Prophylaxis Against Pulmonary Viral and Fungal Infections in Solid Organ Transplant Recipients

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Pulmonary viral and fungal infections in solid organ transplant recipients are one of the most common and potentially life-threatening infections. Understanding the strategies used for prophylaxis and prevention of these infections is critical for the health and well-being of transplant recipients. Prophylactic measures range from simple patient education to complex chemoprophylactic interventions; however, a multifaceted approach is most often required. This article focuses on strategies to prevent pulmonary viral and fungal infections in transplant recipients, with an emphasis on recent evidence that may influence practice guidelines.

Introduction

Pulmonary infection is a major cause of morbidity and mortality for patients with transplanted organs. This article focuses on the currently available preventive and prophylactic measures to minimize the risks of pulmonary viral and fungal infections in solid organ transplant (SOT) recipients. The importance of diagnostics and management of an established infection are not covered in this article.

Pulmonary Viral Infections

In healthy, immunocompetent adults, pulmonary viral infections typically produce a mild and self-limited upper respiratory tract infection. However, in solid organ transplant (SOT) recipients, potent immunosuppressive medications lead to severe dysfunction of cell-mediated immunity, which constitutes an important mechanism of defense against viral infections. For some SOT recipients, this is compounded by postoperative changes of the lung that favor the establishment of infection, including a diminished cough reflex, abnormal lymphatic drainage, and impaired mucociliary clearance. As a consequence, this group of often mild infections causes significant morbidity and mortality in SOT recipients. The causative organisms of pulmonary viral infections in SOT recipients are shown in Table 1. Most are caused by two major groups—the respiratory viruses and the herpesviruses—which are the focus of this article.

Respiratory Viruses

Epidemiology of respiratory viruses in SOT recipients

Common respiratory viral infections in SOT recipients include influenza, parainfluenza, respiratory syncytial virus (RSV), rhinovirus, adenovirus, coronaviruses, and human metapneumovirus. Epidemiologic studies of respiratory viral infections in SOT recipients are limited, and vary widely in their results because of differences in seasonality, location, organ transplant type, and method of viral detection. The most commonly reported include RSV, influenza, parainfluenza virus, adenovirus, and human metapneumovirus [1–3]. Few studies address the incidence of rhinovirus and coronaviruses.

Compared with immunocompetent individuals, infection with the respiratory viruses in SOT recipients is associated with a longer duration of infection, increased risk of lower respiratory tract infection and complications, increased mortality, and increased viral shedding [1,4,5]. For example, about 13% of SOT recipients with influenza develop lower tract infection and extrapulmonary complications are more common, including bacterial superinfection, graft dysfunction, and rejection [6,7]. Moreover, subsequent obliterative bronchiolitis in lung transplant recipients is well described [7]. Parainfluenza virus is associated with acute cellular rejection and bronchiolitis obliterans [8]. Prolonged shedding of RSV in the immunosuppressed is well described [5], and the virus is associated with bronchiolitis obliterans in lung transplant recipients [3].

Table 1. Causative organisms of pulmonary viral infections in solid organ transplant recipients

Respiratory viruses	Herpesviruses	Other rare causes
Respiratory syncytial virus	Herpes simplex virus type 1 and 2	Avian influenza
Influenza	Varicella zoster virus	Human bocavirus
Parainfluenza	Cytomegalovirus	Coronavirus (SARS)
Adenovirus	Epstein-Barr virus	Measles
Rhinovirus	Human herpes virus type 6	Parvovirus B19
Coronaviruses (non-SARS)		Hantavirus
Human metapneumovirus		

SARS—severe acute respiratory syndrome.

Prophylaxis and prevention of respiratory viruses in SOT recipients

Prophylaxis and prevention of the respiratory viruses involve a multifaceted approach including patient education, institution of precautions in the community and acute care settings, and vaccination and chemoprophylaxis against influenza.

General principles

Respiratory viruses are spread through contaminated secretions. Many principles of prevention are applicable to the general population; however, given the potential risks of infection in SOT recipients, the level of adherence should be significantly greater. These measures must also be more strictly enforced during periods of increased immunosuppression (early posttransplant; periods of rejection), during high-risk seasons, and in those who have undergone lung transplantation. Furthermore, the risk of infection acquisition through contact with contaminated surfaces must also be stressed. Regular hand hygiene either with hand washing or an alcohol-based hand rub, especially after touching surfaces in communal areas, is an important education message. Patients should avoid contact with persons who are unwell and be aware that young children, especially those in daycare, can have increased carriage of respiratory viruses. Exposure is particularly risky during periods of increased immunosuppression.

