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Influenza-Associated Morbidity in Children With Cancer

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Abstract

Background—The clinical impact of influenza in children undergoing therapy for cancer is not well-described in the literature.

Procedure—Laboratory-documented influenza infection in pediatric oncology patients cared for in a single regional pediatric medical center between July 2000 and June 2005 was identified by review of medical and laboratory records.

Results—Twenty-seven clinical encounters were identified in 24 pediatric oncology patients with influenza infection. Eighty-three percent of patients were receiving chemotherapy for hematologic or solid malignancies. Two-thirds of patients were hospitalized for a median duration of 7.4 days; 40% of patients experienced a delay in scheduled chemotherapy as result of influenza infection. Most children (67%) were not neutropenic, although 63% were lymphopenic. Importantly, 15% of children with influenza had simultaneously diagnosed bacteremia. Concomitant pathogens included *Pseudomonas aeruginosa*, *Enterobacter cloacae*, *Enterococcus faecalis*, and coagulase-negative *Staphylococcus*. Primary influenza pneumonia and/or respiratory failure occurred in three children, and ventilatory support was required in four clinical encounters. Antiviral medications were administered to 63% of patients within 2 days of influenza diagnosis.

Conclusion—Pediatric oncology patients experienced significant influenza-associated morbidities. Influenza infection should be considered in febrile children with respiratory symptoms during the respiratory viral season, as well as concurrent bacterial or fungal infections.

Keywords

cancer; influenza; pediatric; respiratory virus

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Introduction

Children with intrinsic or acquired immunodeficiencies are more vulnerable to a variety of infectious pathogens, including viruses [1,2]. Because cancer and anti-cancer therapies further impair immune function, patients with malignancies are at higher risk for sequelae from common infections. Children with cancer comprise an important immunocompromised population; they may experience prolonged viral shedding and are at risk for serious influenza-related morbidity [3,4]. Although descriptions of respiratory virus (RV) infections in certain immunosuppressed populations, such as bone marrow transplant (BMT) [5,6], solid organ transplant [7,8], and HIV-infected [9] patients, have been published, similar studies in non-transplant pediatric oncology patients are surprisingly limited. One of the most comprehensive analyses of influenza in children with cancer was published in 1977 [10], with only limited studies reported since then. However, medical care of pediatric oncology patients has changed markedly over the past 30 years with respect to chemotherapy intensity, antiviral medications, and influenza vaccination. Antiviral therapies are now available and approved for pediatric use, and influenza vaccination in younger children is now routine.

Viruses are the most common infectious agents of childhood and thus highly likely to contribute to febrile episodes in children with cancer [11,12]. The significance of influenza infection in this patient population in terms of hospitalization, respiratory complications, use of antibiotics and antivirals, and delays in chemotherapy is not well-described. We conducted a retrospective analysis of all pediatric oncology patients in our institution with laboratory-documented influenza during a 5-year period to determine the incidence and complications of this infection in children with cancer.

Methods

Patients

We retrospectively identified all pediatric patients with cancer who had laboratory-proven diagnoses of influenza A or influenza B infection from July 1, 2000 to June 30, 2005. Pediatric oncology patients ages 0–21 years at CHRMC with symptomatology consistent with RV infection (fever, rhinorrhea, nasal congestion, tachypnea, and/or cough) and with laboratory-confirmed influenza were included. Each subject was assigned a unique study number to preserve confidentiality and anonymity. Discrete data concerning patient age at time of influenza infection, gender, cancer diagnosis, stage of oncologic treatment, presenting signs and symptoms, and other treatment, clinical, and laboratory data were obtained from medical records. The Institutional Review Board approved this study at Children's Hospital and Regional Medical Center (CHRMC), Seattle, Washington.

