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Impact of Multidrug-Resistant Organisms on Patients Considered for Lung Transplantation

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INTRODUCTION

The long-term success of lung transplantation is limited by the development of infections and chronic rejection, otherwise known as bronchiolitis obliterans syndrome (BOS).[1] Infection with multidrug-resistant (MDR) organisms is particularly problematic in patients with cystic fibrosis (CF), which is the third most common indication for lung transplant. Understanding the clinical impact and management options for these pathogens is critical for optimizing posttransplant outcomes and maximizing the benefit of a limited supply of donor organs.

Patients with CF are increasingly colonized and infected with MDR bacteria and fungi before transplant.[1,2] Although *Pseudomonas aeruginosa* remains the predominant pathogen in patients with CF undergoing lung transplant evaluation, the prevalence of other species such as *Stenotrophomonas maltophila*, *Achromobacter xylosoxidans*, *Pandorea*, and *Ralstonia* has also increased over the past decade.[3–5] Outcomes in CF have greatly improved with the introduction of inhaled tobramycin and oral azithromycin, but the increasing use of these and other broad-spectrum antimicrobials has also led to changes in CF sputum microbiology.[6,7] Antibiotic use has led to a loss of diversity in respiratory flora and increases in antimicrobial resistance.[6,8,9] With regard to MDR pathogens, few data are available to guide specific therapy and predict the posttransplant outcomes for pathogens other than *P aeruginosa* (**Table 1**).[10]

SPECIFIC ORGANISMS

Pseudomonas aeruginosa

Microbiology and ecology—*P aeruginosa* is an opportunistic gram-negative aerobic bacillus found commonly in indoor and outdoor freshwater environments.[11] Displaying a multitude of virulence factors, *P aeruginosa* often manifests in 1 of 2 distinct phenotypes, a

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tissue-invasive pathogen causing acute pneumonia and sepsis or as a chronic colonizer in damaged airways, such as in CF.[12,13] Although *P aeruginosa* has a variety of virulence factors that may predispose this organism to severe acute infections, genome analysis of *P aeruginosa* strains in chronically infected recipients with CF has demonstrated that strains tend to display a different set of characteristics that allow the organism to persist as a chronic colonizer. These factors include

- Hyper mutability[14]
- Downregulation of virulence factors including toxin production, flagellum, and lipopolysaccharide O chains[15]
- Mucoid phenotype, characterized by production of alginate biofilm
- Evasion from and inhibition of phagocytosis[15,16]
- Multiple mechanisms of antibiotic resistance

Epidemiology—Among patients being considered for lung transplantation, most pseudomonal infections are seen in chronic suppurative lung diseases, with a prevalence of *P aeruginosa* in up to 80% of patients with CF and bronchiectatic lung diseases.[17] Pretransplant colonization is a significant risk factor for infection after transplant, increasing the risk of infection by an odds ratio of 4.7.[18,19]*Pseudomonas* is the most common cause of pneumonia in the first month after transplant and accounts for one-third of posttransplant pneumonias.[20,21] This organism is particularly problematic in patients with CF.[22] Posttransplant airway colonization with *P aeruginosa* has also been associated with BOS, which is the primary cause of mortality in lung transplant recipients. It is not clear whether the risk of BOS is seen only in patients with de novo infection or whether this extends to patients who were colonized before transplant.[23,24] The posttransplant survival of patients colonized with pan-resistant *P aeruginosa* before transplant is similar to those with sensitive bacteria at 1 year (88% vs 96%), but worse at 3 years (63.2% vs 90.7%).[25] However, the average mortality with pan-resistant bacteria is comparable with that of the entire lung transplant population and thus patients should not be denied transplant candidacy because of pan-resistant *P aeruginosa*.[10]

MDR *P aeruginosa*, defined as resistance to greater than 3 or more classes of antibiotics, is common in patients with CF, with prevalence rates ranging from 10% to 45%.[26–28] Cutting-edge sequencing techniques have provided new insights into the longitudinal effects of antibiotic treatment on the bacterial ecosystem in these patients.[8,9] Findings from these recent studies by Zhao and colleagues[8] and Fodor and colleagues[9] suggest that use of antibiotics seemed to be the primary driver of the loss of diversity in respiratory flora, as opposed to age or lung function. A comparison between 1996 and 2008 demonstrated increased resistance to tobramycin in *P aeruginosa* isolates (11.8% vs 30.4%, $P<.001$), and increased carbapenem-resistant, aztreonam-resistant, and MDR *P aeruginosa* in patients who were exposed to intravenous carbapenems.[6]

Pretransplant management—CF Foundation guidelines recommend chronic use of inhaled antibiotics, such as tobramycin or aztreonam, reserving systemic antibiotics for

symptomatic exacerbations. Antibiotics are typically selected based on local susceptibility testing; typical classes of antibiotics with antipseudomonal activity include extended spectrum cephalosporins, β-lactam/anti-β-lactamase, carbapenems, quinolones, and aminoglycosides. The increase in MDR *P aeruginosa* over the past 2 decades had led to interest in assessment of synergy with antibiotics, using either the checkerboard dilution assay or the multiple combination bactericidal assay (MCBT).[29,30] Synergy is defined as those combinations with demonstrable bactericidal activity. In studies from 1990 to 2006, combinations containing meropenem had the most bactericidal activity, showing in vitro efficacy in greater than 60% of strains.[29] Studies of the clinical efficacy of synergy testing have shown mixed results. In a randomized trial of patients with CF with respiratory exacerbations, antibiotic therapy guided by MCBT therapy did not improve the time interval between exacerbations, lung function, or end-of-treatment bacterial density before transplant.[31]

Posttransplant treatment—Most centers treat recipients with a history of *P aeruginosa* with 2-drug antipseudomonal therapy for 2 to 3 weeks postoperatively to reduce the risk of pneumonia and allograft colonization, based on previous susceptibilities.[32–34] However, most centers avoid systemic colistin and aminoglycosides if possible because of cumulative nephrotoxicity when combined with calcineurin inhibitors for immunosuppression. Synergy testing may be beneficial in patients with CF with MDR *P aeruginosa* who are undergoing lung transplant, based on lower rates of septicemia and pleural infections seen in a retrospective study. Inhaled tobramycin and colistin are components of successful eradication strategies for de novo *P aeruginosa* in pediatric patients with CF, and may have a role in preventing colonization of the new allograft after transplant. However, the efficacy of these agents for posttransplant eradication has not been well studied. Surgical debridement of the sinuses after transplant has also been associated with reduced incidence of bacterial pneumonia and BOS.