Strict adherence to national and local infection control guidelines is essential in health care center areas where SOT recipients are frequent visitors. Broad objectives are to avoid transmission from staff, patient visitors, and other patients. Visual alerts at the entrance of hospitals and high-risk wards are effective in identifying staff and visitors with respiratory symptoms. The US Centers for Disease Control and Prevention (CDC) recommend contact isolation for all patients who have a suspected respiratory viral infection and droplet precautions for influenza, adenovirus, and rhinovirus [9]. It is reasonable to institute droplet precautions until these viral etiologies are excluded. Readers are referred to the CDC guidelines for further details [9].

Prophylaxis using vaccination

At this stage, vaccination is only available for the prevention of influenza. Annual vaccination with the trivalent inactivated vaccine (TIV) is strongly recommended in all SOT recipients [2,10]. The TIV is preferred for vaccinating household members, health care personnel, and all others in close contact with immunosuppressed persons. The safety and efficacy of the live, attenuated influenza vaccine has not been established in this population and should be avoided [11]. Disparity continues to exist between current recommendations for influenza vaccination and clinical practice [12••]. Reasons for withholding influenza vaccination in SOT recipients have included concerns regarding graft rejection and a suboptimal immunologic response [13]. Several recent studies provided further evidence of the safety of influenza vaccination after transplantation. Scharpe et al. [14•] performed a prospective trial in 165 renal transplant recipients and showed no effect on allograft function or rejection. A multicenter study by White-Williams et al. [13] including 3601 heart transplant recipients more than 1 year after transplant demonstrated no difference in the number of rejection episodes vaccinated compared with unvaccinated transplant recipients. The safety of influenza vaccination is also evident in adult liver transplant recipients, with no association to allograft rejection or flares in transaminases reported [15].

The immunogenicity of the TIV in SOT recipients varies in relation to transplant type, time from transplantation, type and intensity of immunosuppression, and annual vaccine-related factors [11,16•]. Previous studies on the efficacy of the TIV in SOT were mostly small, nonrandomized trials with widely varied results. A few recent studies sought to further address this issue. In the study by Scharpe et al. [14•] of renal transplant recipients, seroprotective rates (measured by a hemagglutination-inhibiting antibody titer > 40) and seroresponse rates (defined by a fourfold rise in hemagglutination-inhibiting titer) were comparable with healthy volunteers at more than 6 months posttransplant. A booster dose of vaccine failed to show benefit in the immune response [14•]. A prospective trial in pediatric liver transplant recipients more than 3 months posttransplant and their healthy siblings demonstrated that after one dose of TIV, transplant recipients achieved rates of antibody seropositivity similar to their siblings [17]. However, a significantly decreased cell-mediated immune response was reported [17]. Further studies are needed to establish whether there is a causal link

between neutralizing antibody production, cell-mediated responsiveness, and overall protection against viral infection in patients with varying levels of immunosuppression [16•].

Chemoprophylaxis

Chemoprophylaxis for respiratory viruses in SOT recipients is only available for influenza. CDC guidelines recommend consideration of antiviral prophylaxis in patients who are receiving immunosuppressants and those who are at risk of not responding to the vaccine [2,11]. Antiviral prophylaxis should also be considered for close contacts of immunosuppressed patients and for health care providers who are unvaccinated during times of increased influenza activity or if an outbreak is caused by a strain of influenza that might not be covered by the annual vaccine [11]. Strategies for prophylaxis include the administration of a defined regimen throughout a high-risk period or the administration of a defined regimen to an individual shortly after a high-risk exposure to an active source of infection to prevent or attenuate the clinical manifestation of disease. General chemoprophylaxis should be based on proof through virologic surveillance that an epidemic is occurring in the community. The need for daily compliance, possible side effects, and the risk of resistance development should be taken into account [11].

Two types of anti-influenza medications are available for prophylaxis: the M2 matrix inhibitors amantadine and rimantadine, which only have activity for influenza A, and the neuraminidase inhibitors oseltamivir and zanamivir, which have activity for influenza A and B. Since January 2006, the neuraminidase inhibitors were considered first-line therapy because of their enhanced activity against both influenza A and B and the widespread resistance to the adamantanes among influenza A (H3N2). Increasing resistance to oseltamivir was reported in H1N1 strains in the United States [11,18]. Thus, the CDC recently published revised guidelines for influenza chemoprophylaxis [18]. When an influenza A (H1N1) virus infection or exposure is suspected, zanamivir (10 mg once daily) or a combination of oseltamivir (75 mg daily) and rimantadine (100 mg twice daily) is now preferred over oseltamivir alone. When an influenza B virus infection or exposure is suspected, oseltamivir or zanamivir can be given [18]. The dosage of these antiviral medications may differ in children, the elderly, or in patients with hepatic or renal dysfunction. The recent changes in guidelines highlight the need to review local and state surveillance data to determine the circulating influenza virus strains and the most current recommendations for antiviral use. Despite a paucity of data on the optimal timing, dosing, and efficacy of chemoprophylaxis in the immunocompromised patient, current recommendations are to use the same dose and duration as prescribed for immunocompetent individuals [2].

