

REVIEW

Epidemiology and Potential Preventative Measures for Viral Infections in Children With Malignancy and Those Undergoing Hematopoietic Cell Transplantation

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In pediatric patients with malignancy and those receiving hematopoietic stem cell transplants, bacterial and fungal infections have been the focus of fever and neutropenia episodes for decades. However, improved diagnostic capabilities have revealed viral pathogens as a significant cause of morbidity and mortality. Because of limited effective antiviral therapies, prevention of viral infections is paramount. Pre-exposure and post-exposure prophylaxis and

antiviral suppressive therapeutic approaches are reviewed. Additionally, infection control practices specific to this patient population are discussed. A comprehensive approach utilizing each of these can be effective at reducing the negative impact of viral infections. *Pediatr Blood Cancer* 2012;59:11–15.

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INTRODUCTION

Almost 30 years ago, Pizzo et al. [1] published their landmark study which prospectively evaluated 1,001 pediatric and young adult cancer patients presenting with fever. Bacterial and fungal organisms accounted for over 96% of microbiologically documented infection during febrile neutropenia. Since then, research efforts have largely focused on strategies to reduce or prevent the morbidity and mortality related to infections caused by bacterial and fungal pathogens. However, the advent and clinical availability of an array of sensitive and specific diagnostic tools have afforded clinicians and researchers the opportunity to identify previously undetected viral pathogens. More recent literature has linked as many as 34% of fever and neutropenia episodes to a viral pathogen [2]. Significant morbidity and mortality has been attributed to viruses that cause a variety of presentations either as primary or reactivation infections.

For the majority of clinically important viral pathogens in oncology patients, treatment of active infection is limited by a lack of effective antiviral therapies and the host's compromised immune system. Therefore, preventative and suppressive therapeutic measures are of paramount importance. The epidemiology and relevance of some of the more common viral pathogens in children with malignancy and those undergoing hematopoietic cell transplant (HCT) are reviewed below. Some of the commonly employed preventative and suppressive measures to combat these viral pathogens are discussed and necessary areas for future development in viral prevention are highlighted.

EPIDEMIOLOGY OF VIRAL INFECTIONS

The list of viral pathogens that have led to significant infections in pediatric patients with malignancy or those undergoing HCT is lengthy [3]. The growth of this list is multi-factorial including improved diagnostic modalities to identify previously existing but unrecognized viral pathogens (e.g., human metapneumovirus (HMPV)) as well as previously identified viruses that were thought to be inconsequential but are now considered as important contributors to poor outcomes (e.g., human herpes virus (HHV-6). The epidemiology of common respiratory, herpes, and gastrointestinal viruses are briefly discussed below.

RESPIRATORY VIRUSES

Three relatively large prospective observational studies performed comprehensive respiratory viral testing on children presenting with malignancy and fever [4–6]. The incidence of identified respiratory viral pathogens per febrile episode ranged from 7% to 59%. The variation in frequency of identified pathogens is related to variation in the diagnostic tests utilized, the specimen type collected, and the implications for testing (screening vs. symptom guided testing). Across the three studies, the more commonly identified viral organisms included rhinovirus, respiratory syncytial virus (RSV), parainfluenza, influenza, and adenovirus. Less frequently HMPV, human bocavirus, and coronavirus were also identified. Although less data exist in HCT recipients, one recent prospective study showed that with surveillance PCR testing, 50% of patients receiving an allogeneic HCT have a positive test for a primary respiratory pathogen [7]. The distribution of viral isolates was similar to that of children with malignancy. Among the respiratory pathogens, RSV is of particular concern for resultant mortality in high-risk patients. In immunocompetent patients, RSV is often a self-limiting upper respiratory infection. However, in patients with AML and HCT recipients RSV can progress to a lower respiratory tract process. In this setting RSV is associated with a 14% case fatality rate in patients with AML and a 50% case fatality rate in pediatric recipients of HCT [8,9].

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ADENOVIRUS

As noted above adenovirus is a commonly identified respiratory pathogen. However, adenovirus can also reactivate from latent status and cause significant morbidity and mortality in pediatric HCT recipients [10]. Adenovirus infection rates have ranged from 4.9% to 41% with invasive disease rates ranging from 1% to 17%. A number of these studies suggest that the rates of adenovirus infection in pediatric HCT recipients are higher than those in the adult population [11–16]. Case fatality rates of adenovirus infection in which the death was directly attributable to adenovirus range from 8% to 17% [11,13,14,17].