Burkholderia Species

Microbiology and ecology—*Burkholderia* species are gram-negative bacteria found ubiquitously in the soil and moist environment. Members of this genus include *Burkholderia cepacia* complex, *gladioli* and *mallei*, and *pseudomallei*. Previously believed to represent 1 species, advances in geneticshave shown thatthe *B cepacia* complex (BCC) comprises several phylogenetically similar but distinct species, including *B multivorans* and *B cenocepacia*. The latter has recently been further subdivided into epidemic (transmissible) and nonepidemic strains. Because patient-to-patient transmission of *Burkholderia* species has been consistently documented, the CF Foundation has recommended segregation of patients infected with BCC from each other and from other patients. Recent subclassification of *Burkholderia* species has shown strain-specific differences in the virulence of these pathogens, in the pretransplant and posttransplant settings.

Epidemiology—Although BCC are generally not pathogenic in healthy hosts, *Burkholderia* species colonize the respiratory tract in 15% to 22% of patients with CF. Although early eradication strategies have been used in the CF population, most patients who acquire these organisms develop chronic infection.[35] Chronic infection with BCC,

defined as the isolation of a species on 2 or more occasions over a minimum of 6 months, has been associated with an accelerated decline in lung function and increased mortality in recipients with CF.[36] Unfortunately, pretransplant colonization with *B cenocepacia* has been associated with the highest risk for posttransplant mortality (relative risk 8.43, $P<.005$) and most lung transplant centers have denied transplantation to candidates infected with this species.[37–39] More recently, it has been appreciated that infection with transmissible strains of *B cenocepacia* may not be as hazardous as infection with the nontransmissible strains.[37] Further studies are needed to determine if patient selection criteria or other factors also played a role in the observed mortality differences. Pretransplant colonization with *B gladioli* has also been associated with increased mortality in lung transplant recipients (hazard ratio 2.23, $P = .04$) and complications that include mediastinal abscesses, pleural infection, and chest wall infection.[37,40–42] There is currently insufficient data to determine whether the increased posttransplant mortality is primarily attributable to chronic and MDR infection or also extends to those transiently infected with *B gladioli* before transplant. Many transplant centers currently consider *B gladioli* to be a relative contraindication to lung transplant. Given the strain and species, and the specific virulence of the various members of the BCC, programs should refer specimens to reference laboratories with DNA fingerprinting capacity, if needed to determine the exact species and strain.

Treatment—Treatment of most acute exacerbations with *Burkholderia* species include trimethoprim sulfamethoxazole as the drug of choice as well as typical antipseudomonal antibiotics, such as ceftazidime and meropenem.[40,43] As a result of multiple resistance mechanisms, including an efflux pump, chronic infection with BCC is associated with an 80% prevalence of MDR, defined as resistance to 3 or more classes of antibiotics.[40,44] In this setting, some experts recommend synergy testing to determine optimal antibiotic combinations, although its efficacy is uncertain.[45] There are limited data about the optimal treatment approach after transplant, although most centers recommend prolonged combination antibiotic therapy given the high risk of fatal infection after transplant.

Acinetobacter baumannii

Microbiology—*Acinetobacter* is a gram-negative coccobacillus found in a broad variety of environments. Historically, a pathogen of humid climates, *Acinetobacter* species have become increasingly prevalent as causes of nosocomial infections.[46,47]*A baumannii* can be particularly problematic due to some of the following virulence factors:

- Ability to survive dry environmental conditions for weeks[48]
- Wide range of resistance mechanisms[49,50]
- Enhanced adherence to bronchial epithelium using fimbriae[51]
- Production of a polysaccharide capsule that can delay phagocytosis[52]

In the United States, transmission is typically traced to common source contamination in nosocomial settings, such as respiratory equipment in intensive care units, but community infection has been reported in other continents.

Epidemiology—Most of the nosocomial *A baumannii* infections occur in the setting of outbreaks; however, prolonged colonization can contribute to the endemicity of this pathogen after an outbreak. In 1 multicenter study, the prevalence of *Acinetobacter* in intensive care patients approximated 3%, predominantly as outbreaks.[53] Furthermore, the rapid acquisition of multiple mechanisms of resistance has led to the emergence of strains that are pan resistant.[54]

Peritransplant management—Treatment of *Acinetobacter* infections is based on local susceptibility patterns, but typical antibiotic choices include third-generation or fourth-generation cephalosporins, carbapenems, and β-lactams/anti-β-lactamase combinations. Colistin may be of benefit with resistant strains. In the pretransplant setting, *Acinetobacter* infections may become more prevalent as more centers become willing to transplant candidates who are on mechanical ventilatory or extracorporeal life support. Although there are currently no published reports describing the incidence or effect of pretransplant *Acinetobacter* infections on posttransplant outcomes, the concern for fatal posttransplant infection likely prevents many from being considered for transplantation. Infections with MDR *A baumannii* in lung transplant recipients can have devastating outcomes. In 1 series of 6 patients infected with carbapenem-resistant *A baumannii* during a hospital outbreak, the organism was persistently recovered from the respiratory tract in 4 of 6 recipients despite aggressive treatment and all 4 died as a result of this infection.[55] In another report that included 16 solid-organ transplant recipients with *A baumannii* that was resistant to all antimicrobials except tigecycline and colistin, patients who were initially treated with colistin monotherapy demonstrated 91% mortality.[56] However, following a new protocol to determine the local mechanism of resistance (OXA-23 gene) and subsequent synergy testing, an initial treatment regimen of carbapenem and colistin resulted in a 60% survival rate in subsequent patients infected with *A baumannii*. Further studies are needed to determine the circumstances under which patients with pretransplant *A baumannii* infection can undergo lung transplantation with acceptable posttransplant outcomes.

Nontuberculous Mycobacteria

Infections with nontuberculous mycobacteria (NTM) are fairly prevalent in patients with several pretransplant chronic lung processes including adult-onset bronchiectasis and CF. Overall, there is no difference in posttransplant mortality between patients with or without positive NTM cultures, however the rate of NTM disease is highest in patients with *Mycobacterium abscessus*.[57] Key points about NTM and lung transplant candidates are[57–61]

- Prevalence estimates of carriage are 3% to 13% in pretransplant patients and 10% to 22% after transplant.
- Many patients (~40%) who have pretransplant NTM continue to have positive cultures after transplant.
- *M abscessus* is considered a relative contraindication to transplant because of its virulence and intrinsic resistance to antimicrobial agents.

M abscessus

Microbiology—*M abscessus*, a rapidly growing mycobacterium (ie demonstrating visible growth on solid media within 7 days) is increasingly recognized as an important human pathogen.[62] This bacteria is found in water and soil and is capable of colonizing skin surfaces, the gastrointestinal tract, and the respiratory tract of humans. It is one of the most resistant organisms to antimicrobial agents, the mechanisms of which are the focus of increasing research. Natural and acquired resistance mechanisms include

- The presence of a waxy impermeable cell wall
- Antibiotic-modifying enzymes
- Target-modifying enzymes that confer resistance to macrolides
- Efflux pumps

The complete genome sequence became available in 2009, allowing for further classification of substrains and the discovery that *M abscessus* shares several characteristics with slow-growing mycobacteria.