Limited data regarding drug interactions are available for oseltamivir; however, this drug is generally well tolerated with the most frequent adverse reaction being nausea and vomiting [11]. Zanamivir, which is administered as an inhalation, has no known drug interactions; however, it has a potential side effect of bronchospasm and is only licensed for use in persons age 5 years and older without underlying respiratory or cardiac disease [11]. It was previously avoided in lung transplant recipients. Amantadine and rimantadine are associated with neurologic toxicity in the general population. Amantadine can be substituted for rimantadine but has an increased risk of drug interaction and side effects [18]. Rarely, amantadine is associated with cardiac dysrhythmia and congestive heart failure, and is contraindicated with potassium chloride. Dosing adjustment is required in those with renal impairment for oseltamivir, rimantadine, and amantadine. Readers are referred to the product insert for each antiviral agent for further details.

In specific groups of high-risk infants and children, prophylaxis with the RSV-specific monoclonal antibody (Palivizumab) or high-titer RSV-intravenous immune globulin is effective; however, no studies have adequately evaluated the use of either agent in SOT recipients [2]. Some experts support their use for prophylaxis in children under 1 year of age who undergo transplantation during times of increased RSV activity [2], and a recent survey of pediatric SOT centers showed that about 50% of responding centers use these agents in some fashion [19].

Herpesviruses

Epidemiology of herpesviruses in SOT recipients

Albeit less common, the herpesviruses are an important cause of pulmonary infection in SOT recipients. The major etiologic agents include herpes simplex virus (HSV) type 1 and 2, varicella zoster virus (VZV) and cytomegalovirus (CMV) [20,21]. CMV is a major cause of disease and mortality in SOT recipients, especially high-risk patients (donor seropositive and recipient seronegative) [21]. CMV often shows tissue tropism for the transplanted organ and thus lung or heart-lung transplant recipients are at highest risk for pulmonary disease [21]. In the absence of prophylaxis, the highest risk period is 1 to 3 months after transplantation or during late episodes of rejection [21,22••].

HSV 1 and 2 and VZV are more likely to cause disseminated disease, including pneumonitis, in SOT recipients [20]. Pneumonitis with these viruses should be considered a medical emergency. In the absence of prophylaxis, most cases occur early after transplant, typically within the first 1 to 2 months [20]. HSV pneumonia most commonly occurs in lung and heart-lung transplant recipients but can occur in all transplant patients, particularly if intubation or bronchoscopy is performed during an active HSV infection [23]. VZV disease in posttransplant adults is usually from reactivation of latent virus and occurs later than HSV, often greater than 3 months posttransplant. Primary VZV is rare posttransplant but may occur in seronegative individuals, most commonly in pediatric patients [20].

Prophylaxis and prevention of herpesviruses in SOT recipients

The prevention of herpesviruses in SOT recipients focuses on antiviral chemoprophylaxis. VZV vaccination pre-transplant is also a strategy that may be used. Fortunately, the antiviral agents used for chemoprophylaxis of CMV are also active against HSV and VZV. There are two major strategies for the prevention of CMV infection in the SOT recipient: universal prophylaxis and preemptive therapy [22••,24]. *Universal prophylaxis* refers to the administration of antiviral therapy to all patients during a defined high-risk period after transplantation. *Preemptive therapy* is the administration of antiviral therapy in response to detection of CMV viremia before the patient becomes symptomatic with CMV disease. Although both strategies are associated with a reduction in CMV disease, as well as allograft rejection, only universal prophylaxis was found to reduce bacterial and fungal infections, which are other indirect effects of CMV [24]. Universal prophylaxis also reduced CMV disease in patients at highest risk (donor-positive, recipient-negative patients and patients given antilymphocyte antibodies) [22••,24].

