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Emerging Bacterial, Fungal, and Viral Respiratory Infections in Transplantation

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KEYWORDS

• Emerging • Transplant • Respiratory infections

Kidney, liver, heart, pancreas, lung, and small intestine transplantations are viable therapeutic options for patients with end-stage organ failure. Ongoing advancements of surgical techniques, immunosuppressive regimens, and perioperative management have resulted in improved survival of allograft recipients. Despite these refinements, infections still contribute to substantial morbidity and mortality, limiting long-term success rates of these procedures.

Infections are particularly problematic among transplant recipients for several reasons. Immunosuppressive regimens are necessary to limit allograft rejection but weaken host immune responses to exogenously acquired pathogens and enable endogenous reactivation of latent infection. Frequent medical care of newly transplanted patients exposes them to potentially drug-resistant pathogens. Infections of the respiratory tract are common and could herald the development of more severe diseases. This is largely because of constant contact with the environment, which uniquely predisposes the respiratory system to direct microbial inoculation. Moreover, lung recipients specifically suffer from mucociliary dyskinesia, with reduced mechanical clearance of respiratory pathogens, as a result of airway anastomoses and a denervated allograft.

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Infect Dis Clin N Am 24 (2010) 541–555
doi:10.1016/j.idc.2010.04.005 **id.theclinics.com**
0891-5520/10/$ – see front matter

To help prevent the occurrence of common opportunistic infections in transplant recipients, prophylactic strategies have been used, but despite these efforts, emerging pathogens continue to pose unique challenges for clinicians to recognize, diagnose, and treat. One useful paradigm relevant to emerging infections in recipients of transplants stratifies these microbes into 3 categories.[1] The first category consists of known microbes causing infection with previously unrecognized pathogenicity causing human disease. Category 2 includes known microbes with already appreciated pathogenicity but cause more frequent or severe disease. The third category comprises newly discovered pathogens. This last category is growing apace in large part from technological advances that result in diagnosis or differentiation of new microbial pathogens. This article describes some of the organisms responsible for emerging respiratory infections in transplantation (**Box 1**).

EMERGING BACTERIAL RESPIRATORY INFECTIONS IN TRANSPLANTATION

Nocardia

Nocardia is a gram-positive filamentous aerobic actinomycete with variable acid-fast staining characteristics. Among more commonly reported opportunists in transplantation, pulmonary nocardiosis infection rates range from 0.7% to 3.5%.[2–7] The largest case series in transplantation describes these infections to be more common among lung recipients (3.5%), followed by recipients of heart (2.5%), intestine (1.3%), kidney (0.2%), and liver (0.1%).[7] However, literature reviews are difficult to systematically assess. With more than 50 species in existence, taxonomic classification is fraught with confusion and controversy. Until recently, most isolates causing human disease were labeled "*Nocardia asteroides*" and included organisms with considerable differences in antimicrobial susceptibility patterns.[8] With technological advances in molecular genotyping, isolates previously described as *N asteroides* have been subspeciated.[8] *N asteroides* is now denoted as *N asteroides* complex and includes *Nocardia nova* complex, *Nocardia farcinica*, *Nocardia transvalensis* complex, *Nocardia*

Box 1
Selected emerging pathogens in solid organ transplantation

Emerging bacterial respiratory tract infections
- *Nocardia* spp
- *Mycobacterium abscessus*
- *Rhodococcus equi*

Emerging fungal respiratory tract infections
- *Aspergillus ustus*
- *Aspergillus terreus*
- *Fusarium* spp
- *Scedosporium apiospermum*
- *Scedosporium prolificans*

Emerging viral respiratory tract infections
- Human metapneumovirus
- Lymphocytic choriomeningitis virus
- Severe acute respiratory syndrome virus

abscessus, and, newly, *Nocardia cyriacigeorgica*.[8,9] Moreover, additional species will emerge with continued advances in genotyping methods.

Clinically and radiographically, most nocardial infections are nonspecific and often confined to the lungs, which usually have a favorable prognosis.[10,11] These pathogens hematogenously disseminate in 20% to 25% of cases to the central nervous system, skin, and other organs, and, although much less frequently reported, extrapulmonary extension of infection is almost always fatal.[3,5,7,10,12,13] Therefore, early recognition and prompt therapy is crucial.