Laboratory Diagnosis of Influenza

Nasal wash specimens from non-intubated patients with respiratory symptoms were collected by hospital-designated care providers. Additional samples from bronchoalveolar lavage (BAL) fluid, endotracheal tube aspirations, lung biopsies, and nasal swabs were also submitted as clinically indicated. Direct fluorescent antibody (DFA) testing utilizing

monoclonal influenza A and B antibodies (Chemicon, Temecula, CA) was performed to document the presence of influenza A or B in clinical specimens. In addition, viral culture and quantitative real time reverse-transcriptase polymerase chain reactions (RT-PCR) methods were used in individual cases to document viral shedding [13]. Our laboratory has previously reported excellent correlation between influenza detection using DFA and RT-PCR methods, indicating that DFA is a reliable, specific method for influenza testing in children [13].

Statistics

Data are presented as the mean with 95% confidence intervals (CI), median, or percentage calculations. Ranges are noted when applicable. Statistics were calculated using STATA version 8 (StataCorp LP, College Station, TX).

Results

Demographics

During the study period, 511 episodes of influenza A or influenza B infection were documented in outpatient, emergency department, and hospitalized patients at CHRMC. Of these, 20 influenza A episodes and four influenza B episodes occurred in 24 children with cancer, accounting for 4.7% of all influenza infections. Three patients were each hospitalized twice for prolonged influenza-associated disease, resulting in a total of 27 clinical events included in this analysis. All infections were community-acquired. No patient was concomitantly diagnosed with a second RV, and no child had received BMT prior to influenza infection. During the study period, 1,337 children were diagnosed with cancer at our institution.

Patient characteristics at the time of influenza diagnosis are described in Table I. Underlying oncologic diagnoses included acute lymphoblastic leukemia (ALL; 10 patients), acute myelogenous leukemia (1 patient), Hodgkin lymphoma (1 patient), non-Hodgkin lymphoma (1 patient), Langerhans cell histiocytosis (LCH; 2 patients), Wilms tumor (2 patients), osteosarcoma (2 patient), rhabdomyosarcoma (2 patients), neuroblastoma (3 patients), and brainstem glioma (1 patient). Five patients had influenza infection at time of malignancy diagnosis or during induction chemotherapy, 17 patients had influenza while in remission (receiving maintenance chemotherapy or post-resection/undergoing radiation therapy), and two children had influenza while in relapse.

Clinical Sequelae

Influenza infection sequelae are denoted in Table II. Nearly all patients were febrile at presentation, as defined by temperature $>38.3^{\circ}\text{C}$ with mean temperature 39.2 (95% CI = 38.8–39.6). One-third of patients were neutropenic, while most patients were lymphopenic at the time of infection. Two-thirds of patients with documented influenza were hospitalized for severe respiratory symptoms; median duration of hospitalization was 7 days. A significant proportion of patients did not receive scheduled chemotherapy due to influenza infection-related sequelae: 8 of the 20 patients receiving chemotherapy experienced a median delay of 7 days (range 3–42). Six of these eight patients were hospitalized for their

influenza infections. One patient had persistent influenza A detection by DFA and RT-PCR and was hospitalized twice (Supplemental Fig. 1). Two additional children with influenza A were readmitted with recurrent fever and symptoms. Three influenza episodes were associated with particularly prolonged hospitalizations (34, 35, and 45 days) and significant complications. However, no patient died from influenza-associated sequelae.

Respiratory complications of influenza included hypoxia, pneumonia, and respiratory failure. Six patients required supplemental oxygen for up to 30 days. Chest radiographs were obtained in 19 patients, and nine had radiographic change from baseline, most commonly perihilar or peribronchial thickening (upper tract disease), although one had diffuse bilateral interstitial changes (lower tract disease). Three children with influenza A were intubated due to respiratory failure and subsequently had BAL and/or endotracheal aspiration performed for diagnostic purposes. One of these critically ill patients was diagnosed with a pneumatocele and is further described below.