The peak incidence of CMV disease has shifted from less than 4 months to 4 to 6 months, most likely related to the widespread use of prophylaxis. Intravenous ganciclovir (5 mg/kg/d), oral ganciclovir (3 g/d), and valganciclovir (900 mg/d) (doses based on normal renal function) are the typical antiviral agents used for CMV prophylaxis with a recommended duration of 12 to 14 weeks [21]. Given the improved bioavailability and logistic advantages of once-daily dosing, valganciclovir is becoming the preferred agent for CMV prophylaxis. Increasing evidence of its efficacy equivalent to intravenous ganciclovir is being reported in a range of transplant types [22••,25]. There is concern that valganciclovir in liver transplant recipients leads to a higher incidence of tissue-invasive disease; however, many experts still recommend its use [21].

Guidelines established for lung transplant recipients, who are at higher risk for CMV pneumonitis, recommend that all recipients should be considered for prophylaxis, regardless of recipient and donor serostatus [22••,26]. Valganciclovir is recommended for at least 100 days although longer duration may be considered [26]. Some also believe that CMV immunoglobulin should be considered in combination with antivirals in high-risk lung transplant recipients [22••,26].

If CMV prophylaxis is interrupted or a preemptive approach is used, HSV and VZV prophylaxis should be instituted for a minimum of 30 to 90 days posttransplantation. Oral acyclovir, 200 mg or 400 mg orally, two to three times daily, was shown to effectively prevent HSV and VZV [20,23]. Current guidelines recommend that transplant candidates who are seronegative for VZV receive the live attenuated Varicella vaccine pre-transplant to prevent posttransplant primary varicella infection [10]. It should be given at least 4 to 6 weeks prior to transplant if possible and is contraindicated for patients posttransplant [10,12••]. Vaccination of susceptible family members is an additional method of protecting the high-risk transplant patient.

Postexposure prophylaxis is another important consideration in the prevention of VZV disease in SOT recipients. Seronegative patients with a defined exposure within the previous 96 hours should receive postexposure prophylaxis with varicella zoster immune globulin (VZIG) [20,23]. If the therapeutic window for VZIG has passed, if VZIG is unavailable, or if the patient is at very high risk for disseminated disease, postexposure prophylaxis with oral antiviral agents should be considered [20,23].

Pulmonary Fungal Infections

Epidemiology of pulmonary fungal infections in SOT recipients

Although fungi are not the most common cause of pulmonary infections in SOT recipients, they are a major cause of mortality [27•]. Despite *Pneumocystis jiroveci* being classified as a fungus, it is not covered in this article. Readers are referred to the American Society of Transplantation guidelines for further details on *P. jiroveci* prophylaxis in this population [28]. *Candida* spp and *Aspergillus* spp are the most commonly reported fungal pathogens in SOT recipients. *Candida* is frequently isolated from the respiratory tract; however, it rarely causes invasive pulmonary disease. An exception occurs in lung transplant recipients, in whom *Candida* can cause tracheobronchitis at the anastomotic site [29].

The incidence of invasive aspergillosis in SOT recipients varies according to the transplanted organ. Similar to pulmonary viral infections, the highest incidence is observed in lung transplant recipients, ranging from 6% to 16% [30]. This is followed by heart recipients (1%–14%) [31], liver recipients (1%–8%) [32], and lastly by kidney and pancreas recipients, who have the lowest incidence (0.4%–5%) [33]. New trends in invasive aspergillosis among SOT recipients are documented. More cases of late invasive aspergillosis (ie, occurring > 90 days after transplantation) are being observed [32]. A shift has occurred in the clinical presentation, with a decrease in the number of cases of disseminated disease and those with central nervous system (CNS) involvement, and an increase in the number of patients with isolated pulmonary aspergillosis [32]. Possible explanations for these trends include less occurrence of organ dysfunction postoperatively, particularly renal dysfunction, later occurrence of CMV infection and disease, and earlier diagnosis and initiation of appropriate therapy. Fortunately, a decrease in mortality was also observed [32].

An increase in the number of non-*Aspergillus* molds, such as Zygomycetes, *Fusarium*, *Scedosporium*, and the phaeohyphomycetes, was described as a cause of pulmonary fungal infections in SOT recipients [34,35]. This trend is worrisome for several reasons: these fungi are often resistant to antifungal therapy; they tend to be more associated with disseminated disease and involve the

Table 2. Chemoprophylactic strategies for pulmonary fungal infections in organ transplantation, assuming normal renal and hepatic function

Pathogen	Allograft	Antifungal agent	Duration
Aspergillus	Liver	Lipid formulation of amphotericin B, 5 mg/kg/d	Until resolution of risk factors
Aspergillus	Lung	Aerosolized amphotericin B, 6–30 mg/d, or voriconazole, 400 mg/d	2 wk to lifelong
Candida	Lung	Same strategies as for Aspergillus	2 wk to lifelong
Cryptococcus	All	Not recommended	—
*Coccidioides**	All	Fluconazole, 200–400 mg/d	6 mo to lifelong

*Prophylaxis recommended only in the setting of previous coccidioidal infection or positive serology.