Epidemiology—Before transplant, the most frequently isolated species are *Mycobacterium avium* complex (41%) followed by *M abscessus* (7%). *M abscessus* can cause skin infections in nosocomial settings, bronchopulmonary infections in patients with chronic lung diseases, and disseminated infections in immunocompromised hosts. There are few data on the clinical outcome of *M abscessus* infections in transplant recipients. Chernenko and colleagues[60] conducted a follow-up survey of 62 centers to determine the incidence and clinical outcomes of *M abscessus* infections before and after lung transplant.[61] Seventeen of 5200 transplant recipients were infected with *M abscessus* after transplant; of these, only 2 were infected with *M abscessus* before transplant, suggesting that pretransplant infection with *M abscessus* may have been a contraindication to transplant at many centers.

Peritransplant treatment—Treatment is recommended in patients who have progressive disease, or who may need lung transplantation in the future. *M abscessus* infections are intrinsically resistant to most standard antibiotics and antituberculous agents. Typical modal minimum inhibitory concentrations are less than tissue/serum levels only for clarithromycin, aminoglycosides, cefoxitin, and tigecycline, with some strain-specific variability in susceptibility patterns. Most recommendations are to use a multidrug regimen including clarithromycin, aminoglycoside, and a third agent for 24 months, but the efficacy of the multidrug approach is mixed. The success rates of sputum conversion and maintenance of negative cultures depend significantly on resistance profiles, ranging from 60% for macrolide-sensitive organisms to less than 20% in macrolide-resistant strains. Although *Mycobacterium avium* complex is more frequently recovered from respiratory samples, the isolation of the species rarely meets the American Thoracic Society (ATS) definition of clinical disease and may not require treatment.[58] In those cases that meet the ATS criteria, standard treatment approaches include clarithromycin, ethambutol, and rifampin for a minimum of 12 months.[62]

Scedosporium Species

Scedosporium colonization is common in patients with advanced CF, and infections are a problem in lung transplant recipients.[63] Among North American lung transplant recipients, *Scedosporium* species are the second most common cause of filamentous fungal infection, following only aspergillosis.[64,65]*Scedosporium* colonization is a risk factor for invasive disease after lung transplant.[65] Patients who are colonized with *Scedosporium* before transplant can develop infections with the same strain after the transplant.[66] Identifying patients who are carrying *Scedosporium* before transplant is crucial in that it gives clinicians a chance to try to modify the risk for posttransplant infection. Such information can also be used to inform decisions regarding the suitability of the patient for lung transplant.

Ecology and microbiology of Scedosporium—Clinically relevant species include *S prolificans*, *S apiospermum*, and the closely related *Pseudallescheria boydii*. Recent work has identified *S aurantiacum* as a new species within the *P boydii* complex.[67] Because the nomenclature has evolved in recent years, references to these fungi in the literature can be confusing. For example, *S apiospermum*, *P boydii* and *S aurantiacum* have previously been reported as 1 species.

Scedosporium species are found in soil, water, and air. Their abundance is related to increasing nitrogen concentrations and decreasing pH within a range of 6.1 to 7.5. Human activity, including intense fertilization and hydrocarbon waste, supports growth of *Scedosporium* species in the environment. Some of the highest concentrations of *Scedosporium* species can be found at industrial sites, near gas stations, in urban parks, and within agricultural areas.[68]

Geographic locale affects the epidemiology and microbiology of *Scedosporium* carriage in at-risk patients.

- *Scedosporium* colonization and infection are particularly prevalent in Australia.
- Environmental sampling in Australia has revealed an abundance of *S aurantiacum* and *S prolificans* in locations of high human activity.[69]

In 1 Australian medical center, molecular epidemiology analysis showed a single common type isolated in multiple patients suggesting a shared exposure source.[70] In general, however, exposure tends to be spread out over diverse regions, and in most studies a point source cannot be identified.[71,72]

Epidemiology of Scedosporium carriage—Presence of *Scedosporium* species can be a common finding in the respiratory tract and sinuses of patients with CF, bronchiectasis, and even interstitial lung disease.[70,73–75]

- Patients with late-stage CF are at particularly high risk for carriage.
- After *Aspergillus*, *Scedosporium* species are typically the most commonly isolated filamentous fungi in patients with CF.
- Carriage rates have been reported to be in the 3% to 10% range.[63,76,77]

The intersection of environmental exposure and host factors affects the epidemiology of colonization and infection. In CF, the conditions created by viscous secretions, airway abnormalities, and the impact of chronic and recurrent bacterial colonization and infection favor carriage of these fungi. In 1 study, patients with *Scedosporium* colonization were significantly less likely to be colonized with mucoid strains of *P aeruginosa*, whereas colonization rates were higher in those who had received previous therapy with antistaphylococcal penicillins.[78]

Accurate detection of respiratory tract colonization with *Scedosporium* and identification to the species level can be challenging. Because treatment regimens differ by infecting species, identifying *Scedosporium* to the species level is crucial. Molecular techniques can assist in this task. Additional techniques that are in development include use of mass spectroscopy and assays that detect a siderophore that is specific for *S apiospermum*.[79,80]

- When using standard culture media, *Scedosporium* carriage can be underestimated because of overgrowth by faster-growing bacteria and fungi (eg, *P aeruginosa* and *Aspergillus* species).
- Specialized semiselective mycologic isolation medium such as SceSel can increase yield.[81,82] Such media should be used in addition to standard fungal culture techniques when evaluating patients.[77]
- Once the fungus is grown in culture, a species-specific multiplex polymerase chain reaction (PCR) can differentiate between clinically relevant species.[83]
- Application of PCR directly to sputum is another approach that can be used to detect occult organisms to the species level.[84]

The natural history of *Scedosporium* carriage is variable. Colonization may be transient or persist in the bronchial passages or sinuses for years.[85] Once persistent colonization is established, it becomes difficult to eradicate.[86,87] Patients tend to become exclusively colonized with 1 species (eg, *S prolificans*, *S aurantiacum* or *S apiospermum*), but may carry multiple strains of that species.[88]

Clinical manifestations and treatment before transplant—Clinical manifestations of *Scedosporium* in patients with CF (before transplant) include[63,86]

- Asymptomatic carriage; this is the most common presentation.
- Mycetoma, which tends to occur in preexisting lung cavities and is sometimes referred to as a fungus ball.
- Allergic bronchopulmonary disease, which is a syndrome much like allergic bronchopulmonary aspergillosis.
- Invasive disease is uncommon, but may occur in patients with CF. Can be limited to the lung or present as disseminated infection.[89]

Evaluation of a patient with CF with findings suggestive of invasive infection, mycetoma, or allergic bronchopulmonary disease should include a search for *Scedosporium*.