Patients With Significant Complications

One patient persistently shed influenza A for greater than 5 months and experienced significant complications (Supplemental Figure 1). This 21-month-old infant with disseminated LCH was first diagnosed with influenza infection 19 months after initiation of systemic chemotherapy and 6 weeks after beginning maintenance oral chemotherapy. He required two hospitalizations of 34 and 45 days, respectively. His initial clinical course was associated with severe respiratory compromise necessitating intensive care hospitalization, mechanical ventilation for 3 days, oxygen administration for 30 days, BAL, and multiple chest imaging studies. Infectious comorbidities included *Pseudomonas aeruginosa* and *Enterococcus faecalis* bacteremias, *Clostridium difficile* colitis, and *Pneumocystis carinii* and *Candida tropicalis* pneumonia. He was discharged home from the first hospitalization with continued influenza A shedding by both DFA and RT-PCR, but with improved clinical symptoms. His oral chemotherapy had been held for 6 weeks. He required rehospitalization approximately 4 weeks later for failure-to-thrive and for continued respiratory distress, recurrent fever, and persistent pneumatocele. He underwent a second BAL and required supplemental oxygen for 26 days. His second hospitalization was complicated by multi-organism (*Enterobacter cloacae*, *E. faecalis*, and coagulase-negative *Staphylococcus*) bacteremia and *Candida tropicalis* fungemia. Chemotherapy was held for 26 days during this hospitalization. This patient was treated with multiple antiviral medications, including oseltamivir, rimantadine, and aerosolized ribavirin, which did not significantly impact his viral shedding or clinical condition (Supplemental Figure 1). He ultimately cleared the virus approximately 5 months from initial influenza diagnosis.

Two other patients experienced respiratory failure as result of influenza. One 3-year-old female diagnosed simultaneously with ALL and influenza had primary influenza A pneumonia identified by chest radiograph and BAL. She required intensive care unit admission, intubation, and mechanical ventilation for 9 days and underwent two BALs and lung biopsy. No other infections were detected in this child. She received oseltamivir for 12 days and ultimately cleared her virus by DFA 14 days after initial detection. Induction chemotherapy was delayed 10 days due to severity of influenza infection. A 7-year-old male

with progressive cerebellar LCH receiving salvage therapy when diagnosed with influenza A required an intensive care admission, two intubations, and mechanical ventilation for 9 days. He also underwent BAL. He received 10 days of amantadine and was discharged after 14 days of hospitalization. No other systemic infections were detected.

Antiviral Therapy

In 15 of 27 clinical encounters, patients were treated with one or more antiviral medications, including oseltamivir (14 patients), amantadine (2 patients), rimantadine (1 patient), and aerosolized ribavirin (1 patient). Two of the three patients who were rehospitalized with influenza A received a second course of antiviral therapy. Specific influenza vaccination records during the study period were not available for this review, although it is CHRMC policy to immunize pediatric oncology patients during the annual influenza season.

Antibiotic Therapy and Bacteremia

The majority of clinical encounters (70%) in oncology patients with influenza were initially treated with empiric broad-spectrum intravenous antibiotics. Of the 21 patients from whom blood cultures were obtained, three were bacteremic. One patient each grew coagulase-negative *Staphylococcus* and *Propionibacterium acnes*, both confirmed by multiple blood cultures. The previously described patient with disseminated LCH had multiple systemic infections. In total, 15% of patients were concomitantly bacteremic during their influenza infections.

Discussion

The impact of influenza virus infection was evaluated in pediatric oncology patients receiving care at a single institution. The complications related to influenza in these children were remarkable for the frequency and prolonged duration of hospitalization, severity of pulmonary disease, and significant rate of concurrent bacteremia. Additionally, many patients did not receive anti-cancer therapy as scheduled. To our knowledge, this study is one of the first to describe specifically influenza-associated morbidities in children with cancer in the era of contemporary chemotherapy and antiviral treatment.

Our results demonstrate that influenza is associated with marked respiratory complications, sepsis, and chemotherapy interruption. Life-threatening disease was particularly noted in patients with lymphopenia and/or malignancies not in remission. Feldman et al. [10] first characterized influenza infection in children and young adults with cancer in 1977. They reported prolonged duration of clinical symptoms, a high rate of concurrent bacteremia, and considerable chemotherapy delay. These statistics remain concordant with our findings 30 years later. Chemotherapy was delayed in 40% of our patients as result of influenza infection, although the impact of this interruption remains unknown. With the high RV frequency in winter seasons and the documentation of prolonged viral shedding in immunocompromised children, influenza infection can potentially hinder administration of anti-cancer therapies.

