B. cepacia* was often associated with poor outcomes and considered a contraindication to transplantation (59). *B. cepacia*, however, is actually a complex of several distinct species. Certain species of the *Burkholderia cepacia* complex, such as *B. gladioli* and *B. cenocepacia*, contribute more to poor outcomes than other species (60). The data on the effects of existing microbial flora on outcomes has varied from study to study. Several studies have shown the presence of MDR bacteria does not necessarily increase the risk of infection or death (61,62). Each center needs to decide if colonization or infection with MDR-GNRs precludes lung transplantation (63,64). Non-tuberculous mycobacterial infections may also have excess morbidity and mortality, but again, these infections may not be a contraindication to transplantation (65-71).

### *Microbiome*

New molecular methods have allowed characterization of the microbiome of respiratory tract, gut, and other sites. SOT and stem cell recipients all have changes in the gut microbiome, a consequence of antibiotic therapy (72). The gut microbiome can significantly affect pulmonary health in CF. The microbiome of the lower respiratory tract in patients with chronic pulmonary disease, such as CF, is complex (73). LTRs have a unique microbiome that is different from pre-transplant, and there are further changes over time (57,74,75). Studies are underway to

understand the relationship between the microbiome and post-transplant infections, rejection, and chronic allograft dysfunction.

### Genetics

Genetic studies also have the potential of providing insights into the pathogenesis of BIs in LTRs. Polymorphisms in TLR4 that mediate endotoxin hypo-responsiveness were associated with a significantly lower risk of rejection in the first 3 years in LTRs, with a trend toward decreased risk of BOS (76). Innate immune signaling is a potential therapeutic target for preventing allograft rejection. Genetic studies in heart transplant patients may also be pertinent to the risk of infections in LTRs. Late BIs were associated with polymorphisms of HMOX1, a gene regulating neutrophil activation, while viral infections were associated with polymorphisms of CTLA4, a regulator of T cell activation (77). Stem cell transplant recipients with a genetic deficiency of pentraxin 3 (PTX3), a soluble pattern recognition receptor that is important in innate immunity, have increased risk of invasive aspergillosis due to reduced antifungal capacity of neutrophils (78). In CF, it is known that colonization with PsAR is associated with reduced levels of PTX3 in airway sections (79,80). Future studies will likely uncover other genetic predispositions to BIs in LTRs.

### Other recipient related factors

LTRs with renal failure, morbid obesity, or malnutrition are at increased risk of infection. Preceding viral infections, especially influenza A, can lead to bacterial superinfection (81). Mechanical ventilation and ECMO pre-transplant are associated with higher mortality, possibly related to a higher risk of BIs, but may not be a contraindication (82,83). Recipients treated with corticosteroids or antibiotics prior to transplantation have a higher incidence of BIs. Finally, lung transplantation for HIV-infected patients might be expected to have a greater risk of infection due to impaired immunity. The data is limited compared to kidney and liver transplants, but it seems HIV-infected LTRs have similar survival rates LTRs without HIV (84).

### Effects of bacterial infections on lung allografts

Infections can adversely affect graft function, increasing the risk of rejection and BOS (7,8,15,85-87). Activation of the

innate immune system can potentiate adaptive immunity and induce lung rejection (88). Microbes stimulate chemokine production and recruitment of leukocytes to the transplanted lung (15). Those leukocytes further upregulate chemokine release and recruitment of mononuclear cells that can initiate an alloresponse. Rat models of lung transplantation have shown that CMV and *Listeria* infections enhance chronic rejection (89). Animal studies show BIs can induce production of G-CSF, subsequent neutrophilia and graft infiltration, inducing acute rejection. Neutrophil elastase activity is increased with BI, and this may contribute to lung allograft damage (90).

Colonization with Gram-negative bacteria, in particular PsAR, can increase the risk of BOS (91-93). Interestingly, recolonization with previous Gram-negative flora in LTRs with CF was protective against chronic allograft dysfunction, while *de-novo* colonization with new Gram-negative species is a risk factor for this complication (94). Studies have suggested a connection between PsAR colonization and gastroesophageal reflux disease (95). Yamamoto and colleagues demonstrated that PsAR infection can stimulate B7 expression on neutrophils infiltrating the lung, resulting in CD4+ T cell activation and abolishing graft tolerance (96). They also showed it is possible to block B7 and still clear PsAR, a potential therapeutic strategy. Increased endothelin-1 is associated with bacterial lung infection, resulting in increased fibrosis, a major part of the pathogenesis of bronchiolitis obliterans (97). CDI has also been associated with BOS, presumably due to systemic inflammation (31,98).