HERPES VIRUSES

Although primary herpes virus infections are possible, it is their ability to reactivate from latency that results in the majority of the herpes virus morbidity and mortality in children with malignancy or those receiving HCT. Prospective surveillance testing has detected CMV reactivation in 12.9–29% of pediatric allogeneic HCT recipients [16,18,19]. Despite pre-emptive therapy as many as one-third of patients with CMV reactivation go on to have CMV disease and between 33% and 75% of these patients succumb to their CMV disease [18,19]. Without acyclovir suppressive therapy, HSV reactivation is frequent in HSV seropositive adult HCT recipients (70–80%) and in adult leukemia patients (50–60%) [20–23]. HSV reactivation seems to be less frequent in children but can complicate episodes of fever and neutropenia and prolong mucositis [24]. Similarly, herpes zoster reactivation is common in pediatric HCT recipients (30–33% with 11% of these going on to dissemination) and in patients with acute lymphoblastic leukemia (ALL) (9–28%) [25–28]. Prospective surveillance of pediatric allogeneic HCT recipients suggest that greater than 60% will have evidence of EBV reactivation [29]. Of those with reactivation 1.0–2.8% will develop post-HCT-PTLD which is associated with a mortality rate greater than 80% [29,30].

HHV-6 has gained significant attention as a concerning reactivation virus in HCT recipients. When prospectively monitored by serial plasma PCR testing, up to 67% of pediatric allogeneic HCT recipients will have evidence of HHV-6 viremia [31]. Although the extent to which HHV-6 impacts the post-transplant period is not clear, HHV-6 has been implicated in various clinical complications: neurocognitive decline, encephalitis, delay in engraftment, and secondary graft failure [32–34]. Complicating the interpretation of positive PCR testing for HHV-6 is the potential for inherited HHV-6 secondary to chromosomal integration. Inherited HHV-6 is estimated to exist in 1% of the world's population. When present, inherited HHV-6 can be misinterpreted as actual HHV-6 reactivation resulting in unnecessary medical interventions [35].

GASTROINTESTINAL VIRUSES

Traditionally, testing for primary stool viral pathogens has been limited to antigen tests for rotavirus, and enteric adenovirus serotypes 40 and 41. Specific incidence data for each of these viruses in children with malignancy or those receiving HCT are not available in the medical literature. Nonetheless the impact of such infections relative to dehydration, prolonged hospital stays, and persistent symptoms with the need for parenteral nutrition has been well documented [36]. PCR testing has now made

identification of other gastrointestinal pathogens such as human caliciviruses (norovirus and sapovirus) and astrovirus possible. As with other gastrointestinal pathogens, symptoms are often more pronounced and viral shedding prolonged in patients receiving chemotherapy or those undergoing an HCT [37,38].

PREVENTATIVE MEASURES

Infection Control Measures

Infection control measures serve as a cornerstone of infection prevention. These efforts are particularly important with regards to primary respiratory and gastrointestinal viruses as many of these pathogens have been linked to a nosocomial outbreak in an oncology or HCT ward [39–44]. Arguably the most important infection control component is maintaining healthcare worker (HCW) compliance with hand hygiene. The World Health Organization has proposed recommendations for appropriate hand hygiene technique [45]. Unfortunately, physicians working on oncology and pediatric intensive care units have been found to have less than 60% compliance with appropriate hand hygiene practices [46].

Attempts should also be made to reduce the potential for HCWs to carry viral pathogens into the hospital. HCW compliance with yearly influenza vaccine has been very poor [47]. Although heavily debated [48,49], mandatory influenza vaccination for HCWs has been successfully enacted and reasonably well received at a large children's hospital [47]. It is also necessary that medical institutions maintain policies that prevent HCWs from coming to work when symptomatic from a communicable disease. In one survey of HCWs, 86% of those reporting a recent respiratory infection stated that they provided patient care after their symptoms had started [50]. Guidelines on work restriction in this setting have been published and should be enforced [51]. Finally, patient visitors, both children and adults, can serve as a reservoir for viral transmission to hospitalized children. Although literature documenting the effectiveness of such screening practices is limited, it is reasonable to employ a policy by which visitors are screened for symptoms consistent with an infectious process and if present, are restricted from visitation.

Combining each of these infection control practices can ultimately result in the reduction of nosocomial viral infections. Therefore, collaboration with an infection control team can prove to be invaluable. For example, a comprehensive infection control initiative has proven to be successful in reducing nosocomial RSV infection in an HCT unit [52].

