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Viral Respiratory Infections in Children Receiving Chemotherapy or Undergoing Stem Cell Transplantation

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Abstract

In immunocompromised hematology/oncology patients, respiratory infections are both common and potentially severe. However, there is still a noticeable gap in the medical literature, regarding the epidemiology of viral respiratory infections in pediatric hematology/oncology patients. This is mainly due to research being focused on readily treatable causes and to limitations by time-consuming diagnostic techniques. Recent developments, though, have produced sensitive and accurate methods for detecting viruses, yielding results within hours and able to screen for multiple species and subtypes, illuminating at the same time "novel" viruses that cause disease in immunocompromised patients. In this review, the epidemiology and disease burden of viral respiratory infections among pediatric oncology patients and hemopoietic stem cell transplantation recipients are discussed. Additionally, recent therapeutic and preventive options promising improved outcomes are reviewed.

Keywords: Oncology; Chemotherapy; Children; Respiratory Viral Infections

Abbreviations: HSCT: Hematopoietic Stem Cell Transplantations; ALL: Acute Lymphoblastic Leukemia; URI: Upper Respiratory Infections; Hmpv: Human Metapneumovirus; RSV: Respiratory Syncytial Virus; AML: Acute Myeloblastic Leukemia; LRI: Lower Respiratory Infections; CMV: Cytomegalovirus; Gvhd: Graft Versus Host Disease; BAL: Bronchoalveolar Lavage; PICU: Pediatric Intensive Care Unit; IVIG: Intravenous Immunoglobulin

Introduction

In paediatric oncology patients and those receiving HSCT, infections cause significant morbidity and mortality [1]. Although for decades, bacterial and fungal infections have been the focus of research, recently improved diagnostic capabilities have revealed that viral pathogens are also associated with an increased morbidity and mortality [2,3]. Viral respiratory tract infections are common and may present with a wide range of clinical syndromes from asymptomatic infection to severe pneumonia and death [4,5]. In a pediatric ALL study, 43.5% of all infectious episodes were respiratory, of which 88.5% represented URI [6]. In addition viral respiratory infections in children with HSCT have been associated with mortality ranging from 10% to 14% [7,8]. Research on viruses has been limited by the use of lengthy and complicated techniques, such as viral culture, infected tissue biopsy and serology. The past decades, though, have witnessed studies utilizing molecular methods (PCR/RT-PCR) to determine the epidemiology of respiratory viruses in adult and paediatric cancer patients. These methods have significantly increased the sensitivity of detection and filled the diagnostic gap in cancer patients with either respiratory infections or with "fever of unknown origin" [9]. Moreover, "novel" pathogens, such as hMPV, bocavirus have been identified and seem to play an important role in immunocompromised cancer patients [4,10-12].

Infections of the upper and lower respiratory tract are caused by a number of viruses, mainly influenza A and B, parainfluenza 1-4, RSV, adenovirus, rhinovirus, hMPV and boca-virus (Table 1) . The prevalence of viral respiratory infections depends on the geographic area, season, exposure, virulence, types of circulating viruses and influenced by the detection method used [11]. Often, immunosuppressed patients act as outbreak "sentinels" [11]. Distinction amongst the various respiratory viruses based on clinical symptoms and signs, is not feasible, since clinical presentation is similar. Immunocompromised children may display mild nonspecific signs and symptoms or may exhibit either a prolonged duration of febrile illness or a rapidly deteriorating disease.

Epidemiology

Hematologic malignancies

Two surveys to date, have utilized molecular methods (PCR/RT-PCR) to determine respiratory viruses epidemiology in pediatric leukemia patients [13,14]. In a prospective study of febrile leukemic children, respiratory viruses were detected in 44%, with rhinovirus (22%) and RSV (11%) being the most prevalent. Respiratory infections were usually mild with only two cases (3.2%) progressing to LRI. Lymphopenia was the only risk factor associated with virus acquisition. However it must be mentioned that the choice to use oral washes in this study, may account for the diminished viral yield of the samples [14]. In an earlier study of children with cancer, a viral pathogen was found in only 11%, again with rhinovirus and RSV being the most frequent agents identified. Interestingly, in this cohort 74% of children were neutropenic [13]. These findings are in accordance with an earlier study, utilizing standard methods (serology etc), where rhinovirus was also the predominant isolate (17%), with RSV and parainfluenza 3 following [15].

