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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 virsues 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 adenoinfected 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 neuramidase 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.

Two main types of influenza vaccine exist: inactivated, and live, cold-adapted vaccine for intranasal administration. Safety and efficacy of the intranasal, live vaccine has not been evaluated in HSCT recipients but is safe in HIV-infected adults and children. Because influenza infection occurring early after HSCT might result in severe disease, it would be logical to immunize candidates before HSCT. However, most studies show that adult patients with hematologic malignancies respond poorly to vaccination. In addition, the likelihood that whatever immunity that does exist will be lost is very high.

The time after HSCT is important for vaccine responses. Engelhard et al. [22] studied the antibody response to 2 doses of influenza virus vaccine given 2 to 82 months after HSCT to allogeneic BMT recipients (adults and children) who had received a T cell-depleted transplant, and showed a significant association between the serologic response and the interval between bone marrow transplant (BMT) and vaccination. The second vaccine dose had only a marginal effect. Pauksen et al. [23] found response rates in allogeneic SCT patients vaccinated 4 to 12 months after HCT of 11/35 (31%) for H1N1, 3/35 (9%) for H3N2, and 7/35 (20%) for influenza B. However, despite suboptimal serologic responses, clinical effectiveness of vaccination could potentially exist. Machado et al. [24] found that influenza vaccination performed at least 6 months after SCT had an efficacy in preventing influenza of 80%. It is possible that protection is mediated also by T cells. Avetisyan et al. [25] analyzed the T cell response in adult patients and found a significant increase in the number of IFN-γ producing T cells both in patients vaccinated between 3 and 6 months after HCT and in those vaccinated later, although the response in the late group was stronger. Furthermore, it has been shown in the elderly that the risk for influenza disease is comparable in individuals demonstrating a cell-mediated response alone, an antibody response alone, or both types of responses [26].

The response to vaccination is suboptimal early after transplantation also in autologous HSCT recipients [22,23]. No specific data exist regarding vaccine efficacy in patients receiving rituximab in close proximity to transplantation either during pretransplant chemotherapy, as part of the conditioning regimen, or after HSCT. However, in nontransplant patients the immune response within 6 months of receiving monoclonal antibodies is very poor [27], and it is therefore likely that this will be the case also after autologous HSCT.

When the new pandemic H1N1 strain spread rapidly around the world, new vaccines were rapidly developed. There were uncertainties regarding efficacy and safety of these vaccines, especially those including new adjuvants. Preliminary data suggest that 2 doses of p/H1N1 vaccine were safe and able to induce immune responses. In addition, the development of antiviral resistance to neuraminidase inhibitors has been demonstrated in immunocompromised hosts, although no spreading of resistant virus was documented.

Life-long seasonal influenza vaccination with inactivated influenza vaccine is recommended for all HSCT recipients [28]. It is unknown how early vaccination after HCT is beneficial. Because influenza vaccination is safe, current recommendations are to start 4 months after HSCT [28]. Influenza vaccination of family members and household contacts is strongly recommended during each influenza season to limit risks for influenza exposure in HCT candidates or recipients. Seasonal influenza vaccination is also strongly recommended for health care workers dealing with HCT recipients.

Measles, mumps, and rubella (MMR) vaccine

Although severe and fatal measles has been reported in HSCT recipients [29,30], the risk for serious infection after allogeneic HSCT is likely to be low. However, with more patients undergoing transplantation after reduced intensity conditioning (RIC) regimens, the pregnancy potential for patients is likely to increase and thereby the risk of congenital rubella syndrome. The available MMR vaccines are live, attenuated vaccines, and are not recommended for use in immunocompromised patients. Immunization can be considered in allogeneic HSCT patients without chronic graft-versus-host disease (cGVHD) or ongoing immunosuppression. Data indicates that measles vaccine can be given to such patients without severe adverse effects at 2 years after SCT [31]. During an epidemic in Brazil, patients were safely immunized 1 year after SCT [32].

Varicella vaccines

Although data are limited, varicella vaccine might be considered for seronegative HCT recipients who meet the criteria for live virus vaccination delineated above for measles vaccine. The zoster vaccine should not be used. Two new inactivated varicella vaccines are under development.

Other vaccines

There are no data regarding vaccination of HSCT recipients with the recently licensed vaccines against human papilloma virus, and vaccination cannot yet be recommended. A new CMV vaccine is under development, with phase II data showing promising immunogenicity.

CONCLUSION

Viral infections in an immunocompromised host have the ability to cause severe disease at much higher rates than in the healthy population. Careful attention to viral epidemiology and viral outbreaks in the

community, diagnostic screening of symptomatic patients with the onset of new respiratory symptoms, and the use of careful infection control methods that are rigorously enforced in both the outpatient and inpatient setting are important in limiting viral spread to these high risk patients. The use of antiviral therapy prior to the development of respiratory failure may also be of benefit in these patients. The efficacy of immunoglobulin products or monoclonal antibody products to limit the spread of infection within individual patients is frequently utilized but has yet not been proven in rigorous trials in this patient population. Further clinical studies of agents to both prevent and treat these important viral infections are urgently needed.

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