Scedosporium species are difficult to treat with antifungal agents. Based on in vitro data and clinical experience, treatment options for *S apiospermum* (and the related *P boydii*) and for *S aurantiacum* are[90,91]

- Voriconazole, which is probably the best choice
- Combination therapy with an echinocandin and either voriconazole or amphotericin B (AmB)

S prolificans can be resistant to multiple antifungal agents, including voriconazole and AmB. Treatment options for invasive infection with *S prolificans* include[92–96]

- Surgical management
- Micafungin combined with voriconazole or AmB
- Voriconazole combined with terbinafine has also been effective in vitro and in clinical *S prolificans* infections

The role of posaconazole for any of the *Scedosporium* species is unclear at this time, but may be an option for those that are intolerant or not responding to voriconazole.[97] Susceptibility testing, which generally requires sending the isolate to a reference laboratory, is an important element in constructing an antifungal regimen for such infections.

Treatment considerations in patients with chronic lung disease who are carrying *Scedosporium* depend on the species, the clinical scenario, and the prospects for lung transplant. The decision to treat is generally straightforward in patients with invasive disease. The approach to asymptomatic colonization is a more difficult decision point. Patients who are colonized with *Scedosporium* before transplantation may progress to disseminated infection after lung transplant. Therefore, an effort should be made to control the fungus in such patients.[85] Voriconazole is usually the drug of choice in this situation, but breakthrough infections have developed with this and other agents (eg, AmB and itraconazole).[66,97] Moreover, eradication of *Scedosporium* may not be possible, requiring consideration of indefinite fungal prophylaxis after transplant.

Infections after lung transplant—The clinical manifestations of *Scedosporium* infection after lung transplant are diverse and range from asymptomatic colonization to severe invasive disease.[97–100] In 1 study, proven (including disseminated) infection was diagnosed in 36% of lung recipients from whom *Scedosporium* was recovered.[101]

- Infection in lung transplant recipients generally originates in the lungs and sinuses, which are also the typical sites of pretransplant colonization.
- An important aspect of *Scedosporium* infections in lung transplant recipients is a tendency toward disseminated infection with clinical manifestations that include fungemia, brain abscess, endocarditis, cutaneous involvement, spondylodiscitis, and endophthalmitis.[65,97,100,102]
- Once disseminated infection develops, the disease is nearly always fatal despite use of multiple antifungal agents and surgical excision.

Treatment options for invasive scedosporiosis after lung transplant are generally unsatisfactory.[75] Response to therapy depends on the extent of infection and the infecting organism. Disseminated infection with any of the *Scedosporium* species is nearly always associated with mortality. Infections caused by *S prolificans* are extraordinarily difficult to treat and tend to have poorer responses to antifungal therapy than those caused by *S apiospermum*.[103] The ideal treatment regimens for infection with the various *Scedosporium* species are not known. Treatment failures are common and, when successful, antifungal therapy generally needs to be given for months or longer. Relapses are common and lifelong therapy may be required.

The general approach to *Scedosporium* infection after transplant is

- *S apiospermum* and *S aurantiacum*: voriconazole ± echinocandin
- *S prolificans*: surgical therapy and adjunctive voriconazole ± an echinocandin ± terbinafine

Aspergillus terreus

Aspergillosis is the most common fungal infection in lung transplant recipients.[104] A small but significant proportion of cases are caused by *Aspergullus terreus*. Exposure to this difficult-to-treat fungus is via inhalation of airborne conidia from environmental sources. Colonization or infection in a patient with chronic lung disease before transplant can be particularly problematic. *A terreus* has been identified in outdoor air, home tapwater, and compost.[105–107] After transplant, *A terreus* infection can progress rapidly and is associated with a high mortality rate.[108]*A terreus* tends to be resistant to AmB. Prophylactic use of aerosolized AmB, which is a common practice in lung transplant programs, is a risk factor for infection with this fungus.[109–113]*A terreus* is generally susceptible to voriconazole and this is the drug of choice for invasive disease.

SUMMARY

Advances in supportive care, including broad use of antimicrobial agents, are prolonging the lives of patients with advanced lung disease. A byproduct of these advances has been an increasing prevalence of carriage and infection with MDR organisms. When such infections occur after transplant, the results can be disastrous. In this regard, infections with highly resistant strains of *P aeruginosa*, *Burkholderia*, *Acinetobacter*, nontuberculous mycobacteria, *Scedosporium*, and *A terreus* can be particularly problematic. An understanding of the epidemiology, diagnosis, and treatment of these infections is important when evaluating a pretransplant candidate.

REFERENCES

1. Christie JD, Edwards LB, Kucheryavaya AY, et al. The Registry of the International Society for Heart and Lung Transplantation: twenty-eighth adult lung and heart-lung transplant report–2011. J Heart Lung Transplant. 2011; 30(10):1104–22. [PubMed: 21962018]
2. Liou TG, Woo MS, Cahill BC. Lung transplantation for cystic fibrosis. Curr Opin Pulm Med. 2006; 12(6):459–63. [PubMed: 17053498]