The contribution of chemotherapy intensity, on the epidemiology

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Influenza A,B	Negative sense, single-stranded RNA orthomyxoviruses	Droplet precautions
Parainfluenza 1-4	Single-stranded RNA paramyxoviruses	Droplet precautions
RSV	Single-stranded RNA paramyxoviruses	Droplet precautions
hMPV	Negative-sense nonsegmented RNA paramyxovirus	Droplet precautions
Rhinovirus	RNA Picornavirus	Droplet precautions
Adenovirus	Nonenveloped, double-stranded DNA	Droplet precautions
Bocavirus	Nonenveloped, single-stranded DNA Parvovirus	Droplet and contact precautions

Table 1: Characteristics and precaution measures of the most common respiratory viruses.

of viral respiratory infections has been evaluated in two pediatric studies involving children with AML and ALL respectively. The AML study, compared two groups of patients, allocated to receive either intensive or standard chemotherapy. All types of infection occurred more frequently during intensive versus standard (bacterial-57.7% vs. 39.4%, fungal-27.4% vs. 9.9%, viral-14% vs. 3.9%). During intensive induction, respiratory viruses' percentage consisted of influenza (8%), parainfluenza (6%), adenovirus (4%), and RSV (4%) [16]. In the ALL study, among exclusively infants, receiving a 6-phase chemotherapy protocol viral infections accounted for 13% of overall infections, second only to bacterial (74%). Of note mortality rate was increased during induction (phase 1) (16.5%), in contrast to 1.9% of consolidation (phase 4). During induction, viral infections were quite lethal, with 6 patients out of 23 having a fatal outcome. In particular LRI were predominantly viral in origin (39%), caused by RSV and influenza, followed by fungal (27%) and bacterial (20%) [17]. Another retrospective study of paediatric AML patients focused solely on RSV, and reported mortality of 10% (4/40). Three of the children developed RSV-infection during induction and the fourth during intensification supporting possible association between phase of chemotherapy and outcome [18].

Solid tumors

As a whole, solid tumors represent 60% of childhood cancer, with CNS masses and sympathetic system tumors (neuroblastoma, ganglioneuroblastoma) being most prevalent [19]. Despite this, viral respiratory infections in children with solid tumors haven't been studied independently of hematologic malignancies. A recent study reported that patients with solid tumors had significantly more viral infections but seemed to tolerate them better and required shorter hospitalisation [13]. A study of influenza in a pediatric oncology subpopulation, reported that 27 out of 511 influenza-documented illnesses occurred in children with cancer and more than 1/3 had been diagnosed with solid tumors [20].

Hemopoietic stem cell transplantation

Comprehensive studies, analyzing viral epidemiology and risk factors exist mainly for adults undergoing transplantation. Recent studies in different sizes adult populations have described virus-specific incidence rates for RSV (5%), parainfluenza (7%), adenovirus (5%) and influenza (1-2%) [21-24]. Adult studies have produced conflicting results in evaluating risk factors. A Seattle-based study found that the only factor for virus acquisition was recipient CMV seropositivity [25]. Nichols et al found that female sex and advanced disease were the main identifiable predictors for influenza acquisition and allogeneic patients were more likely to acquire parainfluenza-3 [21,22]. In a paediatric HSCT study, allogeneic transplantation and grade 3-4 GvHD were identified as risk factors associated with increased incidence of viral respiratory infections. Once again parainfluenza-3 was the most frequent viral isolate [7]. A number of HSCT studies focus solely on adenovirus, conveying an unclear image of the incidence, mortality and risk factors, since there is much variation in patients' age, adenovirus detection practices, conditioning used and GvHD-preventive regimens [11]. In the study by Hale et al adenovirus was identified in 13 of 206 pediatric patients undergoing 215 bone marrow transplants, resulting in an incidence of 6%. Most patients did not exhibit respiratory symptoms, while LRI development was associated with significant mortality (50%). Identified risk factors for infection included allogeneic transplantation and total-body-irradiation conditioning [26]. In another study of allogeneic paediatric recipients, adenoviral incidence was 12%, but only 1 patient died of adenovirus pneumonia. Finally immunity recovery post-HSCT (i.e. serum IgM concentrations, peripheral T lymphocytes and subsets counts) was delayed in adenovirus-infected compared with noninfected children [27]. Runde et al. found that moderate to severe GvHD correlated with higher adenovirus infection risk. This study also supports that adenovirus infections do not always represent reactivations in the recipient but may also arrive by "transfusion" of infected cells from seropositive donors [28].