CNS; and the associated mortality is very high. Possible explanations for this trend include the use of intensified immunosuppression and exposure to antifungal agents with poor activity toward these molds. Concerns about an increase in the incidence of zygomycosis with the use of voriconazole were raised. However, data from large transplant centers showed an increase in the number of cases prior to the availability of voriconazole, suggesting that other causes may also be involved [36].

Cryptococcosis occurs in 0.26% to 5% of organ transplant recipients, with an overall mortality of 42% [37]. Recently, an increase in the cumulative incidence of cryptococcosis was associated with the use of two or more doses of antilymphocyte globulin or alemtuzumab [38].

Coccidioidomycosis, histoplasmosis, and blastomycosis are endemic fungal infections that can manifest as isolated pulmonary disease or disseminated infection in SOT recipients. They can occur as a primary infection from an environmental exposure, reactivation of a latent infection, or rarely from primary infection from the donor. The latter was not reported for blastomycosis. The incidence of coccidioidomycosis following organ transplantation ranges from 1% to 9% in highly endemic areas, with a mortality rate as high as 70% [39]. Most cases occur in the first year after transplantation. A study in liver transplant recipients who relocated to an endemic area following transplantation showed that the rate of new infection was 2.7% in the first year [40]. The incidence of histoplasmosis in SOT recipients living in endemic areas is not known, but rates of 0% to 2.1% were reported [41]. Blastomycosis following organ transplantation is rare, and no numbers on incidence are available.

Prophylaxis and prevention of pulmonary fungal infections

General principles

Many of the fungal pathogens are ubiquitous in the environment including soil, decomposing plant material, household dust, ornamental plants, building sites, and water. Several measures, such as the ones described below, can be implemented to minimize patient exposure to high-risk environments. However, no studies were done to determine the effectiveness of these measures [42].

More specific patient education should include advice about avoiding 1) excavation, construction, and other dust-full environments because of high concentrations of mold spores [43]; 2) marijuana use because of its association with *Aspergillus* spores; 3) farming and gardening, if possible, during the first year following transplantation, to minimize exposure to decomposing vegetable matter and soil; 4) exposure to bird droppings, caves, chicken coops, and plant and soil aerosols because of potential exposure to *Cryptococcus*, *Histoplasma*, and *Coccidioides*. If exposure cannot be avoided, use of a mask is recommended. In-hospital construction areas should be carefully isolated to avoid the spread of mold spores to patient areas. Data are currently not available to advise on the use of high-efficiency particulate air filters as a strategy to minimize the incidence of pulmonary fungal infections in SOT recipients. There is also no evidence that protective isolation offers any benefit over standard care while patients are hospitalized [44].

Chemoprophylaxis

Antifungal prophylaxis in SOT recipients is a controversial topic. Very few studies are well-designed and controlled, and most reflect a single center's experience. Furthermore, great variation in antifungal prophylactic strategies exists between the different centers with regard to the agent used and duration of prophylaxis. Finally, several of the available antifungal agents are associated with significant interactions with commonly used immunosuppressive medications.

The different antifungal prophylactic strategies available for SOT recipients are summarized in Table 2. Lipid formulations of amphotericin B at a dose of 5 mg/kg were efficacious in preventing aspergillosis in high-risk liver transplant recipients [45]. However, low doses (1 mg/kg) and amphotericin B deoxycholate were not adequate for prophylaxis in this patient population [46]. As discussed for CMV prophylaxis, two strategies for prophylaxis against *Aspergillus* exist for lung transplant recipients: universal prophylaxis and preemptive therapy. Preemptive therapy consists of administration of antifungal therapy whenever *Aspergillus* is isolated from a respiratory specimen. This is possible in lung transplant recipients because they undergo routine surveillance bronchoscopies with biopsy to monitor for rejection. Overall, however, universal prophylaxis is more common.