### Diagnosis

Prompt diagnosis of BI and initiation of therapy is critical. The diagnostic evaluation depends on the suspected site(s) of infection. Collection of blood, urine, and sputum specimens for smears and cultures as soon as possible in infectious work-up is very important, as these are the usual sources of infection. Urinary antigen testing can identify pneumonia due to *Strep. pneumoniae* and *Legionella pneumophila*. In the case of *Legionella*, however, urinary testing can be used only for diagnosis of *L. pneumophila* serotype 1. Infection with other serotypes or other species (e.g., *Legionella micdadei*) requires culture, typically from BAL fluid. Bronchoscopy is safe and helpful for the etiologic diagnosis of pneumonia, with results of microbiological samples collected leading to modification of antimicrobial therapy in 35% of cases (99). In LTRs,

there is a non-specific increase in procalcitonin (PCT) post-operatively, followed by a progressive decline during the first week post-transplant. After that an increase in PCT is significantly associated with BI (100). The use of any biomarker, however, is still not standard of care.

### Site specific infections

BIs account for more than half of the infections after lung transplantation, and similar to other SOT, the allograft is most common site of BI (5). LTRs, however, also experience a high incidence of BI at other sites.

#### *Early-onset pneumonia*

Bacterial pneumonia is the most common infection in LTRs, and occurs most frequently during the first month post-transplant (1,7,101,102). LTRs are particularly susceptible to pneumonia because of impaired post-operative function of the lung allograft, impaired mucociliary clearance, and denervation, which interferes with the cough reflex. The lung allograft is the only transplanted organ that is directly exposed to the environment. LTRs are at increased risk for early pneumonia from MDR Gram-positive bacteria (such as MRSA) or GNRs (Enterobacteriaceae, PsAR), especially during prolonged exposure to the healthcare setting (1,5,19,101-105). PsAR is the causative organism most often isolated (33%), followed by *Staph. aureus* (26%) and *Acinetobacter* (16%) (101). Another large retrospective study found that 178 of 208 LTRs experienced a total of 859 infections (106). Most were respiratory tract (65.1%), followed by mucocutaneous (oral mucosa, skin, and wound; 10.2%), and bloodstream infection (BSI) (9.9%). The majority of respiratory infections were bacterial (83.6%), most frequently due to GNRs with PsAR being the single most commonly isolated pathogen. Early post-transplant bacterial colonization and pneumonia may also be related to aspiration events, and gastroparesis plays a role as well (107).

#### *Late pneumonia*

Bacterial pneumonias continue to be a significant complication in LTRs, even after 6 months post-transplant. Though traditional risk stratification for post-transplant infection implicated nosocomial pathogens early and opportunistic pathogens later in the post-transplant course, the evolution of immunosuppression regimens and routine antimicrobial prophylaxis has led ongoing risk of non-

opportunistic BIs occurring at any time in the first year after LT. Delayed onset bacterial pneumonia in LTRs is largely driven by patient exposures and residual immune deficits (108). Patients are still exposed to the healthcare environment, and allowing ongoing risk of acquiring nosocomial pathogens (5,108,109). In one study PsAR was responsible for 54% of respiratory infections occurring after 1 year (106). Community-acquired pathogens (such as *Streptococcus pneumoniae* and *Legionella*), however, may become more frequent than nosocomial pathogens in delayed post-transplant pneumonia as immunosuppression is decreased and patients are less frequently exposed to the hospital (110-114). One retrospective analysis noted an incidence of invasive pneumococcal infection in LTRs of 22.7 per 1,000 patient-years, with a median time of diagnosis of 1.3 years post-transplant (111). Interestingly, all the patients with pneumococcal infections were receiving TMP/SMX, and the isolates obtained were resistant to this agent in 71% of cases. The diagnosis of *Legionella* infection may be difficult and should be considered in patients with progressive pneumonia despite broad-spectrum antibiotic therapy (112-114). *Legionella* infection can be nosocomial or community acquired. LTRs with legionellosis may develop empyema or non-pulmonary infections (8,112).