With ill-defined clinicoradiographic features, diagnosis is frequently delayed. *Nocardia* is a slow growing organism, with a mean duration of 2 weeks before a diagnosis is established. Concurrent infection or contamination by other microbes can overwhelm the growth of *Nocardia* species in laboratory culture media and further impede diagnosis.[6] Several studies suggest that *Nocardia* as the sole pathogen is uncommon in comparison with nocardial infections with other coisolates of cytomegalovirus, *Aspergillus*, or opportunistic fungi.[14–16] Given the delays in diagnosis, the clinician should have a low threshold to institute therapy early while awaiting culture results.

Trimethoprim-sulfamethoxazole (TMP-SMX) prophylaxis for *Pneumocystis jiroveci* pneumonitis is widely thought to afford protection against *Nocardia* infections.[13] However, more than 60% of nocardiosis have occurred in patients receiving TMP-SMX prophylaxis. Conversion to high-dose therapy has been curative, suggesting that prophylaxis dosages are ineffective for nocardiosis prevention but does not indicate a reduced susceptibility once infection is established.[3,6,7,10,17] Most therapeutic regimens use TMP-SMX combined with imipenem, amikacin, third-generation cephalosporins, minocycline, moxifloxacin, or linezolid from concerns about resistance.[6,18] To avoid recidivism, a protracted course of at least 6 to 12 months in immunocompromised patients is recommended.[5]

Mycobacterium abscessus

M abscessus is a gram-positive rod classified as rapid-growing nontuberculous mycobacteria. It is ubiquitously present in sewage, drinking water, decaying vegetation and the normal skin flora. Genotyping by polymerase chain reaction (PCR) methods have enabled distinction and subspeciation of this pathogen from *Mycobacterium chelonae* in 1992.[19]

M abscessus is identified frequently in patients with cystic fibrosis (CF), less often in others with structural lung abnormalities caused by chronic respiratory disease, and occasionally among immunocompromised hosts. In a prevalence study of nontuberculous mycobacterium isolated from sputum cultures of patients with CF, *M abscessus* was second to *Mycobacterium avium* complex (72%). The sensitivity of sputum culture to detect disease due to *M abscessus* is low and increases little with serial sputum samples from 7% to 13%.[20] Clinicoradiological findings are nonspecific and complicated by underlying structural lung disease, making the diagnosis elusive.[21,22] Infection is confined to the lungs in patients with CF, but dissemination is not uncommon among immunocompromised patients, including transplant recipients, which usually portends a poor prognosis.[20,23–27]

Whether *M abscessus* colonization before lung transplantation should be a contraindication is unknown.[24–26] Current guidelines urge caution in the face of virulent or resistant mycobacteria, especially with positive results for sputum smears before transplant, reflecting high airway mycobacterial loads.[25] The allograft can be secondarily colonized by microbes that persist proximally to the anastomoses and predisposes the recipient to infection of the newly transplanted lung. Treatment to

establish and maintain serial smear negativity before transplantation and extension of treatment intraoperatively and postoperatively have had some success.[25]

Treatment of *M abscessus* is complex and difficult for patients and clinicians. *M abscessus* isolates are resistant to most antimycobacterial agents, including tetracyclines, fluoroquinolones, and sulfonamides.[28] Initial therapy should include a combination of clarithromycin, amikacin, and cefoxitin or a carbapenem, pending sensitivity studies. Directed combination therapy should continue a minimum of 12 months after negative results of sputum cultures to avoid relapse.[20,29] Maintenance suppressive therapy with clarithromycin and aerosolized amikacin has also been suggested, as relapse after extended therapy has occurred.[29] The toxic effects of therapy and interactions with transplant medications limit adequate treatment.

Rhodococcus equi

R equi is an asporogenous, nonmotile, pleomorphic gram-positive coccobacilli and an obligate aerobe belonging to the family Nocardioform, order Actinomycetes.[30] The organism is present in soil, thrives in freshwater and marine habitats, and can live in the intestines of bloodsucking arthropods. It can be acquired by inhalation from the soil, direct inoculation, ingestion, colonization, and person-to-person transmission.[30]

R equi was first isolated as a causative agent of equine bronchopneumonia in 1923. The first human infection of *R equi* was reported in 1967 as cavitary pneumonia in a patient with autoimmune hepatitis receiving immunosuppressive therapy. Only 13 other cases have been reported up to 1983.[30] Subsequently, a marked increase in reported cases has occurred commensurate with human immunodeficiency virus, advances in cancer therapies, and transplantation.[30] More than 100 cases have now been reported, with 29 involving organ recipients, of which 23 involved the lungs.[31]