Aerosolized amphotericin B is the most common form of prophylaxis used in lung transplant recipients. Its use is attractive because it delivers the antifungal agent directly to the infection site, minimizing systemic side effects and drug interactions. A disadvantage of this strategy is that in single-lung transplant recipients, the distribution of the aerosolized amphotericin B occurs preferentially in the transplanted lung, leaving the native lung as a potential source of infection [47•]. Both amphotericin B deoxycholate and the lipid formulations were studied, with the lipid formulations being better tolerated. Side effects include cough, nausea, and bronchospasm. Voriconazole is also used for *Aspergillus* prophylaxis in lung transplant recipients. Husain et al. [48] showed that prophylactic voriconazole for a minimum of 4 months posttransplant decreased the rate of invasive aspergillosis 23% to 1.5%; however, liver enzyme abnormalities occurred in a large proportion of patients. All the strategies described above are also effective for the prevention of *Candida* infections.

Use of antifungal prophylaxis is not recommended for the prevention of cryptococcosis. Patients with a history of coccidioidomycosis and/or with a positive coccidioidal serology should receive lifelong prophylaxis with fluconazole following organ transplantation [49•]. The risk of reactivation of histoplasmosis in patients who live in an endemic area and have evidence of remote *Histoplasma* infection was deemed very low. Pretransplant *Histoplasma capsulatum* serologies are not predictive of disease risk [41]. Therefore, antifungal prophylaxis following SOT is not currently recommended; however, histoplasmosis should be considered in the differential diagnosis if a febrile illness occurs. The availability of posaconazole (an azole with a broader spectrum of activity against molds, including the Zygomycetes) has raised interest in the use of this agent for prophylaxis in SOT recipients. However, no data on its safety and efficacy in this setting are currently available.

Conclusions

The saying "an ounce of prevention is worth a pound of cure" has a special poignancy in the care of transplant recipients. Pulmonary viral and fungal infections remain a persistent cause of morbidity and mortality in SOT recipients, and strategies to better prevent them are desperately needed. The development of new vaccines targeting other respiratory viruses, particularly RSV, and newer antimicrobial agents for chemoprophylaxis should be areas of active development. A discussion of rapid diagnostics was beyond the scope of this article, but future efforts should focus on the development of such technologies. Studies that aim to better stratify patients at risk for invasive fungal infection are also needed. This may include the use of novel immunologic assays that monitor the patient's overall net state of immunosuppression [50], more directed use of fungal biomarkers, or early molecular diagnostics.

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References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. Barton TD, Blumberg EA: **Viral pneumonias other than cytomegalovirus in transplant recipients.** *Clin Chest Med* 2005, **26:**707–720, viii.
2. **Community-acquired respiratory viruses.** *Am J Transplant* 2004, **4(Suppl 10):**105–109.
3. Hopkins P, McNeil K, Kermeen F, et al.: **Human metapneumovirus in lung transplant recipients and comparison to respiratory syncytial virus.** *Am J Respir Crit Care Med* 2008, **178:**876–881.
4. **Adenovirus.** *Am J Transplant* 2004, **4(Suppl 10):**101–104.
5. Ison MG, Hayden FG: **Viral infections in immunocompromised patients: what's new with respiratory viruses?** *Curr Opin Infect Dis* 2002, **15:**355–367.
6. Fishman JA: **Common pulmonary infections in immunocompromised patients. Up to Date Online, 2007.** Available at http://www.uptodate.com/online/content/topic.do?topicKey=immuninf/5252&selectedTitle=2~150&source=search_result. Accessed January 2009.
7. Vilchez RA, Fung J, Kusne S: **The pathogenesis and management of influenza virus infection in organ transplant recipients.** *Transpl Infect Dis* 2002, **4:**177–182.
8. Vilchez RA, Dauber J, McCurry K, et al.: **Parainfluenza virus infection in adult lung transplant recipients: an emergent clinical syndrome with implications on allograft function.** *Am J Transplant* 2003, **3:**116–120.
9. Siegel JD, Rhinehart E, Jackson M, Chiarello L, and the Healthcare Infection Control Practices Advisory Committee: **2007 Guideline for isolation precautions: preventing transmission of infectious agents in healthcare settings, June 2007.** Available at http://www.cdc.gov/ncidod/dhqp/pdf/isolation2007.pdf. Accessed January 2009.
10. **Guidelines for vaccination of solid organ transplant candidates and recipients.** *Am J Transplant* 2004, **4(Suppl 10):**160–163.
11. Fiore AE, Shay DK, Broder K, et al.: **Prevention and control of influenza: recommendations of the Advisory Committee on Immunization Practices (ACIP), 2008.** *MMWR Recomm Rep* 2008, **57:**1–60.
12. •• Avery RK, Michaels M: **Update on immunizations in solid organ transplant recipients: what clinicians need to know.** *Am J Transplant* 2008, **8:**9–14.