3. Wine JJ. The genesis of cystic fibrosis lung disease. J Clin Invest. 1999; 103(3):309–12. [PubMed: 9927490]
4. Mayer-Hamblett N, Rosenfeld M, Emerson J, et al. Developing cystic fibrosis lung transplant referral criteria using predictors of 2-year mortality. Am J Respir Crit Care Med. 2002; 166(12 Pt 1):1550–5. [PubMed: 12406843]
5. Emerson J, Rosenfeld M, McNamara S, et al. *Pseudomonas aeruginosa* and other predictors of mortality and morbidity in young children with cystic fibrosis. Pediatr Pulmonol. 2002; 34(2):91–100. [PubMed: 12112774]
6. Emerson J, McNamara S, Buccat AM, et al. Changes in cystic fibrosis sputum microbiology in the United States between 1995 and 2008. Pediatr Pulmonol. 2010; 45(4):363–70. [PubMed: 20232473]
7. Knudsen PK, Olesen HV, Hoiby N, et al. Differences in prevalence and treatment of *Pseudomonas aeruginosa* in cystic fibrosis centres in Denmark, Norway and Sweden. J Cyst Fibros. 2009; 8(2): 135–42. [PubMed: 19157995]
8. Zhao J, Schloss PD, Kalikin LM, et al. Decade-long bacterial community dynamics in cystic fibrosis airways. Proc Natl Acad Sci U S A. 2012; 109(15):5809–14. [PubMed: 22451929]
9. Fodor AA, Klem ER, Gilpin DF, et al. The adult cystic fibrosis airway microbiota is stable over time and infection type, and highly resilient to antibiotic treatment of exacerbations. PLoS One. 2012; 7(9):e45001. [PubMed: 23049765]
10. Orens JB, Estenne M, Arcasoy S, et al. International guidelines for the selection of lung transplant candidates: 2006 update–a consensus report from the Pulmonary Scientific Council of the International Society for Heart and Lung Transplantation. J Heart Lung Transplant. 2006; 25(7): 745–55. [PubMed: 16818116]
11. Favero MS, Carson LA, Bond WW, et al. Pseudomonas aeruginosa: growth in distilled water from hospitals. Science. 1971; 173(3999):836–8. [PubMed: 4999114]
12. Bodey GP, Jadeja L, Elting L. *Pseudomonas bacteremia*. Retrospective analysis of 410 episodes. Arch Intern Med. 1985; 145(9):1621–9. [PubMed: 3927867]
13. Kosorok MR, Jalaluddin M, Farrell PM, et al. Comprehensive analysis of risk factors for acquisition of *Pseudomonas aeruginosa* in young children with cystic fibrosis. Pediatr Pulmonol. 1998; 26(2):81–8. [PubMed: 9727757]
14. Oliver A, Canton R, Campo P, et al. High frequency of hypermutable *Pseudomonas aeruginosa* in cystic fibrosis lung infection. Science. 2000; 288(5469):1251–4. [PubMed: 10818002]
15. Smith EE, Buckley DG, Wu Z, et al. Genetic adaptation by *Pseudomonas aeruginosa* to the airways of cystic fibrosis patients. Proc Natl Acad Sci U S A. 2006; 103(22):8487–92. [PubMed: 16687478]
16. Li Z, Kosorok MR, Farrell PM, et al. Longitudinal development of mucoid *Pseudomonas aeruginosa* infection and lung disease progression in children with cystic fibrosis. JAMA. 2005; 293(5):581–8. [PubMed: 15687313]
17. Doring G, Conway SP, Heijerman HG, et al. Antibiotic therapy against *Pseudomonas aeruginosa* in cystic fibrosis: a European consensus. Eur Respir J. 2000; 16(4):749–67. [PubMed: 11106223]
18. Bonvillain RW, Valentine VG, Lombard G, et al. Post-operative infections in cystic fibrosis and non-cystic fibrosis patients after lung transplantation. J Heart Lung Transplant. 2007; 26(9):890–7. [PubMed: 17845927]
19. Palmer SM, Alexander BD, Sanders LL, et al. Significance of blood stream infection after lung transplantation: analysis in 176 consecutive patients. Transplantation. 2000; 69(11):2360–6. [PubMed: 10868641]
20. Aguilar-Guisado M, Givalda J, Ussetti P, et al. Pneumonia after lung transplantation in the RESITRA cohort: a multicenter prospective study. Am J Transplant. 2007; 7(8):1989–96. [PubMed: 17617864]
21. Campos S, Caramori M, Teixeira R, et al. Bacterial and fungal pneumonias after lung transplantation. Transplant Proc. 2008; 40(3):822–4. [PubMed: 18455028]
22. Valentine VG, Bonvillain RW, Gupta MR, et al. Infections in lung allograft recipients: ganciclovir era. J Heart Lung Transplant. 2008; 27(5):528–35. [PubMed: 18442719]

23. Vos R, Vanaudenaerde BM, Geudens N, et al. Pseudomonal airway colonisation: risk factor for bronchiolitis obliterans syndrome after lung transplantation? Eur Respir J. 2008; 31(5):1037–45. [PubMed: 18256072]
24. Botha P, Archer L, Anderson RL, et al. *Pseudomonas aeruginosa* colonization of the allograft after lung transplantation and the risk of bronchiolitis obliterans syndrome. Transplantation. 2008; 85(5):771–4. [PubMed: 18337673]
25. Hadjiliadis D, Steele MP, Chaparro C, et al. Survival of lung transplant patients with cystic fibrosis harboring panresistant bacteria other than *Burkholderia cepacia*, compared with patients harboring sensitive bacteria. J Heart Lung Transplant. 2007; 26(8):834–8. [PubMed: 17692788]
26. Lechtzin N, John M, Irizarry R, et al. Outcomes of adults with cystic fibrosis infected with antibiotic-resistant *Pseudomonas aeruginosa*. Respiration. 2006; 73(1):27–33. [PubMed: 16113513]
27. Lambiase A, Raia V, Del Pezzo M, et al. Microbiology of airway disease in a cohort of patients with cystic fibrosis. BMC Infect Dis. 2006; 6:4. [PubMed: 16405721]
28. Johnson C, Butler SM, Konstan MW, et al. Factors influencing outcomes in cystic fibrosis: a center-based analysis. Chest. 2003; 123(1):20–7. [PubMed: 12527598]
29. Saiman L. Clinical utility of synergy testing for multidrug-resistant *Pseudomonas aeruginosa* isolated from patients with cystic fibrosis: 'the motion for'. Paediatr Respir Rev. 2007; 8(3):249–55. [PubMed: 17868923]
30. Lang BJ, Aaron SD, Ferris W, et al. Multiple combination bactericidal antibiotic testing for patients with cystic fibrosis infected with multiresistant strains of *Pseudomonas aeruginosa*. Am J Respir Crit Care Med. 2000; 162(6):2241–5. [PubMed: 11112146]
31. Aaron SD, Vandemheen KL, Ferris W, et al. Combination antibiotic susceptibility testing to treat exacerbations of cystic fibrosis associated with multiresistant bacteria: a randomised, double-blind, controlled clinical trial. Lancet. 2005; 366(9484):463–71. [PubMed: 16084254]
32. Flume PA, O'Sullivan BP, Robinson KA, et al. Cystic fibrosis pulmonary guidelines: chronic medications for maintenance of lung health. Am J Respir Crit Care Med. 2007; 176(10):957–69. [PubMed: 17761616]
33. Bauldoff GS, Nunley DR, Manzetti JD, et al. Use of aerosolized colistin sodium in cystic fibrosis patients awaiting lung transplantation. Transplantation. 1997; 64(5):748–52. [PubMed: 9311714]
34. Flume PA, Mogayzel PJ Jr, Robinson KA, et al. Cystic fibrosis pulmonary guidelines: treatment of pulmonary exacerbations. Am J Respir Crit Care Med. 2009; 180(9):802–8. [PubMed: 19729669]
35. Horsley A, Webb K, Bright-Thomas R, et al. Can early *Burkholderia cepacia* complex infection in cystic fibrosis be eradicated with antibiotic therapy? Front Cell Infect Microbiol. 2011; 1:18. [PubMed: 22919584]
36. Kalish LA, Waltz DA, Dovey M, et al. Impact of *Burkholderia dolosa* on lung function and survival in cystic fibrosis. Am J Respir Crit Care Med. 2006; 173(4):421–5. [PubMed: 16272450]
37. Murray S, Charbeneau J, Marshall BC, et al. Impact of *Burkholderia* infection on lung transplantation in cystic fibrosis. Am J Respir Crit Care Med. 2008; 178(4):363–71. [PubMed: 18535253]
38. De Soyza A, McDowell A, Archer L, et al. *Burkholderia cepacia* complex genomovars and pulmonary transplantation outcomes in patients with cystic fibrosis. Lancet. 2001; 358(9295): 1780–1. [PubMed: 11734238]
39. Alexander BD, Petzold EW, Reller LB, et al. Survival after lung transplantation of cystic fibrosispatients infectedwith *Burkholderia cepacia*complex. Am J Transplant. 2008; 8(5):1025–30. [PubMed: 18318775]
40. Kennedy MP, Coakley RD, Donaldson SH, et al. *Burkholderia gladioli*: five year experience in a cystic fibrosis and lung transplantation center. J Cyst Fibros. 2007; 6(4):267–73. [PubMed: 17137846]
41. Church AC, Sivasothy P, Parmer J, et al. Mediastinal abscess after lung transplantation secondary to *Burkholderia gladioli* infection. J Heart Lung Transplant. 2009; 28(5):511–4. [PubMed: 19416783]
42. Kanj SS, Tapson V, Davis RD, et al. Infections in patients with cystic fibrosis following lung transplantation. Chest. 1997; 112(4):924–30. [PubMed: 9377954]