Bacterial pneumonia as a consequence of viral respiratory tract infection is another important infectious risk in LTRs. Influenza, parainfluenza, and respiratory syncytial virus are all commonly isolated viral pathogens, particularly pneumonia occurring in the past post-transplant period (1,80,106). Secondary bacterial pneumonia contributes significantly to morbidity and mortality associated with influenza infection, responsible for up to 25% of influenza deaths (115-118). The typical superinfecting pathogens are *Staph. aureus*, *Strep. pneumoniae*, and *Haemophilus influenzae*.

#### *Donor-derived BIs*

Donor-derived infections may manifest during the first few weeks after lung transplant. BIs derived from deceased donors may include nosocomial MDR pathogens resistant to routine surgical prophylaxis, such as MRSA, VRE, or MDR GNRs (103,119,120). Culture data on bacteria present in the donor allograft and recipient lungs prior to transplant can be helpful in targeting post-transplant antimicrobial prophylaxis (100). One study found that 21% of BIs in LTRs were due to bacteria colonizing the donor lung, compared to 40% of BIs due to bacteria colonizing the recipient pre-transplant (106). Other studies have shown donor lung colonization does not

change the incidence of pneumonia post-transplant, and outcomes may not be different if donor-derived bacteria are not appropriately covered by the prophylactic antibiotics administered (121-123).

### ***BIs in CF***

Patients with CF are at increased risk for both early and delayed bacterial pneumonia after lung transplantation due to underlying bacterial colonization with MDR pathogens, as well as ongoing dysfunction of native sinus tracts and upper airways (33,52,56,57,62-64,124). Many studies have shown that CF patients are more likely to have positive pre-transplant sputum or BAL cultures and are at increased risk for post-transplant pneumonia from these colonizing organisms. The data on outcomes with pre-transplant colonization are variable, and it is not clear that mortality is higher (54,59-64,124,125). CF patients may also be at increased risk for BSI or SSTI after lung transplant, though most case series are limited by small numbers patients in single-center cohorts (16,126).

### ***Tracheobronchitis***

Bacterial tracheobronchitis occurs when airways with prior mucosal damage develop infection, most frequently from pathogens colonizing the upper respiratory tract, and thus occurs most frequently in the first 3 months after lung transplantation. In LTRs the anastomosis of native upper airways with donor bronchi is particularly prone to infection, especially when the anastomosis is poorly vascularized or bronchial stenosis is present (36,108). Diagnosis of tracheobronchitis is typically made by bronchoscopy revealing purulence, ulceration, necrosis, or dehiscence. Tracheobronchitis occurred before bacterial pneumonia in 90% of cases in one cohort study (105). Gastroparesis and aspiration increase the risk for both tracheobronchitis and pneumonia in mechanically ventilated patients, and ventilator-associated tracheobronchitis has been associated with longer duration of ventilation and length of stay (107,127).

### ***Empyema***

Infections of the pleural space early after LT are often precipitated by accumulation of fluid after removal of post-surgical chest tubes, either related to pneumonia or hemorrhage. Empyema has been reported in 3–5%

of LTRs, often occurring during the first 2 weeks post-transplant (20,128,129). Although uncommon, it is particularly important to identify pleural space infection in LTRs as this is associated with increased mortality. In a study of 392 LTRs, the incidence of empyema did not differ between type of lung transplant (unilateral or bilateral) or among indications for transplant (128). The investigators did note that prophylactic antibiotics may have lowered the expected rate of empyema among the few CF patients in this study.