This article provides an excellent, up-to-date review of vaccination efficacy and safety in solid organ transplant recipients.

13. White-Williams C, Brown R, Kirklin J, et al.: **Improving clinical practice: should we give influenza vaccinations to heart transplant patients?** *J Heart Lung Transplant* 2006, **25:**320–323.
14. • Scharpe J, Evenepoel P, Maes B, et al.: **Influenza vaccination is efficacious and safe in renal transplant recipients.** *Am J Transplant* 2008, **8:**332–337.

This article reports a prospective trial assessing the efficacy and safety of the standard trivalent inactivated influenza vaccine in renal transplant recipients.

15. Lawal A, Basler C, Branch A, et al.: **Influenza vaccination in orthotopic liver transplant recipients: absence of post administration ALT elevation.** *Am J Transplant* 2004, **4:**1805–1809.

16.• Gangappa S, Kokko KE, Carlson LM, et al.: **Immune responsiveness and protective immunity after transplantation.** *Transpl Int* 2008, **21:**293–303.

This review outlines the immunologic response to vaccination in transplant recipients and provides a brief overview of the mechanism of action of immunosuppressant drugs and how they may affect immune response to vaccination.

17. Madan RP, Tan M, Fernandez-Sesma A, et al.: **A prospective, comparative study of the immune response to inactivated influenza vaccine in pediatric liver transplant recipients and their healthy siblings.** *Clin Infect Dis* 2008, **46:**712–718.

18. Centers for Disease Control and Prevention: **CDC Issues Interim Recommendations for the Use of Influenza Antiviral Medications in the Setting of Oseltamivir Resistance among Circulating Influenza A (H1N1) Viruses, 2008–09 Influenza Season.** Available at http://www2a.cdc.gov/HAN/ArchiveSys/ViewMsgV.asp?AlertNum=00279. Accessed January 2009.

19. Michaels MG, Fonseca-Aten M, Green M, et al.: **Respiratory syncytial virus prophylaxis: a survey of pediatric solid organ transplant centers.** *Pediatr Transplant* 2008 (Epub ahead of print).

20. **Other herpesviruses: HHV-6, HHV-7, HHV-8, HSV-1 and -2, VZV.** *Am J Transplant* 2004, **4(Suppl 10):**66–71.

21. **Cytomegalovirus.** *Am J Transplant* 2004, **4(Suppl 10):**51–58.

22.•• Torres-Madriz G, Boucher HW: **Immunocompromised hosts: perspectives in the treatment and prophylaxis of cytomegalovirus disease in solid-organ transplant recipients.** *Clin Infect Dis* 2008, **47:**702–711.

This article is a comprehensive and practical review of prevention and management of CMV in solid organ transplantation.

23. Miller GG, Dummer JS: **Herpes simplex and varicella zoster viruses: forgotten but not gone.** *Am J Transplant* 2007, **7:**741–747.

24. Kalil AC, Levitsky J, Lyden E, et al.: **Meta-analysis: the efficacy of strategies to prevent organ disease by cytomegalovirus in solid organ transplant recipients.** *Ann Intern Med* 2005, **143:**870–880.

25. Paya C, Humar A, Dominguez E, et al.: **Efficacy and safety of valganciclovir vs. oral ganciclovir for prevention of cytomegalovirus disease in solid organ transplant recipients.** *Am J Transplant* 2004, **4:**611–620.

26. Zamora MR, Davis RD, Leonard C: **Management of cytomegalovirus infection in lung transplant recipients: evidence-based recommendations.** *Transplantation* 2005, **80:**157–163.

27.• Silveira FP, Husain S: **Fungal infections in solid organ transplantation.** *Med Mycol* 2007, **45:**305–320.

This article reviews the epidemiology, risk factors, clinical presentation, treatment, and prophylactic strategies of the most common fungal infections in organ transplant recipients.

28. **Pneumocystis jiroveci (formerly Pneumocystis carinii).** *Am J Transplant* 2004, **4(Suppl 10):**135–141.

29. Grossi P, Farina C, Fiocchi R, Dalla Gasperina D: **Prevalence and outcome of invasive fungal infections in 1,963 thoracic organ transplant recipients: a multicenter retrospective study. Italian Study Group of Fungal Infections in Thoracic Organ Transplant Recipients.** *Transplantation* 2000, **70:**112–116.