Pre-Exposure Prophylaxis

Vaccination is the most effective approach for pre-exposure prophylaxis. Although a number of vaccines are live virus vaccines and thus contraindicated in immunocompromised children, it is still important to encourage families to maintain compliance with vaccine recommendations in all close family contacts. This practice is referred to as “cocooning” which can help to provide protection around the more vulnerable immunocompromised patient [53]. Oral poliovirus vaccine (no longer administered in the US) is the only live virus vaccine with a definitive contraindication for administration to household contacts of immunocompromised patients. The Advisory Committee on Immunization Practices offers the suggestion that close contacts of patients

with “severely weakened immune systems being cared for in a protective environment” should not receive the live attenuated nasal spray influenza vaccine (LAIV) [54], however this suggestion is not supported by published data or the biology of the vaccine. In actuality the LAIV may be superior to the trivalent inactivated vaccine in preventing the transmission of wild-type influenza virus from close contacts to immunocompromised patients. In LAIV recipients local production of mucosal IgA antibodies neutralize wild type virus at its portal of entry thus limiting the potential for shedding of wild type virus. Additionally, LAIV provides some protection against circulating influenza strains not included in the vaccine. Furthermore, fear of transmission and subsequent infection from the attenuated and cold-adapted vaccine virus is unfounded, as the LAIV virus cannot replicate at core body temperatures [55]. Given this, it is not at all surprising that there have been no cases of documented infection from the attenuated virus in close contacts of LAIV recipients.

Vaccines available against the aforementioned viral pathogens include influenza, varicella, and rotavirus. Of these, only the former is routinely recommended for children with malignancy or those undergoing HCT. Clearly, the immune status of the patient at the time of vaccination will have a significant impact on that patient’s response to the influenza vaccine but seroconversion in children receiving chemotherapy is possible [56,57]. Additionally, influenza vaccination of children that recently completed chemotherapy has been shown to reduce in the rate of respiratory tract infections, hospitalization, and antibiotics [58,59]. Despite the universal recommendation for influenza vaccination, only two-thirds of pediatric oncologists recommend the vaccine to their patients [60]. It is never unsafe to administer the inactivated influenza vaccine and thus it should be administered to all children prior to the start of the influenza season. Even in children with previously noted egg allergy, influenza vaccination can be safely performed [61].

Although the varicella vaccine is a live attenuated vaccine, there are multiple publications documenting the safety and effectiveness of the vaccine after administration to children in remission for ALL with or without suspension of maintenance chemotherapy [62,63]. However, the recommendation to hold chemotherapy around the time of vaccination and the report of a fatal event in a child with ALL after varicella vaccination has raised concern about administering the vaccine routinely to patients with ALL [64]. As for HCT recipients, it is safe to administer live attenuated varicella vaccination when various parameters are met (off all immunosuppressive agents, documented response to inactive vaccines, and demonstration of an adequate absolute lymphocyte count and lymphocyte function) [65]. Two small clinical trials have evaluated the efficacy of heat inactivated varicella vaccine in three or four dose schedules during the peri-transplant period among adult autologous and allogeneic HCT recipients [66,67]. In a meta-analysis of the two studies, there was a trend toward reduced herpes zoster infection [58,68]. Unfortunately, heat inactivated varicella vaccine is not currently available.

Two rotavirus vaccines (live, oral human-bovine pentavalent vaccine, and the oral live attenuated monovalent vaccine) are currently licensed in the United States. To date no data on the safety or efficacy of either vaccine exist in children with malignancy or those receiving HCT [69]. Therefore, neither can be recommended for this patient population.

Post-Exposure Prophylaxis

Post-exposure prophylaxis is primarily limited to influenza and varicella exposures. The efficacy of influenza chemoprophylaxis in healthy household contacts of index influenza cases has been well established in randomized trials [70,71]. Although randomized trials specific to immunocompromised patients have not been performed, CDC recommendations support post-exposure chemoprophylaxis after close (face-to-face) exposure in an unvaccinated patient [72]. Various regimens have been suggested, but typically such prophylaxis should begin within 48 h and be continued for 10 days. The choice of the antiviral agent used should be guided by the current year’s influenza sensitivity profile as reported by the CDC. Influenza vaccine should also be administered to the exposed individual.

Recommendations for varicella post-exposure prophylaxis are provided in the 2009 Redbook: Report of the Committee on Infectious Diseases [73]. Patients without a history of varicella or unknown or negative varicella serologies and receiving chemotherapy for malignancy or recipients of HCT are considered at risk for varicella infection after a true exposure. The definition of “true” exposure can be challenging but close face-to-face contact with someone who has chicken pox or intimate contact with someone who has herpes zoster are often considered real exposures. Passive immunoprophylaxis within 96 h should be established by administering Varicella Zoster Immunoglobulin (VariZIG). VariZIG is available for routine use in Canada but in the United States it must be administered via an investigational new drug protocol from FFF Enterprises (800-843-7477; www.fffenterprises.com/Products/VariZIG.aspx). If VariZIG is not available conventional intravenous immunoglobulin can be substituted. If 96 h from the time of exposure has elapsed then immunoprophylaxis will be less effective. In this setting chemoprophylaxis with acyclovir started 7–10 days after the exposure and continued for 7 days can be administered. Fisher et al. [74] recently reviewed the available data for the effectiveness of both of these post-exposure approaches in immunocompetent and immunocompromised children. There are reasonably strong data to support the effectiveness of immunoglobulin in reducing the risk of severe disease in immunocompromised children. The data for the effectiveness of acyclovir chemoprophylaxis in immunocompromised children are limited to case reports and small case series. However, this approach has been effective in exposed immunocompetent children and thus it is considered a reasonable secondary option in immunocompromised hosts [74].