### ***Mediastinitis and sternal osteomyelitis***

Mediastinitis after sternotomy is associated with high morbidity and mortality, especially after heart and lung transplantation. The incidence of mediastinitis after cardiothoracic surgery is usually reported to be 1%, but there is a higher risk associated with ECMO, cardiac assist devices, or organ transplantation (16,130-132). In one single center study, 16% of patients at a single center developed mediastinitis post-transplant (16). Although *S. aureus* has been identified as the most common causative organism in cardiac transplant-associated mediastinitis, numerous other pathogens (including PsAR, *Staph. epidermidis*, *Escherichia coli*, and *Klebsiella pneumoniae*) have been implicated in mediastinitis occurring in LTRs (130). Sternal osteomyelitis is also on the spectrum of deep surgical site infections and has been reported in 6% of LTRs (16). Surgical approach, presence of hardware, and sternal vascularization may increase the risk of sternal osteomyelitis. Surgical debridement for mediastinitis and sternal osteomyelitis has been associated with better outcomes than antibiotic therapy alone.

### ***Blood stream infections***

BSIs have been reported to occur in 11.5% of LTRs (133). While the lungs are an important source of BSI, especially in the early post-transplant period, vascular catheters and CF have also been found to increase the risk for BSI. BSI in LTRs have been independently associated with increased mortality, up to 25% (106,126,133,134).

### ***Other BIs***

LTRs are also at risk for other BIs, including urinary tract infections (UTIs), skin and soft tissue infection (SSTI), and diarrhea from CDI. UTI has been reported in 3.1%

of LTRs in one study, with PsAR being most frequently implicated (106). SSTIs may be seen in the early post-transplant period. One study found that 29% of LT recipients experienced soft tissue surgical site infection (36). The risk of SSTI is supported by more recent guidelines on surgical site infections (SSI) in LTRs (135). ECMO may increase the risk for SSI infection in LTRs (136). SSTI occurring later in the post-transplant period may be related to poor wound healing associated with certain immunosuppressive agents.

SOT recipients are at increased risk for CDI due to prolonged hospital exposure, immunosuppressive use, and antibiotic prophylaxis (31,32,98). CDI incidence in LTRs has been estimated between 7–33% (137). In the Swiss Transplant Cohort Study, LTRs had higher incidence of CDI compared to all other SOT recipients (31). CDI after lung transplantation has been associated with increased risk of graft loss, as well as being an independent risk factor for mortality.

### Atypical pathogens

Mycobacterial infection after lung transplantation is relatively uncommon, but the risk of infection with MTB and non-tuberculous mycobacteria (NTM) is greater than the general population (65-71,103,138). SOT recipients have increased incidence of MTB infection, and in general LTR are at greater risk (139-144). In countries where MTB disease is endemic, disease most often occurs from reactivation of latent TB infection (LTBI). MTB can also be derived from the donor (145).

Several NTM have been reported to cause infection, but *M. abscessus* has been particularly problematic (65-71,146-149). Doucette *et al.* reported a case of a LTR with *M. abscessus* of the sternum requiring extensive debridement (146). Recipient cultures were positive for *M. abscessus* prior to the transplant. *M. abscessus* is observed in LTRs at an increased incidence compared to other SOT. In LTRs, it may cause SSTIs, pneumonia, and even disseminated disease. The most common presentation in all SOT recipients is cutaneous disease. These infections are reported throughout the post-transplant period without a partiality to a specific time period. Pleuropulmonary disease is most commonly described in LTRs. There is an increase in both mortality and disseminated disease associated with *M. abscessus* in SOT recipients. *Mycobacterium avium complex* and other NTM infections occur less frequently, and in general these infections are less severe compared with *M. abscessus*

infection. If clinical, microbiological, and radiographic evidence is concerning for NTM infection pre-transplant, this must be addressed by further evaluation and treatment prior transplantation.

*Nocardia spp.*, partially acid-fast organisms, are encountered less frequently, but infection is associated with increased mortality in LTR (150,151). Husain and coworkers reported that *Nocardia* infections were diagnosed in 0.6% to 2.1% of LTRs, but these patients had a mortality rate 40%, attributed to *Nocardia* in 75% of the deaths (150). LTR who had *Nocardia* infections typically had nonspecific findings on imaging and the tendency for native lung involvement in single LTR. The authors hypothesized that this was the result of structural and functional abnormalities of the native lung versus reactivation of pre-existing infection. LTR receiving TMP/SMX prophylaxis were among those who developed *Nocardia* infection, highlighting that TMP/SMX resistant strains exist and prophylaxis should not preclude *Nocardia* as a potential pathogen in LTRs. Cutaneous disease are the most common form of extra-pulmonary disease and skin lesions have been reported in liver and renal transplant recipients, but in the Hussain study they did not find any cutaneous lesions in their LTRs or reports from other cases they reviewed. *Nocardia* should always be considered as a potential pathogen in LTRs with progressive disease despite appropriate antibiotic therapy. *Rhodococcus equi*, another partially acid-fast organism, has also been reported in SOT, including LTR (152).