30. Singh N, Husain S: **Aspergillus infections after lung transplantation: clinical differences in type of transplant and implications for management.** *J Heart Lung Transplant* 2003, **22:**258–266.

31. Montoya JG, Chaparro SV, Celis D, et al.: **Invasive aspergillosis in the setting of cardiac transplantation.** *Clin Infect Dis* 2003, **37(Suppl 3):**S281–S292.

32. Singh N, Avery RK, Munoz P, et al.: **Trends in risk profiles for and mortality associated with invasive aspergillosis among liver transplant recipients.** *Clin Infect Dis* 2003, **36:**46–52.

33. Cornet M, Fleury L, Maslo C, et al.: **Epidemiology of invasive aspergillosis in France: a six-year multicentric survey in the Greater Paris area.** *J Hosp Infect* 2002, **51:**288–296.

34. Husain S, Alexander BD, Munoz P, et al.: **Opportunistic mycelial fungal infections in organ transplant recipients: emerging importance of non-Aspergillus mycelial fungi.** *Clin Infect Dis* 2003, **37:**221–229.

35. Husain S, Munoz P, Forrest G, et al.: **Infections due to Scedosporium apiospermum and Scedosporium prolificans in transplant recipients: clinical characteristics and impact of antifungal agent therapy on outcome.** *Clin Infect Dis* 2005, **40:**89–99.

36. Kauffman CA: **Zygomycosis: reemergence of an old pathogen.** *Clin Infect Dis* 2004, **39:**588–590.

37. Vilchez RA, Fung J, Kusne S: **Cryptococcosis in organ transplant recipients: an overview.** *Am J Transplant* 2002, **2:**575–580.

38. Silveira FP, Husain S, Kwak EJ, et al.: **Cryptococcosis in liver and kidney transplant recipients receiving anti-thymocyte globulin or alemtuzumab.** *Transpl Infect Dis* 2007, **9:**22–27.

39. Blair JE, Logan JL: **Coccidioidomycosis in solid organ transplantation.** *Clin Infect Dis* 2001, **33:**1536–1544.

40. Blair JE, Douglas DD: **Coccidioidomycosis in liver transplant recipients relocating to an endemic area.** *Dig Dis Sci* 2004, **49:**1981–1985.

41. Vail GM, Young RS, Wheat LJ, et al.: **Incidence of histoplasmosis following allogeneic bone marrow transplant or solid organ transplant in a hyperendemic area.** *Transpl Infect Dis* 2002, **4:**148–151.

42. **Strategies for safe living following solid organ transplantation.** *Am J Transplant* 2004, **4(Suppl 10):**156–159.

43. Praz-Christinaz SM, Lazor-Blanchet C, Binet I, et al.: **Occupational risk assessment of aspergillosis after renal transplantation.** *Transpl Infect Dis* 2007, **9:**175–181.

44. Walsh TR, Guttendorf J, Dummer S, et al.: **The value of protective isolation procedures in cardiac allograft recipients.** *Ann Thorac Surg* 1989, **47:**539–544; discussion 544–545.

45. Fortun J, Martin-Davila P, Moreno S, et al.: **Prevention of invasive fungal infections in liver transplant recipients: the role of prophylaxis with lipid formulations of amphotericin B in high-risk patients.** *J Antimicrob Chemother* 2003, **52:**813–819.

46. Tollemar J, Hockerstedt K, Ericzon BG, et al.: **Liposomal amphotericin B prevents invasive fungal infections in liver transplant recipients. A randomized, placebo-controlled study.** *Transplantation* 1995, **59:**45–50.

47.• Corcoran TE, Venkataramanan R, Mihelc KM, et al.: **Aerosol deposition of lipid complex amphotericin-B (Abelcet) in lung transplant recipients.** *Am J Transplant* 2006, **6:**2765–2773.

This article illustrates the preferred deposition of aerosolized amphotericin B into the transplanted lung, a limiting factor for the use of this prophylactic strategy in single-lung transplant recipients.

48. Husain S, Paterson DL, Studer S, et al.: **Voriconazole prophylaxis in lung transplant recipients.** *Am J Transplant* 2006, **6:**3008–3016.

49.• Blair JE: **Approach to the solid organ transplant patient with latent infection and disease caused by Coccidioides species.** *Curr Opin Infect Dis* 2008, **21:**415–420.

This article provides an excellent review of the treatment and prevention of coccidioidomycosis following organ transplantation.

50. Kowalski RJ, Post DR, Mannon RB, et al.: **Assessing relative risks of infection and rejection: a meta-analysis using an immune function assay.** *Transplantation* 2006, **82:**663–668.