Establishing a diagnosis of *R equi* is difficult. Imaging is nonspecific and occasionally normal.[32–34] Identification of *R equi* from culture has proven difficult because of variable acid-fast staining and pleomorphic appearance in laboratory media.[30] Two studies have reported *R equi* lung infections in heart recipients initially misdiagnosed when laboratory cultures grew "diptheroids" mistaken for contaminants. Two other cases involving the kidney and pancreas and a pancreas recipient were misdiagnosed as tuberculosis, based on acid-fast staining and radiographs showing an upper lobe cavity, small satellite nodules, perihilar mass, and nonspecific infiltrate.[35,36] Final diagnosis was confirmed by bronchoalveolar lavage cultures prompted by worsening respiratory symptoms.

Given the limited number of cases, heterogeneous patient populations, and diverse clinical manifestations, standard treatments for *R equi* infection do not exist. However, success has been reported with dual antibiotic therapy for a minimum of 6 months and surgical drainage of complicated cases.[30,37,38] Combinations using vancomycin, imipenem, aminoglycosides, and fluoroquinolones are suggested empiric regimens until antimicrobial susceptibilities of the isolate are known.[30,34,39]

EMERGING FUNGAL RESPIRATORY INFECTIONS IN TRANSPLANTATION

Aspergillus species: Aspergillus ustus and Aspergillus terreus

Aside from *Candida* species, *Aspergillus* species are the most common fungal pathogens causing infection in transplant patients. This genus comprises more than 175 species, and although only a few are human pathogens, mortality of invasive aspergillosis varies from 74% to 92%.[40] *Aspergillus fumigatus* is the most common cause of disease, followed by *Aspergillus flavus* and rarely *A terreus, Aspergillus niger*, *or*

Aspergillus nidulans.[41] Recently, *A ustus* and *A terreus* have gained attention as rare, mycelial fungi responsible for fatalities with posttransplant respiratory infection.[40,42–50] Primary modes of acquisition are inhalation of environmental microconidia, similar to other mycelial fungi, or direct inoculation through the skin.[51] Predisposing factors include prolonged and severe neutropenia, high-dose steroid treatment, nosocomial exposure in hospitals undergoing construction, and prophylactic use of amphotericin B aerosols.[42,49,50,52] Once a primary respiratory infection is established, the organism has a proclivity to disseminate.

Most cases of *A terreus* and *A ustus* infections were described in the last 15 years.[45] This increase is attributed to the growing population of severely immunosuppressed patients and better diagnostic methods. Among cases reviewing these pathogens in transplant recipients, infection involved the lungs in all but one case noted with *A ustus.*[51,53–63] More than half disseminated and a third involved the central nervous system or skin.[62] *A terreus* is emerging as the next most common invasive pulmonary aspergillosis after *A fumigatus* and *A flavus.*[42–50]

Clinicians must possess an index of suspicion and a low threshold for aggressive and often invasive diagnostic procedures necessary for sampling. In many instances, *Aspergillus* species have unique histomorphologic characteristics from culture isolates facilitating identification. However, rarely encountered *Aspergillus* species such as *A ustus* and *A terreus* are not readily identified. Diagnoses by growth in culture may also be hindered by concurrent infecting organisms, most frequently other *Aspergillus* species, in nearly half of patients.[44] PCR analysis has advantages for rapid diagnosis because definitive speciation by culture takes weeks.[43,51,56,58,60,63] Early antifungal therapy is routinely initiated once a fungal pathogen is suspected or presumptively identified. However, this strategy is tempered by highly variable susceptibilities of *A terreus* and *A ustus.*[42,43,45,47,49]

Growing recognition of *A ustus* and *A terreus* is clinically important, as these species are resistant to amphotericin B, which has been standard therapy for most invasive *Aspergillus* infections.[42,45,47] Reports involving a series of 17 patients noted that 3 of 4 patients with *A ustus* who survived received voriconazole combined with caspofungin, although other reports using the same antifungal regimen as prophylaxis or as empiric therapy have not proven successful.[51,54,56,62,63] Unfortunately, *A terreus* infections are difficult to treat, with few reported successes. Only isolated respiratory infection has been amenable to amphotericin B with itraconazole after surgical lobectomy in a nonneutropenic transplant recipient.[43] Firm data for treating *A ustus* and *A terreus* infections are not available, as reflected by the multitude of antifungal regimens used. Other nonpharmacologic methods such as reduction in immunosuppression and local surgical debridement have had some success as adjunctive therapy.[42,47,49,52,57,64] Overall, however, treatment results are disappointing.