*Mycoplasma hominis* may cause infection in LTRs (29,30). Another infection, which may be donor-derived, with unusual consequences is infection with *Ureaplasma urealyticum* or *Ureaplasma parvum* (153-156). Donors with this organism have been young, presumably sexually active, and often had a documented aspiration event prior to death (152). Infection is characterized by lung infiltrates and sepsis, but also a potentially lethal hyperammonemia syndrome with mental status changes and cerebral edema. The hyperammonemia can be prevented or treated with antibiotic therapy, ideally azithromycin with doxycycline or a fluoroquinolone. These atypical pathogens do not grow on routine media, so special cultures or PCR are required for diagnosis.

### Therapy

Therapy of post-transplant BI depends on the time after transplant and results of microbiologic studies. Early removal of infected or potentially infected central venous

catheters, arterial catheters, and urinary catheters is important. In the first month after transplant, nosocomial pathogens predominate, and empiric therapy should have broad-spectrum coverage. Interestingly, MDR pathogens such as *Acinetobacter baumannii*, which are classically seen in the early post-transplant period are now increasingly being seen late (>6 months) in the post-transplant course (157).

Overall rates of infections in LTRs have decreased, but now more infections in SOT involve MDR bacteria, particularly GNRs with extensive resistance (58,158-160). Mortality is higher in thoracic transplant recipients infected with nosocomial pathogens. LTRs may require extended ventilator support and significant exposure to broad-spectrum antibiotics, resulting in extensive drug-resistant GNR infections and CDI. One study of LTRs that excluded patients with CF or survival <30 days looked at the development of *C. difficile* and/or a MDR infection (161). MDR infections occurred in 34% and CDI in 6%. ICU days and duration of receiving Gram-positive antimicrobials were associated with an increased risk. Infections with carbapenem-resistant GNRs have been associated with decrease in allograft and patient survival (158).

### Choice of antibiotic(s)

Directed anti-microbial therapy depends on the pathogen causing disease and the pattern of antimicrobial resistance. The emergence of multi-drug resistant (MDR) pathogens makes this choice particularly difficult, and therapeutic decisions should be based on the results of susceptibility testing (160,161). MRSA can be treated with vancomycin, linezolid, or daptomycin, although daptomycin should be avoided in pneumonia due to MRSA. Vancomycin-resistant *Enterococci* (VRE) can be treated with daptomycin or linezolid. GNRs producing AmpC  $\beta$ -lactamases can be treated with cefepime, but those producing extended spectrum  $\beta$ -lactamases (ESBLs) must be treated with carbapenems. Unfortunately, carbapenem-resistant Enterobacteriaceae (CRE) and carbapenem-resistant PsAR have emerged. *Acinetobacter baumannii* isolates can be extremely drug-resistant, often to most antibiotics. Some of the options for treatment of infections with this pathogen are high-dose ampicillin-sulbactam (with the beta-lactamase inhibitor having the antibacterial effect), carbapenems, or colistin. Colistin has also been used for MDR PsAR infections in LTRs (162). Unfortunately colistin has poor pulmonary penetration when given intravenously, and adjunctive therapy with inhaled colistin is frequently used.

A number of new drugs have been developed for MDR Gram negative pathogens, including ampC beta-lactamase and ESBL producing Enterobacteriaceae, CRE, carbapenem-resistant PsAR, and extensively drug-resistant (XDR) *Acinetobacter* (163,164). Delafloxacin has been shown to be active against ampC and ESBL producing Enterobacteriaceae. Eravacycline has shown potent broad-spectrum activity against a wide variety of microorganisms, including ESBL-producing Enterobacteriaceae and *Acinetobacter*. Drugs that have been approved for treatment of certain CRE infections include ceftazidime-avibactam, meropenem-vaborbactam, cefiderocol, and plazomicin. Ceftazidime-avibactam has been used successfully to treat a LTR with CF who developed *Bulkholderia multivorans* bacteremia and brain abscess (165). It is important that labs have the capability to perform susceptibility testing with established phenotypic tests or multiplex PCR methods for detection of the various  $\beta$ -lactamases. There are some published society recommendations on the management of MDR GNRs in SOT, including lung transplantation (166). *Table 1* lists increasingly prevalent MDR pathogens and reasonable empirical anti-microbial coverage or alternative agents to test for susceptibility.