Passive immunoprophylaxis (both pre-exposure and post-exposure) against RSV for immunocompromised patients with the monoclonal antibody palivizumab (Synagis), has been explored but the data are limited. A study of rats immunosuppressed with 3 weeks of cyclophosphamide and exposed to RSV suggested that respiratory viral replication can be reduced when palivizumab is administered on the day prior to RSV inoculation [75]. More recently, a decision tree mathematical model utilizing estimated rates of RSV exposures, hospitalizations, and deaths in pediatric HCT recipients concluded that monthly palivizumab administration to HCT recipients would result in a 10% decrease in mortality [76]. Although these data are compelling, the number of assumptions that were made to execute the decision tree analysis makes it difficult to recommend this intervention for all pediatric patients undergoing an HCT. Clearly, additional research

is necessary to better define the benefits of palivizumab for passive prophylaxis in HCT recipients.

Suppressive Therapy

Data from clinical trials have supported the efficacy of prophylaxis with ganciclovir compared to placebo in CMV seropositive HCT recipients [77]. However, neutropenia was a noted risk in those receiving ganciclovir. In comparing ganciclovir to a pre-emptive therapeutic approach, there was no difference in the rate of CMV disease or death [78]. Additionally, foscarnet has also been suggested in the peri-transplant period for high-risk patients due to a decreased incidence of bone marrow suppression. No clear consensus exists and published adult recommendations have supported either the prophylactic or pre-emptive approach in higher-risk HCT recipients (e.g., seropositive recipient or donor, T-cell depleted transplant, or mismatched donor) [78–80]. Although CMV disease has been reported in children receiving chemotherapy for various malignancies, CMV prophylaxis in this patient population is typically not recommended [81].

In controlled trials, acyclovir prophylaxis has proven effective in various adult HCT and malignancy patient populations [22,23,82]. Given the high rate of HSV reactivation without suppressive therapy, most adult guidelines support the administration of acyclovir prophylaxis to HSV seropositive allogeneic HCT recipients until engraftment and resolution of mucositis [80,83,84]. A similar approach is suggested for HSV seropositive pediatric HCT recipients. It has also been deemed reasonable to administer acyclovir prophylaxis to adult and pediatric patients with leukemia and receiving chemotherapy [81,84]. However, monitoring for and treating clinically apparent breakthrough HSV infections seems more prudent in non-HCT pediatric patients as the frequency of HSV reactivation is likely much less in children. In patients with frequent HSV recurrences prolonged acyclovir prophylaxis should be discussed with the family.

Combined pediatric and adult trials have demonstrated the benefit of acyclovir prophylaxis at reducing herpes zoster episodes in VZV seropositive HCT recipient [85,86]. Based on these data, more recently published guidelines support the administration of acyclovir to VZV serology positive allogeneic HCT recipients for up to 1 year [84]. Although herpes zoster infections are common in children with ALL, currently there are no recommendations for prophylaxis in these patients as the time at risk is quite prolonged. Instead clinical monitoring and treatment of herpes zoster episodes is suggested. Acyclovir prophylaxis in patients with ALL with two or more herpes zoster episodes should be considered at least for the duration of chemotherapy exposure.

Data on the prophylactic use of antivirals directed at suppressing the reactivation of adenovirus are limited. In 2006, an abstract presentation at the European Study Group for Blood and Bone Marrow Transplantations suggested that ribavirin prophylaxis may be beneficial at reducing adenovirus infection and mortality in pediatric HCT recipients versus historical controls [87]. These data have yet to be published and currently most experts support using cidofovir in a pre-emptive therapeutic approach, especially among high-risk HCT recipients [88].

FUTURE DIRECTIONS

We have entered an era where advanced and commonly available diagnostic modalities have made it possible to identify the

presence of many viral pathogens. This technology has helped to establish the significant impact that viral infections are having on the morbidity and mortality of children with malignancy and those receiving HCT. Despite this knowledge, there continues to be a paucity of effective interventions available to prevent or suppress these infections. Research efforts should focus on discovering novel therapies that are both effective at preventing and treating infection and that also have an attractive safety profile. However, even when effective antiviral agents or vaccines are available there is often a lack of data and consensus for best practice recommendations. Therefore, at this time, establishment of rigorous and consistent guidelines for both infection control measures and prophylactic therapies may be the most effective way to reduce the impact of viral pathogens. Such guidelines should be formally proposed, evaluated and appropriately adjusted by committees composed of experts representing the disciplines of oncology, infectious diseases, and infection control and prevention.

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