43. Avgeri SG, Matthaiou DK, Dimopoulos G, et al. Therapeutic options for *Burkholderia cepacia* infections beyond co-trimoxazole: a systematic review of the clinical evidence. Int J Antimicrob Agents. 2009; 33(5):394–404. [PubMed: 19097867]
44. Nair BM, Joachimiak LA, Chattopadhyay S, et al. Conservation of a novel protein associated with an antibiotic efflux operon in *Burkholderia cenocepacia*. FEMS Microbiol Lett. 2005; 245(2): 337–44. [PubMed: 15837391]
45. Lipuma JJ. Update on the *Burkholderia cepacia* complex. Curr Opin Pulm Med. 2005; 11(6):528–33. [PubMed: 16217180]
46. Urban C, Segal-Maurer S, Rahal JJ. Considerations in control and treatment of nosocomial infections due to multidrug-resistant *Acinetobacter baumannii*. Clin Infect Dis. 2003; 36(10): 1268–74. [PubMed: 12746772]
47. Fournier PE, Richet H. The epidemiology and control of *Acinetobacter baumannii* in health care facilities. Clin Infect Dis. 2006; 42(5):692–9. [PubMed: 16447117]
48. Wendt C, Dietze B, Dietz E, et al. Survival of *Acinetobacter baumannii* on dry surfaces. J Clin Microbiol. 1997; 35(6):1394–7. [PubMed: 9163451]
49. Boucher HW, Talbot GH, Bradley JS, et al. Bad bugs, no drugs: no ESKAPE! An update from the Infectious Diseases Society of America. Clin Infect Dis. 2009; 48(1):1–12. [PubMed: 19035777]
50. Mak JK, Kim MJ, Pham J, et al. Antibiotic resistance determinants in nosocomial strains of multidrug-resistant *Acinetobacter baumannii*. J Antimicrob Chemother. 2009; 63(1):47–54. [PubMed: 18988680]
51. Lee JC, Koerten H, van den Broek P, et al. Adherence of *Acinetobacter baumannii* strains to human bronchial epithelial cells. Res Microbiol. 2006; 157(4):360–6. [PubMed: 16326077]
52. Kaplan N, Rosenberg E, Jann B, et al. Structural studies of the capsular polysaccharide of *Acinetobacter calcoaceticus* BD4. Eur J Biochem. 1985; 152(2):453–8. [PubMed: 4054115]
53. Chatellier D, Burucoa C, Pinsard M, et al. Prevalence of *Acinetobacter baumannii* carriage in patients of 53 French intensive care units on a given day. Med Mal Infect. 2007; 37(2):112–7. [in French]. [PubMed: 17258416]
54. Lolans K, Rice TW, Munoz-Price LS, et al. Multicity outbreak of carbapenem-resistant *Acinetobacter baumannii* isolates producing the carbapenemase OXA-40. Antimicrob Agents Chemother. 2006; 50(9):2941–5. [PubMed: 16940085]
55. Nunley DR, Bauldoff GS, Mangino JE, et al. Mortality associated with *Acinetobacter baumannii* infections experienced by lung transplant recipients. Lung. 2010; 188(5):381–5. [PubMed: 20607268]
56. Shields RK, Kwak EJ, Potoski BA, et al. High mortality rates among solid organ transplant recipients infected with extensively drug-resistant *Acinetobacter baumannii*: using in vitro antibiotic combination testing to identify the combination of a carbapenem and colistin as an effective treatment regimen. Diagn Microbiol Infect Dis. 2011; 70(2):246–52. [PubMed: 21353436]
57. Chalermskulrat W, Sood N, Neuringer IP, et al. Non-tuberculous mycobacteria in end stage cystic fibrosis: implications for lung transplantation. Thorax. 2006; 61(6):507–13. [PubMed: 16601086]
58. Knoll BM, Kappagoda S, Gill RR, et al. Non-tuberculous mycobacterial infection among lung transplant recipients: a 15-year cohort study. Transpl Infect Dis. 2012; 14(5):452–60. [PubMed: 22676720]
59. Fowler SJ, French J, Screaton NJ, et al. Nontuberculous mycobacteria in bronchiectasis: prevalence and patient characteristics. Eur Respir J. 2006; 28(6):1204–10. [PubMed: 16807259]
60. Chernenko SM, Humar A, Hutcheon M, et al. *Mycobacterium abscessus* infections in lung transplant recipients: the international experience. J Heart Lung Transplant. 2006; 25(12):1447–55. [PubMed: 17178340]
61. Sanguinetti M, Ardito F, Fiscarelli E, et al. Fatal pulmonary infection due to multidrug-resistant *Mycobacterium abscessus* in a patient with cystic fibrosis. J Clin Microbiol. 2001; 39(2):816–9. [PubMed: 11158161]
62. Griffith DE, Aksamit T, Brown-Elliott BA, et al. An official ATS/IDSA statement: diagnosis, treatment, and prevention of nontuberculous mycobacterial diseases. Am J Respir Crit Care Med. 2007; 175(4):367–416. [PubMed: 17277290]