Less common pathogens include *Nocardia*, *Listeria*, and *Rhodococcus*. For *Nocardia*, treatment with TMP/SMX is generally the first line therapy, although given that many patients are on TMP/SMX develop breakthrough infections, alternative and even therapy (often with carbapenems, cephalosporins, or fluoroquinolones) should be considered (150,151). *Listeria* is occasionally an opportunistic pathogen after SOT, and ampicillin is the drug of choice for this infection (167). Treatment of *Rhodococcus equi* may require administration of multiple agents, guided by the results of susceptibility testing (168). There are guidelines for management of MTB and NTM infections that also pertain to lung transplantation (169,170). Therapy usually consists of multiple anti-mycobacterial drugs, and should be guided by susceptibility data and in consultation with ID specialists. Unfortunately rifamycins, which are frequently a component of these regimens interact with multiple immunosuppressive agents.

### Future options

Another promising approach to treatment of MDR organisms is bacteriophage therapy, and this has already been explored in LTRs with difficult to treat infections. Aslam and co-workers treated 3 LTRs with MDR



**Table 1** Therapeutic options for drug-resistant and multi-drug resistant pathogens

Pathogen	Common sites of infection	Empiric therapy
Gram-positive		
Community- and Hospital-acquired MRSA	Bacteremia	Vancomycin
	Pneumonia (often post-viral)	Daptomycin (not for pneumonia)
	Skin and soft tissue infection	Linezolid
VRE	Bacteremia	Daptomycin (not for pneumonia)
	Intraabdominal	Linezolid
	Pneumonia	
CDI	UTI	
	Colitis	Vancomycin oral + IV flagyl for severe disease Fidaxomicin Bezlotoxumab
Gram-negative		
AmpC beta-lactamase producers	Bacteremia	Cefepime
	Intraabdominal	
	Pneumonia	
	UTI	
Extended-spectrum beta-lactamase producers	Bacteremia	Carbapenems (not Ertapenem for <i>Pseudomonas aeruginosa</i> )
	Intraabdominal	
	Pneumonia	Delafloxacin Eravacycline
CRE	UTI	
	Bacteremia	Cefiderocol
	Intraabdominal	Ceftazidime-avibactam
	Pneumonia	Colistin Meropenem-vaborbactam Plazomicin
<i>Stenotrophomonas maltophilia</i>	UTI	
	Pneumonia	TMP/SMX
	Sinusitis	Fluoroquinolones
<i>Acinetobacter baumannii</i>	Skin and soft tissue infection	Minocycline Tigecycline
	Bacteremia	Colistin
	Intraabdominal	Carbapenems
	Pneumonia	Eravacycline
Pan drug-resistant organisms	UTI	Tigecycline Consider combination therapy
	Bacteria	
	Pneumonia	Consider phage therapy (Compassionate use)
	Non-tuberculous Mycobacteria	Consider phage therapy

VRE, vancomycin-resistant *Enterococci*; UTI, urinary tract infection; CDI, *clostridium difficile* infection; CRE, carbapenem-resistant Enterobacteriaceae.

infections (2 with PsAR, 1 with *Burkholderia dolosa*) (171). Lytic phages were selected against their isolates. The two patients with PsAR infection responded clinically and were discharged. The patient with *B. dolosa* initially responded, but later relapsed and died. Bacteriophage therapy has also been successfully used in treating a LTR with CF with a disseminated *M. abscessus* infection (172).

## Prevention

Infection prevention is critical to reduce the morbidity and mortality associated with BIs in LTRs. This involves a detailed assessment of prior infections, vaccination status in the pre-transplant period, peri-transplant chemoprophylaxis, and reduction of infectious exposures.