Fusarium

Fusarium solani is a colorless, septated mycelial fungus found in the soil, with increased frequency among transplant recipients.[65] The portal of entry is unclear, but inhalation, ingestion, and direct inoculation are suspected. Infection disseminates by vascular invasion with formation of yeast-like structures in the blood (adventitious sporulation), which are easily cultured.[65] Other than the characteristic fusiform or canoe-shaped macroconidia, *Fusarium* species are indistinguishable from *Aspergillus* species by routine histology.[65] Diagnosis ultimately requires speciation from culture.[66]

Among transplant recipients, reported infections have mostly occurred in hematopoietic stem cell transplantation (HSCT) recipients with prolonged neutropenia and are rarely seen in solid organ recipients. Notable differences exist between HSCT

and organ recipients. First, fusariosis in HSCT recipients occurs in a trimodal distribution: early posttransplant during extreme neutropenia, a median of 70 days after transplant associated with acute graft versus host disease (GvHD) (while receiving corticosteroid therapy), and more than 1 year posttransplant in association with extensive GvHD; however, in solid organ recipients, fusariosis occurs after the first year of transplantation.[67,68] Next, HSCT recipients typically have fungemia with disseminated fusariosis, whereas organ recipients develop isolated infection. Only 6 cases have been reported up to 2001 in solid organ recipients, with only 1 disseminated and others isolated to lung (n = 1) or skin (n = 4).[68–70] Localized infection in HSCT recipients, although much less reported, includes septic arthritis, endophthalmitis, osteomyelitis, cystitis, brain abscess, and cutaneous necrotizing lesions.[66] Lung (pneumonia, nonspecific alveolar or interstitial infiltrates, nodules, cavities) is the most commonly involved site of infection, accounting for 39% of HSCT recipients who develop invasive disease.[67] Last, especially in the setting of prolonged neutropenia, fusariosis mortality rates are up to 70% to 100% in HSCT recipients. No deaths due to fusariosis have been seen in organ recipients.[68]

Effective treatment regimens for fusariosis in transplantation are unknown but invariably require correction of neutropenia.[66,67] Response rates of disseminated fusariosis to antifungal therapy are disappointing, as most organisms are resistant to currently available antifungals.[66,71] Surgical resection of localized disease combined with topical antifungal therapy has been successful in most patients,[66] whereas treatment with amphotericin B alone has only a 32% response rate.[72] Response rates up to 45% are reported with voriconazole and posaconazole salvage treatment after amphotericin B failure.[48,73] Adjunctive therapy with granulocyte transfusions and granulocyte colony-stimulating factor has shown some benefit but has not been extensively studied.[65]

Scedosporium apiospermum and Scedosporium prolificans

The genus *Scedosporium* includes two important human pathogens, *S apiospermum* and *S prolificans.* Historically, *Scedosporium* species are found in patients with hematologic malignancy or destructive chronic lung disease such as CF. *Scedosporium* species are the second most common mold (after *Aspergillus* species) colonizing airways of patients with CF.[74–77] These organisms are found ubiquitously in soil, sewage, and polluted waters and are histologically indistinct from *Aspergillus*, *Fusarium*, and other mycelial fungi.[78] Infection occurs via inhalation of spores or direct tissue inoculation and most commonly involves the respiratory tract.[78,79]

Before 2000, there were only 4 cases of disseminated infection in organ transplant recipients.[80] Recently, *Scedosporium* has emerged as a pathogen among the growing immunocompromised population, particularly transplant recipients. PCR methods are being developed to facilitate early identification of this pathogen.[75] The spectrum of disease for both *Scedosporium* species resembles aspergillosis. However, there are notable clinical differences between these 2 pathogens. *S apiospermum*, the asexual anamorph of *Pseudallescheria boydii,* is found throughout the world, whereas *S prolificans* is geographically concentrated in Spain, Australia, and the southern United States.[76–78,81] Rates of invasive infection are reported in 6% of cases with *S apiospermum* and in more than half of patients with *S prolificans.*[76] In addition, mortality rates of *S apiospermum* and *S prolificans* infection range from 47% to 68% and from 50% to 100%, respectively, with respiratory involvement associated with higher mortality.[74,76,77,79,82,83]