63. Paugam A, Baixench MT, Demazes-Dufeu N, et al. Characteristics and consequences of airway colonization by filamentous fungi in 201 adult patients with cystic fibrosis in France. Med Mycol. 2010; 48(Suppl 1):S32–6. [PubMed: 21067327]
64. Park BJ, Pappas PG, Wannemuehler KA, et al. Invasive non-*Aspergillus* mold infections in transplant recipients, United States, 2001-2006. Emerg Infect Dis. 2011; 17(10):1855–64. [PubMed: 22000355]
65. Morio F, Horeau-Langlard D, Gay-Andrieu F, et al. Disseminated *Scedosporium/Pseudallescheria* infection after double-lung transplantation in patients with cystic fibrosis. J Clin Microbiol. 2010; 48(5):1978–82. [PubMed: 20220160]
66. Symoens F, Knoop C, Schrooyen M, et al. Disseminated *Scedosporium apiospermum* infection in a cystic fibrosis patient after double-lung transplantation. J Heart Lung Transplant. 2006; 25(5):603–7. [PubMed: 16678041]
67. Alastruey-Izquierdo A, Cuenca-Estrella M, Monzon A, et al. Prevalence and susceptibility testing of new species of *Pseudallescheria* and *Scedosporium* in a collection of clinical mold isolates. Antimicrob Agents Chemother. 2007; 51(2):748–51. [PubMed: 17101671]
68. Kaltseis J, Rainer J, De Hoog GS. Ecology of *Pseudallescheria* and *Scedosporium* species in human-dominated and natural environments and their distribution in clinical samples. Med Mycol. 2009; 47(4):398–405. [PubMed: 19085459]
69. Harun A, Gilgado F, Chen SC, et al. *Abundance* of *Pseudallescheria/Scedosporium* species in the Australian urban environment suggests a possible source for scedosporiosis including the colonization of airways in cystic fibrosis. Med Mycol. 2010; 48(Suppl 1):S70–6. [PubMed: 21067333]
70. Williamson EC, Speers D, Arthur IH, et al. Molecular epidemiology of *Scedosporium apiospermum* infection determined by PCR amplification of ribosomal intergenic spacer sequences in patients with chronic lung disease. J Clin Microbiol. 2001; 39(1):47–50. [PubMed: 11136746]
71. Delhaes L, Harun A, Chen SC, et al. Molecular typing of Australian *Scedosporium* isolates showing genetic variability and numerous *S. aurantiacum*. Emerg Infect Dis. 2008; 14(2):282–90. [PubMed: 18258122]
72. San Millan R, Quindos G, Garaizar J, et al. Characterization of *Scedosporium* prolificans clinical isolates by randomly amplified polymorphic DNA analysis. J Clin Microbiol. 1997; 35(9):2270–4. [PubMed: 9276400]
73. Cooley L, Spelman D, Thursky K, et al. Infection with *Scedosporium apiospermum* and *S. prolificans*, Australia. Emerg Infect Dis. 2007; 13(8):1170–7. [PubMed: 17953087]
74. Castiglioni B, Sutton DA, Rinaldi MG, et al. *Pseudallescheria boydii* (Anamorph *Scedosporium apiospermum*). Infection in solid organ transplant recipients in a tertiary medical center and review of the literature. Medicine (Baltimore). 2002; 81(5):333–48. [PubMed: 12352630]
75. Rodriguez-Tudela JL, Berenguer J, Guarro J, et al. Epidemiology and outcome of *Scedosporium prolificans* infection, a review of 162 cases. Med Mycol. 2009; 47(4):359–70. [PubMed: 19031336]
76. Cimon B, Carrere J, Vinatier JF, et al. Clinical significance of *Scedosporium apiospermum* in patients with cystic fibrosis. Eur J Clin Microbiol Infect Dis. 2000; 19(1):53–6. [PubMed: 10706182]
77. Blyth CC, Harun A, Middleton PG, et al. Detection of occult *Scedosporium* species in respiratory tract specimens from patients with cystic fibrosis by use of selective media. J Clin Microbiol. 2010; 48(1):314–6. [PubMed: 19906904]
78. Blyth CC, Middleton PG, Harun A, et al. Clinical associations and prevalence of *Scedosporium* spp. in Australian cystic fibrosis patients: identification of novel risk factors? Med Mycol. 2010; 48(Suppl 1):S37–44. [PubMed: 21067328]
79. Coulibaly O, Marinach-Patrice C, Cassagne C, et al. *Pseudallescheria/Scedosporium* complex species identification by matrix-assisted laser desorption ionization time-of-flight mass spectrometry. Med Mycol. 2011; 49(6):621–6. [PubMed: 21281060]
80. Bertrand S, Bouchara JP, Venier MC, et al. N(alpha)-Methyl coprogen B, a potential marker of the airway colonization by *Scedosporium apiospermum* in patients with cystic fibrosis. Med Mycol. 2010; 48(Suppl 1):S98–107. [PubMed: 21067336]

81. Horre R, Marklein G, Siekmeier R, et al. Selective isolation of *Pseudallescheria* and *Scedosporium* species from respiratory tract specimens of cystic fibrosis patients. Respiration. 2009; 77(3):320–4. [PubMed: 18957840]
82. Borman AM, Palmer MD, Delhaes L, et al. Lack of standardization in the procedures for mycological examination of sputum samples from CF patients: a possible cause for variations in the prevalence of filamentous fungi. Med Mycol. 2010; 48(Suppl 1):S88–97. [PubMed: 21067335]
83. Harun A, Blyth CC, Gilgado F, et al. Development and validation of a multiplex PCR for detection of *Scedosporium* spp. in respiratory tract specimens from patients with cystic fibrosis. J Clin Microbiol. 2011; 49(4):1508–12. [PubMed: 21325557]
84. Lu Q, van den Ende AH, de Hoog GS, et al. Reverse line blot hybridisation screening of *Pseudallescheria/Scedosporium* species in patients with cystic fibrosis. Mycoses. 2011; 54(Suppl 3):5–11. [PubMed: 21995657]
85. Tintelnot K, Just-Nubling G, Horre R, et al. A review of German *Scedosporium prolificans* cases from 1993 to 2007. Med Mycol. 2009; 47(4):351–8. [PubMed: 19301173]
86. Borghi E, Iatta R, Manca A, et al. Chronic airway colonization by *Scedosporium apiospermum* with a fatal outcome in a patient with cystic fibrosis. Med Mycol. 2010; 48(Suppl 1):S108–13. [PubMed: 21067322]
87. Defontaine A, Zouhair R, Cimon B, et al. Genotyping study of *Scedosporium apiospermum* isolates from patients with cystic fibrosis. J Clin Microbiol. 2002; 40(6):2108–14. [PubMed: 12037073]
88. Lackner M, Rezusta A, Villuendas MC, et al. Infection and colonisation due to *Scedosporium* in Northern Spain. An in vitro antifungal susceptibility and molecular epidemiology study of 60 isolates. Mycoses. 2011; 54(Suppl 3):12–21. [PubMed: 21995658]
89. Guignard S, Hubert D, Dupont B, et al. Multifocal *Scedosporium apiospermum* spondylitis in a cystic fibrosis patient. J Cyst Fibros. 2008; 7(1):89–91. [PubMed: 17567545]
90. Lackner M, de Hoog GS, Verweij PE, et al. Species-specific antifungal susceptibility patterns of *Scedosporium* and *Pseudallescheria* species. Antimicrob Agents Chemother. 2012; 56(5):2635–42. [PubMed: 22290955]
91. Cortez KJ, Roilides E, Quiroz-Telles F, et al. Infections caused by *Scedosporium* spp. Clin Microbiol Rev. 2008; 21(1):157–97. [PubMed: 18202441]
92. Rodriguez MM, Calvo E, Serena C, et al. Effects of double and triple combinations of antifungal drugs in a murine model of disseminated infection by *Scedosporium prolificans*. Antimicrob Agents Chemother. 2009; 53(5):2153–5. [PubMed: 19223617]
93. Heyn K, Tredup A, Salvenmoser S, et al. Effect of voriconazole combined with micafungin against *Candida*, *Aspergillus*, and *Scedosporium* spp. and *Fusarium solani*. Antimicrob Agents Chemother. 2005; 49(12):5157–9. [PubMed: 16304192]
94. Yustes C, Guarro J. In vitro synergistic interaction between amphotericin B and micafungin against *Scedosporium* spp. Antimicrob Agents Chemother. 2005; 49(8):3498–500. [PubMed: 16048969]
95. Meletiadis J, Mouton JW, Meis JF, et al. In vitro drug interaction modeling of combinations of azoles with terbinafine against clinical *Scedosporium prolificans* isolates. Antimicrob Agents Chemother. 2003; 47(1):106–17. [PubMed: 12499177]
96. Howden BP, Slavin MA, Schwarer AP, et al. Successful control of disseminated *Scedosporium prolificans* infection with a combination of voriconazole and terbinafine. Eur J Clin Microbiol Infect Dis. 2003; 22(2):111–3. [PubMed: 12627286]
97. Sahi H, Avery RK, Minai OA, et al. *Scedosporium apiospermum* (*Pseudoallescheria boydii*) infection in lung transplant recipients. J Heart Lung Transplant. 2007; 26(4):350–6. [PubMed: 17403476]
98. Vagefi MR, Kim ET, Alvarado RG, et al. Bilateral endogenous *Scedosporium prolificans* endophthalmitis after lung transplantation. Am J Ophthalmol. 2005; 139(2):370–3. [PubMed: 15734012]
99. Raj R, Frost AE. *Scedosporium apiospermum* fungemia in a lung transplant recipient. Chest. 2002; 121(5):1714–6. [PubMed: 12006471]