Disease Burden and Complications

Viral respiratory infections are often complicated by bacterial or fungal super-infections in cancer patients; 39% of pediatric oncology patients with RSV had a concurrent bacterial infection [29]. Twenty five percent of adults and 22.7% of children with viral pneumonia had bacterial co-pathogens isolated from BAL [30]. Additionally, cancer patients are at a higher risk to develop LRI and respiratory failure. For adult HSCT patients respiratory viral infections have been reported to progress from URI to LRI in 18% to 44% of cases, depending on the population studied [21-24]. A risk factor for influenza progression to LRI seems to be autologous (47%) versus allogeneic HSCT (31%) [22]. Disease burden is an important issue; In a study of El Saleeby et al. 36% of children with cancer and RSV infection required hospitalization, 22% oxygen administration, while 9% mechanical ventilation [31]. In Mendoza-Sanchez et al. study, 21% of children with respiratory tract infection receiving anticancer therapy had to be admitted to the PICU [32].

Mortality is a major concern and data refers mainly to RSV infections. In the AML- RSV study, RSV-specific mortality was 0.2% (4 out of 2,078 patients enrolled), however the risk of RSV-related mortality among RSV infections was high (10%- 4 out of 40 patients with RSV infection), prompting discussion about the importance of appropriate management, rather than prophylaxis [18]. In the infantile- ALL study RSV mortality rate was 66% during induction versus an overall rate of 33% [17]. In another study, young age (≤2 years) and profound lymphopenia where associated with increased RSV mortality [31]. Influenza mortality seems to be associated with the development of LRI; since influenza LRI mortality was 28% in HSCT patients, significantly higher than that among subjects with URI (3%) [22]. Overall, in adult HSCT patients mortality post viral respiratory infections is high, ranging from 25-45% [21-24]. Finally, in a study referring to children post allogeneic HSCT, the mortality rate due to viral infections was 9.7%, with a respiratory virus being identified in only 20% of deaths [33].

Moreover, clinicians should also consider prolonged viral shedding.

In a study of HSCT recipients the median duration of shedding for rhinovirus was 5 weeks (range, 1-49 weeks) [34]. The median duration of parainfluenza-3 shedding in hematologic malignancies patients was 72 days [35]. This point needs further elucidation, since asymptomatic shedding might eventually progress to symptomatic respiratory disease and may be associated with long-term decline in lung function [25]. These findings may also have implications for the role of nosocomial transmission within oncology units [25].

Finally an important consequence, when acquiring a viral infection is the delay in the chemotherapy regimen. Forty to fifty per cent of oncology patients experienced a median delay of 7 days in scheduled chemotherapy due to respiratory viral infections [20,32].

Treatment

Until recently, symptomatic therapy (adequate fluids, fever treatment, monitoring, oxygen supplementation) was the only feasible treatment option. Over the last years though, novel antiviral agents have become available, targeting specific viruses [10,12].

Amongst the first antivirals used were the M2 inhibitors, amantadine and rimantadine (Table 2) [36]. Both have efficacy against Influenza A and can also be used for chemoprophylaxis. Unfortunately the emergence of resistant influenza A strains, in combination with increased toxicity of these agents have led to a decline in their use. As a result the current mainstays for influenza treatment are the neuraminidase inhibitors oseltamivir and zanamivir. This class of antivirals has the added advantage of efficacy against both Influenza A and B. In immunocompromised patients, these drugs have been shown to be effective when used in standard regimens, but also increased doses and prolonging the administration in persistent cases have been suggested [11]. Concerns have arisen, though, in cancer patients, regarding the pulmonary bioavailability of zanamivir [37]. Currently novel compounds such as peramivir are being studied in clinical trials [11].