Scedosporium infections have been reported since 1985 in bone marrow transplant recipients but only recently in solid organ transplantation with prominent differences in

manifestations of infection within these 2 populations.[77] In a comparison between 23 HSCT and 57 solid organ recipients with *Scedosporium* species infection, the former were more likely to have infection by *S prolificans* and have early infections (within 90 days compared with >1 year) given that solid organ recipients rarely become neutropenic. HSCT recipients were also more likely to develop fungemia and had the poorest response to therapy (40%–45% compared with 63%).[77,80,81,84] Reported rates of fungemia (70%) and dissemination (44%) with *S prolificans* are notably greater than with *Aspergillus* species and is attributed to the organism's ability to undergo adventitious sporulation.[83,84]

Unfortunately, effective antifungal therapy for *Scedosporium* infection is lacking. *S apiospermum* and *S prolificans* are resistant to amphotericin B and most antifungals. *S apiospermum* may have some susceptibility to the newer triazoles, and anecdotal regimens based on prior successfully treated cases are reported using voriconazole as monotherapy or in combination with terbinafine or an echinocandin.[74,81,82,85,86] *S prolificans*, however, remains resistant to all antifungals, as no therapy was shown to reduce mortality.[83,85] Only surgical excision and recovery from neutropenia were independently associated with survival from *S prolificans*.[83] Long-term itraconazole treatment in combination with fluconazole among patients with structurally abnormal airways who were colonized with *Scedosporium* species have lower rates of dissemination, suggesting a possible role of maintenance therapy to prevent disease progression.[84]

EMERGING VIRAL RESPIRATORY INFECTIONS IN TRANSPLANTATION

Human Metapneumovirus

Human metapneumovirus (hMPV) is a nonsegmented, single-stranded RNA virus belonging to the Paramyxoviridae family. First described in 2001 in the Netherlands among children with acute respiratory viral symptoms, hMPV has since been increasingly noted to have worldwide distribution among children and immunocompromised adults, including transplant recipients.[87–91]

Infection with hMPV mimics the course of respiratory syncytial virus (RSV), with a spectrum from mild respiratory symptoms and wheezing to severe bronchiolitis and pneumonia. Symptomatic infection occurs in less than 5% of the general population and up to about 5% to 10% of the immunocompromised population.[87,89,92] In temperate climates, seasonal variation occurs predominantly in late winter (January to April).[87–89] The clinical and radiographic courses of the disease closely resemble that of RSV infection, and this diagnosis should be considered after RSV infection is ruled out.[87]

The first case of hMPV in transplantation involved an HSCT recipient who died within a week because of pneumonia and respiratory failure.[93] Since then, multiple series among HSCT, lung, and a liver recipient have been published.[88–90,93–101] One study involving lung transplantation recipients showed an association between detection of replicating hMPV in bronchoalveolar lavage specimens and allograft rejection.[96] Despite intensifying immunosuppression to treat acute rejection, viral clearance and reduced viral replication to lower than detectable levels was still achievable in contrast to other respiratory viral data, particularly cytomegalovirus infection data, which show increased viral replication with intensification of immunosuppression.[96] This observation suggests differing mechanisms of viral clearance between these 2 pathogens, which has not been elucidated.

Diagnosis of hMPV disease is confounded by several factors. First, persistent detection of the virus in nasopharyngeal aspirates is reported in up to 85% of asymptomatic HSCT and lung recipients.[96,98] No long-term respiratory sequelae in

persistently infected patients have been noted.[98] Second, primary infection is nearly universal by age 5 years, necessitating a 4-fold increase in antibody titer or seroconversion to establish a diagnosis in adults.[87] Third, although isolation of hMPV with standard cell culture techniques is the definitive method of detection, it is technically difficult, as the virus does not grow efficiently in traditional cell lines used for viral isolation.[87] PCR is the most widely used method of detection of hMPV but largely limited to research investigation.[87] Fourth, although nasopharyngeal aspirates are easily obtainable, detection is less sensitive than in bronchoalveolar lavage specimens.[95]

No agent has been approved to treat hMPV in immunocompromised hosts, but because of the close clinical correlation to RSV, similar therapies have been used.[99] A combination of intravenous ribavirin and immunoglobulin has been successful in the treatment of an HSCT recipient.[88,99] Intravenous ribavirin treatment has been used in a lung transplant recipient after isolated respiratory symptoms progressed to systemic disease and shock despite inhalational treatment. After repeat bronchoalveolar lavage specimens tested negative by PCR, therapy was discontinued.[88]