100. Rabodonirina M, Paulus S, Thevenet F, et al. Disseminated *Scedosporium prolificans* (*S. inflatum*) infection after single-lung transplantation. Clin Infect Dis. 1994; 19(1):138–42. [PubMed: 7948515]

101. Heath CH, Slavin MA, Sorrell TC, et al. Population-based surveillance for scedosporiosis in Australia: epidemiology, disease manifestations and emergence of *Scedosporium aurantiacum* infection. Clin Microbiol Infect. 2009; 15(7):689–93. [PubMed: 19549223]

102. Miraldi F, Anile M, Ruberto F, et al. *Scedosporium apiospermum* atrial mycetomas after lung transplantation for cystic fibrosis. Transpl Infect Dis. 2012; 14(2):188–91. [PubMed: 22093620]

103. Troke P, Aguirrebengoa K, Arteaga C, et al. Treatment of scedosporiosis with voriconazole: clinical experience with 107 patients. Antimicrob Agents Chemother. 2008; 52(5):1743–50. [PubMed: 18212110]

104. Neofytos D, Fishman JA, Horn D, et al. Epidemiology and outcome of invasive fungal infections in solid organ transplant recipients. Transpl Infect Dis. 2010; 12(3):220–9. [PubMed: 20113459]

105. Mortensen KL, Mellado E, Lass-Florl C, et al. Environmental study of azole-resistant *Aspergillus fumigatus* and other aspergilli in Austria, Denmark, and Spain. Antimicrob Agents Chemother. 2010; 54(11):4545–9. [PubMed: 20805399]

106. Blum G, Perkhofer S, Grif K, et al. A 1-year *Aspergillus terreus* surveillance study at the University Hospital of Innsbruck: molecular typing of environmental and clinical isolates. Clin Microbiol Infect. 2008; 14(12):1146–51. [PubMed: 19076844]

107. Vesper SJ, Haugland RA, Rogers ME, et al. Opportunistic *Aspergillus* pathogens measured in home and hospital tap water by quantitative PCR (QPCR). J Water Health. 2007; 5(3):427–31. [PubMed: 17878557]

108. Lass-Florl C, Griff K, Mayr A, et al. Epidemiology and outcome of infections due to *Aspergillus terreus*: 10-year single centre experience. Br J Haematol. 2005; 131(2):201–7. [PubMed: 16197450]

109. Steinbach WJ, Marr KA, Anaissie EJ, et al. Clinical epidemiology of 960 patients with invasive aspergillosis from the PATH Alliance registry. J Infect. 2012; 65(5):453–64. [PubMed: 22898389]

110. Ruping MJ, Gerlach S, Fischer G, et al. Environmental and clinical epidemiology of *Aspergillus terreus*: data from a prospective surveillance study. J Hosp Infect. 2011; 78(3):226–30. [PubMed: 21440331]

111. Caston JJ, Linares MJ, Gallego C, et al. Risk factors for pulmonary *Aspergillus terreus* infection in patients with positive culture for filamentous fungi. Chest. 2007; 131(1):230–6. [PubMed: 17218581]

112. Zhou J, Chen Y, Tabibi S, et al. Antimicrobial susceptibility and synergy studies of *Burkholderia cepacia* complex isolated from patients with cystic fibrosis. Antimicrob Agents Chemother. 2007; 51(3):1085–8. [PubMed: 17158942]

113. Segonds C, Clavel-Batut P, Thouverez M, et al. Microbiological and epidemiological features of clinical respiratory isolates of *Burkholderia gladioli*. J Clin Microbiol. 2009; 47(5):1510–6. [PubMed: 19297595]

KEY POINTS

- In prospective transplant recipients, the most important multidrug-resistant (MDR) organisms are *Pseudomonas aeruginosa*, and species of *Burkholderia*, *Acinetobacter*, nontuberculous mycobacteria, and *Scedosporium*.
- Carriage of MDR organisms before transplant can predict the development of difficult-to-treat infections after lung transplantation.
- Identification of colonization and infection with MDR organisms is important to help guide antimicrobial decisions before and after transplant, and to determine suitability for lung transplantation.
- Development of personalized antimicrobial regimens for lung transplant recipients depends on an understanding of the epidemiology, microbiology, and clinical implications of these organisms.

Table 1

Commonly used antimicrobials for MDR pathogens

Organism	1st Line Antimicrobials	Contraindication to Transplant
MDR. *P aeruginosa*	Carbapenem, piperacillin/tazobactam, cefepime +/− an aminoglycoside or quinolone	Rare
Pan resistant *P aeruginosa*	Any of above +/− colistin	
B cenocepacia	Ceftazidime, tetracyclines, trimethoprim-sulfamethoxazole, carbapenem	Probable
B gladioli	Piperacillin, aminoglycosides, carbapenem, ciprofloxacin	Possible
A baumannii	Carbapenem, colistin, tigecycline, ampicillin/sulbactam	Possible
M abscessus	Clarithromycin + amikacin	Possible
	2nd line: Clarithromycin + imipenem or cefoxitin	
M avium complex	Clarithromycin, ethambutol, rifampin	Rare
S apiospermum	Voriconazole +/− echinocandin	Possible
S prolificans	Voriconazole +/− echinocandin +/− terbinafine	Possible
A terreus	Voriconazole +/− echinocandin	Rare

Data from. 62,112,113