Another antiviral drug that has been used is ribavirin, a synthetic nucleoside analog of guanosine. Ribavirin has been studied for treatment against RSV, influenza, parainfluenza, hMPV and adenovirus, mainly in adult populations. When initiated before the onset of respiratory failure in the course of uncomplicated influenza, ribavirin seems to have some benefit. However results for parainfluenza are conflicting [10]. In a HSCT study of adults with parainfluenza-3, ribavirin with or without IVIG failed to show noticeable results in lowering mortality or shortening viral shedding [21]. Regarding hMPV, ribavirin demonstrates activity both in vitro and in animal models [11]. For severe RSV, there has been some limited data on potentially beneficial effect of nebulized ribavirin for both previously healthy and immunosuppressed patients [10,12]. One study of RSV in adults with leukemia reported that patients in which ribavirin was not administered early (while at the URI stage), were at increased risk for progression to pneumonia (96% vs. 68%). Treatment with ribavirin plus IVIG lowered mortality from 36% to 6% [38]. Despite its benefit ribavirin via inhalation poses various challenges, requiring complicated and expensive techniques (continuous delivery, small particle aerosol generator unit, scavenging tent) as well as contamination prevention for healthcare workers due to its teratogenicity.

Passive immunoprophylaxis with humanised monoclonal antibodies against the F- protein of the virus (palivizumab) is not established in paediatric cancer patients [5]; in addition combination therapies of ribavirin and palivizumab have produced conflicting results. Motavizumab, an ultra-potent, affinity matured, humanised monoclonal antibody is under investigation for children with malignancies with severe RSV, as well as a RNAi molecule (ALN-RSV01) that silences the nucleocapsid gene of the RSV genome [12].

Cidofovir has been used to treat severe adenovirus infections after HSCT with promising results, using various treatment regimens [39-41]. As cidofovir therapy poses major toxicity risks, mainly nephrotoxicity, adequate hydration and the co- administration of probenecid are paramount (Table 3) [42].

Amantadine (Symmetrel)[a]	Treatment or prophylaxis, PO • 1-9 years old: 5 mg/kg/24 h bid • ≥10 years old: 5 mg/kg/24 h bid if <40 kg and 200 mg/24 h bid if ≥40 kg. • Alternative prophylaxis for children >20 Kg and adults, PO: 100 mg/24 h
Rimantadine (Flumadine)[b]	Treatment (≥13 years old), PO 200 mg/24 h bid Prophylaxis (>1 year old), PO • 1-9 years old: 5 mg/kg/24 h • ≥10 years old: 5 mg/kg/24 h bid if <40 kg and 200 mg/24 h bid if ≥40 kg
Oseltamivir (Tamiflu)[c]	Treatment for 5 days, PO • 1-12 years old: 30 mg bid (≤15 kg), 45 mg bid (16-23 kg), 60 mg bid (24-40 kg) and 75 mg bid (≥40 kg) • ≥13 years old: 75 mg bid • Prophylaxis for 10 days, PO same dosage as treatment but given once daily
Zanamivir (Relenza)[d]	Treatment for 5 days, inhaled • ≥7 years old: 10 mg bid Prophylaxis, inhaled • ≥5 years old: 10 mg/24 h once daily for 28 days (community outbreaks) or 10 days (household setting)

[a]Endo Pharmaceuticals, 100 Painters Drive, Chadds Ford, PA USA.
[b]Forest Laboratories, 13600 Shoreline Drive, St. Louis, MO USA.
[c]Roche Laboratories, 340 Kingsland Street Nutley, NJ USA.
[d]GlaxoSmithKline Pharmaceuticals, 5 Moore Drive, PO Box 13398 Research Triangle Park, NC USA.

Table 2: Recommended antiviral regimens for influenza infection.

Cidofovir (Vistide)[a]	- 5 mg/Kg/dose IV once weekly x3, followed by 5 mg/Kg/dose IV once every 2 weeks. - Administer oral probenecid 1-1,25 g/m^2/dose, 3 hr prior to and 1 hr and 8 hr after each dose of cidofovir. - Administer IV normal saline x3 maintenance fluid, 1 hr prior to and 1 hr after cidofovir, followed by x2 maintenance fluid for an additional 2 hr

[a]Gilead Sciences, 333 Lakeside Drive Foster City, CA USA.

Table 3: Recommended cidofovir regimen for adenoviral infection.