### *Pre-transplant screening*

During the transplant evaluation, it is important to review the patient's travel history, prior infections and exposures. This allows the clinician to have a complete understanding of a patient's risk factors in order to develop an appropriate plan to minimize infectious complications peri-transplant. Obtaining sputum samples for bacterial, fungal, and mycobacterial analysis can identify colonization patterns and help inform chemoprophylaxis (173). Of particular importance is screening for tuberculosis (TB). TB is 20–74 times more common in SOT recipients compared to the general population, although the incidence varies significantly by region (140). Post-transplant, active TB infection most commonly results from reactivation of previously latent disease, so identification and treatment of latent TB infection (LTBI) prior to transplant is recommended (140,174). Screening of donors by Quantiferon TB testing has been shown to decrease the risk of donor-derived TB (175).

### *Vaccination*

Vaccination is another important part of the pre-transplant management. All candidates undergoing evaluation for lung transplant should have their immunization status reviewed and assure that routine vaccinations are up to date. At adults with end-stage lung disease receive all vaccines recommended by the Center for Disease Control and Prevention (CDC) guidelines for immunocompetent patients with equivalent age, exposure history, and immune status (176). Protection of LTRs also requires vaccination

of household members and close contacts with all recommended inactivated vaccines.

Necessary vaccines should be administered as early as possible pre-transplant as the immune response to vaccines is decreased in the setting of organ failure and immunosuppression (177). Live attenuated vaccines and inactivated vaccines should be administered at least 4 and 2 weeks prior to transplant, respectively (176). After transplant, the optimal time to vaccinate is not known. Poor immune response to vaccination occurs in the immediate post-transplant period in the setting of intense immunosuppression. Most centers wait 3–6 months after transplant when maintenance immunosuppression is reached to initiate vaccination (177). Live attenuated vaccines should be avoided, but inactivated vaccines can be safely administered.

In the studies of invasive pneumococcal disease by de Bruyn and Kumar, the vast majority of isolates in serotypes are covered by the PPSV23-associated serogroups (100% and 85% respectively) (110,111). Protection, however, is limited due to suboptimal vaccine responses. To improve protection, all vaccinees, immunocompetent or immunocompromised, should be vaccinated using a prime-boost strategy against pneumococcal disease, receiving both the PCV13 and PPSV23 vaccines (176,177). PCV13 should be administered first followed by PPSV23 at least 8 weeks later. A booster dose of PPSV23 should be given 5 years later (177). If the vaccines are not given prior to transplant, they should be given 3–6 months following transplant when immunosuppression is at maintenance levels. Despite the availability of guidelines, a cross-sectional study of one transplant center found that only 62.4% of lung transplant candidates had received pneumococcal vaccination (178).

While SOT recipients can mount an immunologic response to vaccination, it is diminished compared to healthy controls (47,179). Patients vaccinated against pneumococcus pre-transplant frequently have a decline in immunoglobulin levels, including anti-pneumococcal polysaccharide antibodies, in the first post-transplant year (46). On revaccination, there were still suboptimal responses seen, even when boosters were given a median of 4.4 years post-transplant. In one study of renal transplant recipients, vaccine response durability was similar amongst patients who have received the PPSV23 or the PCV7 vaccine (179). A retrospective study of LTRs found PCV7 was immunogenic, but there was no benefit from an additional PPSV23 dose (180). Several studies have investigated whether a prime-boost strategy (PCV7 followed by a

booster with PPSV23 versus PPSV23 alone) may enhance immunogenicity post-transplant. In studies of kidney and liver transplant recipients, there was no significant difference in immunogenicity with either approach (181-183).

LTTs or candidates for lung transplant may also benefit from vaccination against *Haemophilus influenzae* type B (Hib), *Neisseria meningitidis*, and tetanus. There is limited data on the use of these vaccines in transplant patients, but in general, guidelines should be followed (176,177).

Small case-control and cohort studies have implicated vaccinations in allograft. Most of the reports were in heart or kidney transplant recipients receiving seasonal influenza vaccine, particularly the H1N1 vaccine (184,185). Larger studies have not shown any significant association. A recent systematic review and meta-analysis investigated rates of *de novo* donor-specific antibody (DSA) production and rejection after vaccination of SOT recipients (186). This review found no increased risk of DSA development, rejection, or graft failure among vaccinated patients. These studies support the safety and efficacy of vaccination in transplant populations (178,187).