With increasing reports in the transplant literature of hMPV causing disease, it would be prudent to include hMPV in the differential diagnosis of respiratory infections, especially in winter months. Early diagnosis of hMPV infection may reduce injudicious use of antibiotics and invasive diagnostic investigations and promote appropriate infection control practices to prevent nosocomial spread.[94]

Lymphocytic Choriomeningitis Virus

Lymphocytic choriomeningitis virus (LCM) is an RNA arenavirus. Serologic surveys estimate that 5% of the US population has been infected but remained asymptomatic or had only mild self-limited infection.[102,103] LCM in immunocompromised individuals, however, can cause an acute febrile illness with fatal dissemination.[102–104] Posttransplant infections present as an acute, nonspecific febrile illness, often with abdominal symptoms that frequently progress to severe illness. Diagnosis is made by serologic testing for anti-LCM IgG or IgM antibodies, isolation of the virus from blood or cerebral spinal fluid, and immunohistochemical staining of tissue specimens or PCR.[102,103]

Infection occurs from either direct or indirect exposure to aerosolized rat urine or excrement of the common house mouse, the natural host for the virus.[102,103] Human-to-human transmission has also been documented from mother to fetus and via donor organs to recipients.[102–104] Among the clusters of LCM transmission by donor organs, 12 of 13 recipients died of multisystem organ failure, and the lone surviving patient responded to ribavirin therapy and reduction of immunosuppression.[102–104] Interestingly, none of the donors responsible for transmission had clinical signs of infection, none had IgG or IgM antibodies to LCM, and only one had an identified rodent exposure. No known treatment trials have been reported. Ribavirin use is based on in vitro viral susceptibility, but the effectiveness of this therapy and need to reduce immunosuppression remains unclear.

Diagnosis of lymphocytic choriomeningitis is difficult. Current assays to detect LCM are notably insensitive, with frequent false-negative test results during donor screening.[102,103] Lack of accurate and sensitive diagnostics for LCM necessitate rapid 2-way communication between organ procurement organizations and transplantation centers to help identify clustering of patient infections stemming from a common donor.

Severe Acute Respiratory Syndrome

A corona virus causes the severe acute respiratory syndrome (SARS) associated with an outbreak in the Toronto area linked to an index case of a traveler from Hong Kong.

Several SARS cases diagnosed by PCR of bronchoalveolar lavage samples occurred in 2003 among solid-organ and HSCT recipients. In 2 cases, despite treatment with ribavirin and reduction of immunosuppression, rapid, fatal progression to respiratory failure ensued.[1,105] One allogeneic bone marrow recipient survivor was treated with oral prednisolone and ribavirin.[106]

Subsequently, a risk stratification tool initially used for donor screening of SARS based on hospital exposure, clinical symptoms, imaging studies, and contact history was developed.[1,105] A modified version was later implemented for potential recipients. This screening protocol highlights the need for high clinical suspicion and early initiation of specific diagnostic testing with existing serologic tests or PCR methods, if available.

SUMMARY

Respiratory infections in transplantation medicine will continue to pose significant obstacles with associated detrimental effects on morbidity and mortality. The high morbidity and mortality observed from emerging infections stem from protean manifestations of disease, which delay diagnosis as well as appropriate diagnostic and therapeutic interventions. Early institution and maintenance of antimicrobial therapy is often restricted by toxicity and interactions with necessary immunosuppressive drugs. Also, limited data on effective antimicrobial regimens exist, with most therapeutic strategies based on anecdotal experiences.

Despite the introduction of newer antimicrobials, infections continue to emerge, especially among transplantation recipients. The interaction of several additional factors including transplant type, surgical technique, underlying metabolic defects, epidemiologic exposures, extent and nature of immunosuppression, and prior antimicrobial use contribute to development of infection. Technological advances have improved diagnostic techniques and modalities to define few new, previously uncharacterized pathogens. Innovations have also enabled definitive genotypic distinctions of pathogens formerly characterized exclusively by phenotypic differences. Finally, the transplant population has experienced increasing numbers, intensification of immunosuppressive regimens, and prolonged survival. Clinicians should focus on prevention of infections if at all possible, consider a broad but rational range of causes of infections in patients presenting with respiratory symptoms and perform early interventional procedures such as bronchoscopy with bronchoalveolar lavage and/or transbronchial biopsy or surgical biopsy as clinically indicated for adequate diagnostic sampling while maintaining awareness of the potential for multidrug resistance.

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