

Viral Infections in Immunocompromised Patients

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EPIDEMIOLOGY AND CLINICAL ASPECTS OF COMMUNITY-ACQUIRED RESPIRATORY VIRUSES

Viruses that cause acute respiratory illness in the general population and are responsible for hospitalizations in persons of all ages with underlying medical conditions are also a common cause of respiratory disease in transplant recipients. With the widespread availability of sensitive and reliable molecular detection methods, common respiratory viruses including respiratory syncytial virus (RSV), influenza and parainfluenza viruses (PIVs), adenoviruses, rhinoviruses (RhV), and coronaviruses have been detected worldwide in transplant recipients. More recently, newly identified viruses such as human metapneumoviruses (HMPV) [1,2], new strains of coronaviruses [3], and bocavirus have also been detected in symptomatic transplant recipients [4].

Community-acquired respiratory viruses (CRV) have a significant impact on the morbidity and mortality of the transplant recipient, causing a variety of diseases ranging from self-limited upper respiratory tract illnesses (URIs) to life-threatening lower respiratory tract infection (LRTI) and occasionally disseminated disease. Disease manifestations are dependent on the specific virus, the type of transplant, and the type, degree, and duration of immune deficiency. Pneumonia following infection with these viruses may be primarily viral, bacterial, fungal, or mixed in origin. Some

respiratory viruses, such as parainfluenza viruses, may also have higher associated rates of copathogens.

Nosocomial transmission of CRVs is common, and widespread hospital outbreaks of CRVs have occurred with sometimes devastating sequelae [5,6]. Because these viruses are so easily transmitted from person to person in both inpatient and outpatient settings, infection control measures and enforcement of these measures are critical in controlling the spread of these infections [5-7]. Community outbreaks of RSV infections typically occur during the late fall, winter, and early spring, frequently followed by outbreaks of human metapneumovirus. Influenza outbreaks typically occur during the winter in temperate climates, but may occur throughout the year in more tropical areas. Parainfluenza virus infections occur throughout the year, with outbreaks occurring primarily in the spring, summer, and fall. Other viruses, such as rhinoviruses, coronaviruses, and adenoviruses, tend to take place throughout the year, although sporadic outbreaks of all these respiratory viruses may occur.

Prompt and accurate identification of the respiratory viral pathogen is critically important in the transplant recipient because it enables specific infection control precautions to be instituted, the initiation of specific antiviral therapy, and the potential delay of immunosuppressive therapy or transplantation. The appropriate collection of specimens is critically important for the successful identification of viruses in clinical samples. Different diagnostic methods have been used, but during recent years, the use of multiplex PCR techniques has gained popularity because this method may detect multiple respiratory viruses from a single, readily obtained specimen [8,9].

Management of CRV infections has been controversial. With the exception of influenza infections for which neuramidase inhibitors have been shown to be effective, there are no established treatments. Several uncontrolled studies have been performed with ribavirin, suggesting some efficacy at least in preventing progression to lower tract disease [10]. Although there is no licensed or proven therapy for parainfluenza virus infections, ribavirin has antiviral effects against parainfluenza virus in cell culture and has been used for the treatment of lower respiratory tract disease in

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immunocompromised hosts [11]. Case reports have documented decreased viral load and clinical improvement in several children with severe combined immunodeficiency and parainfluenza virus infection following multiple treatments with aerosolized ribavirin [12,13]. There is no laboratory data supporting antiviral activity of oseltamivir against parainfluenza viruses, although new parainfluenza-specific antiviral agents with activity against the neuraminidase of parainfluenza viruses are under development. Preliminary data indicates that infections from human bocavirus, human coronavirus, and other newly identified viruses such as WU/KI viruses are less likely to cause severe problems in transplant patients compared with the well-described viral pathogens above.