Adoptive cellular immunotherapy using either donor adenovirus-specific T cells or T cells depleted from alloreactive cells offer new therapeutic options [27]. Future fields of research include the efficacy of combination antivirals, as to avoid the emergence of resistance and also to minimize adverse effects through the decrease of the required dosages of the respective agents [10,11]. Importantly, newer, so-called broad spectrum antivirals such as pyrimidine biosynthesis inhibitors or dsRNA activated caspase oligomerizers promise to treat a wide array of DNA and RNA viruses [43,44].

Prevention and Control Strategies

Vaccination provides an established preventive method for influenza infection. The annual administration of the trivalent inactivated subunit vaccine, which contains two influenza A and one influenza B strains is recommended for children with cancer [11]. Unfortunately actual vaccination rates are still extremely low (9%–31%) [45]. Among children with ALL vaccinated during re-induction, a seroresponse of 24%–60%, and protective response rates of 57%–85% have been reported [46]. The protective antibody titres, although lower than in healthy children were considered satisfactory. In a recent study in children with solid tumors, the protective response rates were 60%-84%, suggesting similar immunogenicity with leukemic children [47]. Overall, influenza vaccination in children receiving chemotherapy is strongly supported, since antibody titres are adequate and there are no safety issues. However, seroresponse rates vary according to chemotherapy phase and lymphocyte count. Although, new adjuvanted influenza vaccines are being evaluated in clinical trials, to prevent health-care related influenza spread, special emphasis must be placed on the promotion of yearly hospital staff vaccination [45,48]. Moreover, caregivers and family members in close contact with children with cancer should be educated on respiratory infections and "cocooning", i.e. the indirect protection of the susceptible person through their own vaccination [5]. Currently there are numerous studies for the development of commercial vaccines against RSV and adenovirus [11].

Moreover, general control measures for respiratory viruses include droplet and contact precautions (Table 1). These involve placing the infected patient in a single room or in the circumstance of multiple cases by the same pathogen, cohorting of the infected patients. Persons entering the room, including the health-care personnel, should wear a gown, gloves, mask, and eye protection. In the majority, a surgical mask is appropriate but for more contagious viruses, such as influenza H1N1 a fit-tested N95 mask is required. For more virulent viruses, negative pressure isolation is suggested [36,49]. Additionally to that, in the event of an outbreak, measures reducing effectively nosocomial transmission and increasing patient safety include: discharge of patients admitted for investigation or elective procedures, daily respiratory symptoms screening of staff, prompt sick-leave for staff exhibiting symptoms and discontinuation of transplantations as well as reduction of outpatient appointments for HSCT patients [11]. In the case of adenovirus infection, monitoring, similar to cytomegalovirus, prior and at specific intervals post HSCT may permit early detection in certain high-risk settings. Initiation and adherence to these control measures has been shown to cause significant reduction in the nosocomial spread of respiratory infections and increase patient safety at several oncology centres [10].

Conclusions – Gaps in Knowledge

Pediatric studies have often focused on a particular virus or a specific underlying malignancy making the overall assessment of the epidemiology of respiratory viral infections arduous. More studies are needed in order to define the true impact of these infections on mortality and morbidity of paediatric oncology patients, to better delineate therapeutic options and to identify ways of preventing such infections in these patients. Furthermore, few studies have utilized the latest -more sensitive and accurate-methods for viral detection. As a result there is a paucity of data regarding the epidemiology of recently emerged viral pathogens such as hMPV, bocavirus that play an important role in immunocompromised children [2,9,11]. Furthermore, it is hypothesized but not studied, that viral-bacterial co-infections are more frequent in immunocompromised patients compared to healthy subjects and are associated with increased clinical severity of respiratory infections due to impaired immune system and /or extensive pre-exposure to antibiotics. Moreover, it is difficult to compare incidence and disease burden between immunocompetent children and pediatric oncology patients since there have not been any studies evaluating URIs during the same period among these different cohorts. Recently, in a study involving immunocompetent children viral co-infection was a major factor associated with hospitalization [50]. This is in accordance with the aforementioned data since among pediatric oncology patients co-infections are associated with disease burden. Finally and most importantly, previous studies have focused on mortality as an outcome, while the issue of delays in chemotherapy due to respiratory viral infections and their potential association with patients' survival, has not been satisfactorily addressed to date.

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