### *Passive immunization*

There are no specific recommendations regarding the use of nonspecific intravenous immunoglobulin (IVIG) or pathogen-specific immunoglobulin preparations to prevent BI in LTRs. Uncontrolled studies of IVIG replacement in heart transplant recipients have shown benefit (188). Studies investigating the effects of IVIG replacement therapy for LTRs with HGG, however, have not shown any impact of IVIG on rates of infection, chronic lung allograft dysfunction, or survival (189,190). Further study is needed in this area.

### *Peri-transplant prophylaxis*

Peri-transplant infection can occur as a result of pathogens present in the donor, the recipient, or from new hospital-acquired pathogens. Microbiologic evaluation of samples from the donor lungs obtained via bronchoscopy are important for the management of post-transplant infections (99,173). The majority of donor lungs are colonized, often with multiple organisms identified (100). While colonization of the donor lungs is common, the risk of subsequent recipient infection is relatively low when the infection is identified prior to procurement and proper prophylaxis is employed (191,192). MDR bacteria, including

methicillin-resistant *Staphylococcus aureus* (MRSA), Vancomycin-resistant *Enterococcus* (VRE), and MDR Gram-negative rods represent a major challenge in peri-transplant management (193). CREs are emerging MDR pathogens that cause infection in 3–10% of SOT recipients in endemic areas (194,195). Depending on transplant center location, the prevalence of MDR bacteria among donors ranges from 4.9% to 10.5% (192). Rates of MDR donor-derived infection are low, but the mortality can be higher when these infections are unknown at the time of procurement and appropriate prophylaxis is not given (196).

CF patients are known to be colonized with bacteria in both the upper and lower airways. The sinuses may serve also as a reservoir for bacteria that can spread to the lung allograft post-transplant (194,197). Some centers endorse either pre- or post-transplant sinus surgery, although data is conflicting (57,197-199).

MRSA is certainly an important nosocomial pathogen, and prevention of MRSA colonization and infection is important for LTRs, as well as other surgical patients (200). Data from heart transplant recipients suggests that active surveillance for MRSA followed by selective decolonization can reduce surgical site infections (201). Modeling using data on LTRs with respect to the incidence of MRSA colonization post-LT, the risk of subsequent *Staph. aureus* infection, and estimates on the efficacy of decolonization with mupirocin and chlorhexidine suggested active surveillance for MRSA colonization and decolonization could reduce infections and save costs (202). Results of clinical trials in other SOTs have been conflicting. Currently active surveillance for MRSA, pre- and post-transplantation, followed by selective decolonization is not generally recommended by guidelines, although this can be considered if a site has high rates of MRSA infection (203). Rather, general infection control strategies to minimize risk of acquiring MDROs are recommended.

Finally, isoniazid is effective in preventing active TB in patients with LTBI (204).

### *Minimizing risk*

Similar to all hospitalized patients, LTRs are at risk for nosocomial infections (200). Proper precautions, including basic hand hygiene, should always be used to minimize the risk for nosocomial infections and outbreaks. Other interventions, including chlorhexidine bathing, central line bundles, disinfection protocols, and antimicrobial stewardship, all help to reduce the incidence of nosocomial

infections (204). Breaks in infection control measures have resulted in outbreaks of BIs in SOT populations (205,206).

## Acknowledgments

*Funding:* None.

## Footnote

*Provenance and Peer Review:* This article was commissioned by the Guest Editor (Jonathan D’Cunha) for the series “Lung Transplantation: Past, Present, and Future” published in *Journal of Thoracic Disease*. The article has undergone external peer review.

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at: <http://dx.doi.org/10.21037/jtd-2021-12>). The series “Lung Transplantation: Past, Present, and Future” was commissioned by the editorial office without any funding or sponsorship. The authors have no other conflicts of interest to declare.

*Ethical Statement:* All authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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**Cite this article as:** McCort M, MacKenzie E, Pursell K, Pitrak D. Bacterial infections in lung transplantation. *J Thorac Dis* 2021;13(11):6654-6672. doi: 10.21037/jtd-2021-12