T Cell Therapy for Adenovirus Infections

Adenoviruses (ADV) are nonenveloped lytic DNA viruses. Fifty-two different human serotypes have been identified divided into 7 subgroups or species. In immunocompromised patients, ADV can cause lethal disease, with damage occurring in many different organs. During the last decade ADV infection in the context of allogeneic hematopoietic stem cell transplantation (HSCT) has been increasingly recognized as a cause of transplant-related mortality (TRM), especially in children and the most severely immunocompromised adults, such as those undergoing haploidentical or T cell-depleted transplants.

Runde et al. reported a significantly higher incidence of ADV-infection in patients receiving antithymocyte globulin (ATG), and a study by van Tol et al. [14] found the risks of ADV infection and disease were increased in patients with more intensive T cell depletion. They also demonstrated that patients with delayed T cell recovery have a significantly higher risk of ADV infection and disease. Other studies found a strong correlation between the presence of ADV-specific T cells and the clearance of ADV infection.

Feuchtinger et al. showed that patients with ADV-specific T cells could be found in higher numbers in patients who cleared ADV infection compared to those who did not. Myers et al. found that a delayed recovery of ADV-specific T cells in recipients of unrelated or haploidentical grafts correlated with an increased risk for ADV disease. The observation that the outcome of ADV disease is related to specific immune reconstitution suggests that the recovery of ADV-specific immunity is a critical process that can be improved by decreasing the intensity of immunosuppression. In addition, the transfer of virus-specific T cells has been shown to be effective in controlling cytomegalovirus (CMV) and Epstein-Barr Virus (EBV) infections in HSCT recipients. Although the different ADV subtypes are to some extent antigenically distinct, these same subtypes share T cell epitopes on the hexon

protein. Furthermore, crossreactivity has been shown *ex vivo*. Early *in vitro* experiments showed that ADV-specific T cells can be generated by ADV pulsed dendritic cells, and that these can lyse adenovirus-infected cells. Chatziandreou et al. [15] and Feuchtinger et al. [16] isolated ADV-specific T cells through an interferon (INF)- γ -secretion and capture assay and could show specific antigen responses of both CD4⁺ and CD8⁺ T cells upon restimulation with different ADV strains. Another promising approach is the adoptive immunotherapy with allodepleted donor T cells to improve immune reconstitution concerning all common viruses.

In a pilot study, Feuchtinger et al. [17] treated 6 patients with ADV-viremia with virus-specific donor T cells generated by INF- γ secretion assays. In 3 of 4 evaluable patients receiving this adoptive T cell transfer, the infused T cells underwent an *in vivo* expansion and the viral load decreased in peripheral blood. *In vivo* expansion of specific T cells was dose-independent, suggesting that even very low numbers of ADV-specific donor T cells expand easily *in vivo* in the presence of viremia.

Vaccination of Stem Cell Transplant Recipients Against Viral Pathogens

Influenza

The mortality rate following influenza infections in HSCT recipients was previously reported to be around 15% [18,19], although recent data reporting outcome after more widespread utilization of neuraminidase inhibitors suggest a somewhat lower risk for fatal outcome [20,21]. The recent outbreak of new pandemic strain A/H1N1 stressed the importance of having strategies in place for management of these patients.

Influenza infection is controlled by different parts of the immune system including both the innate and adaptive immune systems. After vaccination, both T cell and B cell responses are activated. Clearance of the primary infection depends on CD8 cells. These cells recognize epitopes from both the hemagglutinin (HA) and internal proteins of the influenza virus. Following recovery from influenza, antigen-specific T cells maintain long-lasting immunologic memory that responds quickly to restimulation. The B cells produce antibodies to the influenza proteins and HA-specific antibodies appear within 2 weeks of the infection. In contrast to antibodies directed to HA, antibodies directed to NA do not neutralize virus but reduces the release of virus from infected cells. A problem specific for influenza viruses is the antigenic shifts and drifts of circulating influenza virus that regularly occur, requiring adaptation of the seasonal tri-valent influenza vaccines that must be administered to provide protection.

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