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Review

Respiratory viruses in transplant recipients: more than just a cold. Clinical syndromes and infection prevention principles

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ABSTRACT

Objectives: The aim of this review is to provide updated information on the clinical spectrum, treatment options, and infection prevention strategies for respiratory viral infections (RVIs) in both solid organ (SOT) and hematopoietic stem cell transplant (HSCT) patients.
Methods: The MEDLINE and PubMed databases were searched for literature regarding the aforementioned aspects of RVIs, with focus on respiratory syncytial virus, adenovirus, influenza virus, parainfluenza virus, human metapneumovirus, and rhinovirus.
Results: Compared to immunocompetent hosts, SOT and HSCT patients are much more likely to experience a prolonged duration of illness, prolonged shedding, and progression of upper respiratory tract disease to pneumonia when infected with respiratory viruses. Adenovirus and respiratory syncytial virus tend to have the highest mortality and risk for disseminated disease, but all the RVIs are associated with higher morbidity and mortality in these patients than in the general population. These viruses are spread via direct contact and aerosolized droplets, and nosocomial spread has been reported.
Conclusions: RVIs are associated with high morbidity and mortality among SOT and HSCT recipients. Management options are currently limited or lack strong clinical evidence. As community and nosocomial spread has been reported for all reviewed RVIs, strict adherence to infection control measures is key to preventing outbreaks.

Contents

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Introduction

Respiratory viral infections (RVI) such as those caused by respiratory syncytial virus (RSV), adenovirus (ADV), influenza virus, parainfluenza virus (PIV), human metapneumovirus (hMPV), and rhinoviruses typically cause self-limited upper respiratory tract infections (URTI) in immunocompetent hosts, but are associated with high morbidity and mortality in both bone marrow and solid organ transplant (SOT) recipients. The rates of these infections typically mirror epidemiological prevalence in the community, but the clinical course tends to be more aggressive early post-transplant. Most patients initially develop a URTI, and up to half may develop complicated lower respiratory tract infections (LRTI) (Raad et al., 1997; Lee and Barton, 2007), resulting in a prolonged duration of illness with viral shedding, graft dysfunction, graft loss, and sometimes even bronchiolitis obliterans among lung transplant recipients (LTRs) (Ison, 2009; Lee and Barton, 2007).

These respiratory infections are known to be community-acquired in the general population, but in transplant patients, nosocomial transmission is frequently encountered. In a study performed among bone marrow transplant (BMT) patients, 48% of RVIs were associated with nosocomial transmission (Whimbey et al., 1996).

The Centers for Disease Control and Prevention (CDC) recommend the implementation of specific measures to prevent the spread of RSV, PIV, ADV, and influenza virus infections within healthcare settings (Tablan et al., 2004). Studies suggest that infection control practices vary across institutions throughout the country and unfortunately are not widely implemented. Strict adherence to infection control measures such as hand hygiene and contact precautions, staff education regarding modes of transmission and disease prevention, regular monitoring of healthcare worker practices, and surveillance are key elements in the prevention of outbreaks (Tablan et al., 2004).

This article aims to review the literature on RVIs among transplant recipients, including their management and principles of infection prevention.

Respiratory syncytial virus

RSV is a common infectious complication of transplantation, with an incidence of up to 12% in hematopoietic stem cell transplant (HSCT) patients and 16% in adult LTRs. It has year-round prevalence, with peak incidence from September through April (Hirsch et al., 2013; Renaud and Campbell, 2011). Infections from RSV typically manifest as self-limiting URTIs in immunocompetent adults. However, LRTIs develop in about two-thirds of HSCT recipients (Hattington et al., 1992; Weigt et al., 2011). The progression to an LRTI is commonly observed in patients with an allogeneic stem cell transplant, mismatched donor transplant, graft-versus-host disease, old age, myeloablative therapy, long duration of lymphopenia, and early post-transplant infection (Weigt et al., 2011; Lavergne et al., 2011; Neemann and Freifeld, 2015). RSV infections in this patient population are associated with higher morbidity and mortality when compared to other RVIs.

Although the incidence of these infections typically follows community outbreaks, one study reported that up to two-thirds of RSV infections were hospital-acquired (Whimbey et al., 1995). During an outbreak of RSV infection among BMT recipients, pre-engraftment patients had a higher risk of acquiring RSV infections than engrafted patients (Hattington et al., 1992). If patients developed an infection isolated to the upper respiratory tract, outcomes were generally good, with 100% survival; however, mortality rose to 78% among patients with RSV pneumonia despite treatment with inhaled ribavirin. Prolonged viral shedding (21.7 days) was also associated with a higher rate of mortality (Hattington et al., 1992). In another study, RSV pneumonia was associated with 100% mortality among adult BMT recipients in whom antiviral therapy was started after the onset of respiratory failure.

The LTR population is the best studied group among adult SOT recipients for RSV infections. The overall mortality for RSV infections ranges from 10% to 20% among immunocompromised patients (Weigt et al., 2011). Although mortality is lower in LTRs than in BMT patients, morbidity remains high. According to one study, 72% of LTRs with RSV infections developed graft dysfunction (Hopkins et al., 2008). In terms of long-term sequelae, LRTIs caused by RSV have been associated with the development of reactive airway disease in pediatric patients, airflow decline in HSCT patients, and bronchiolitis obliterans syndrome in LTRs (Weigt et al., 2011).

Transmission

RSV infection is transmitted via droplets and direct skin contact (Jensen et al., 2016). Droplet transmission requires close contact (<1 m) with large-particle virus-containing droplets (>5 μm). While this may occur during sneezing, coughing, and procedures such as bronchoscopy, it is a less common means of nosocomial transmission, because larger particles do not remain suspended in air for a long time (Garner, 1996). Skin contamination, likely of healthcare workers, results in the nosocomial spread of RSV from one patient to another (Raad et al., 1997).

Treatment and prevention

Currently, no vaccines are available for the prevention of RSV infections (Weigt et al., 2011). Early diagnosis of infection and timely institution of antiviral therapy is critical to prevent progression to LRTI and to achieve a favorable outcome (Jones et al., 2000). Although there are no clear recommendations or randomized study data regarding the treatment of RSV, there are early reports of improved outcomes with inhaled ribavirin. However, aerosolized ribavirin is logistically difficult to administer and has teratogenic potential. Dispensing systemic oral and intravenous ribavirin has been effective in some cohort studies, with no available evidence to strongly recommend a specific route of administration (Weigt et al., 2011; Neemann and Freifeld, 2015; Lehners et al., 2013; Gross and Bryson, 2015; Beaird et al., 2016). Several reports describe combining ribavirin with intravenous immunoglobulin (IVIG) or RSV-specific immune globulin