While the pediatric literature is limited, RVs have been more thoroughly studied in adults with cancer. In prospective surveillance studies, 31% of adult BMT recipients and 18% of

adult leukemia patients hospitalized with respiratory symptoms were positive for community-acquired RVs [14,15]. Most infections progressed to pneumonia and were associated with a 51% mortality rate. In hospitalized adults with leukemia and respiratory symptoms, influenza A was isolated in 33% of patients [16]. Most of our patients had prolonged respiratory symptoms and required hospitalization due to the severity of influenza infection. Many also exhibited pulmonary changes by chest radiography, and several patients necessitated supplemental oxygen or developed respiratory failure and required mechanical ventilation. Although no child died from influenza, careful monitoring and timely interventions were necessary, and morbidity remained high.

Our patients also experienced a high incidence of leukopenia. In one Finnish population, documented RV infection occurred in 37% of leukopenic and 38% of non-leukopenic febrile children undergoing anti-cancer treatment [11]. While most of our patients were not neutropenic, the majority were lymphopenic, which is concerning because innate anti-viral immunity is generally cell-mediated. Lymphopenia is considered an important risk factor for serious respiratory sequelae in BMT patients infected with influenza [17].

Most concerning was that 15% of our patients were concurrently bacteremic (11% within 24 hr of presentation and influenza detection) and required extensive antibiotics. This bacteremia rate challenges the hypothesis that fever in children with respiratory symptoms is attributable to a single infectious etiology. Influenza detection in our patients did not preclude co-infection with other pathogens. Because of impaired immunity, pediatric oncology patients with influenza should also be screened for co-pathogens.

While antiviral medications are widely available, no agent has been approved in the United States for children fewer than 12 months old. In our study, 12.5% of patients were younger than 1 year old. Emerging resistance in vitro and in vivo to both M2 ion channel inhibitors and neuraminidase inhibitors is also well described in immunocompromised children and adults [18–21].

Influenza vaccination remains another important consideration. In 1989, Kempe et al. [3] prospectively noted that influenza infection occurred more commonly in unimmunized children with cancer. While annual vaccination of pediatric oncology patients and their families is generally recommended [22,23], this practice has not been universally implemented [24]. Suboptimal immunogenicity and efficacy in pediatric oncology patients is also problematic, especially in comparison to healthy children [3,25,26]. We believe that assessment of antibody titers following vaccination is not feasible in oncology patients, does not necessarily confer protection, and thus should not be recommended.

Although relatively uncommon, influenza infection in children with cancer is significant. We suggest that febrile oncology patients with respiratory symptoms have nasal washes for RV DFA testing, CBC with differential, and bacterial (and fungal if indicated) blood cultures performed. Empiric antibiotics should be administered until negative blood cultures are obtained, and patients should be hospitalized if clinically indicated. The diagnosis of influenza should be entertained, particularly when the virus is circulating in the community. Prompt antiviral treatment should be considered, although our data show that standard

monotherapy did not always mitigate viral shedding or influenza-associated complications. The consideration of combination antiviral therapy could be entertained for severely immunocompromised patients [27]. Oncology patients with influenza should also anticipate delay in chemotherapy administration while waiting for cytopenias to recover and for respiratory symptoms to resolve.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table I
Clinical Characteristics of Pediatric Oncology Patients With Laboratory-Proven Influenza Infection

Clinical characteristic	Pediatric oncology patients with influenza (N=24)
Age, median years (range)	5.0 (0.4–18.2)
Influenza A positive, n (%)	20 (83)
Influenza B positive, n (%)	4 (17)
Male, n (%)	15 (63)
Hematologic cancer, n (%)	15 (63)
Solid tumor, n (%)	9 (37)
Disease status at time of influenza infection	
At diagnosis/induction, n (%)	5 (21)
Remission, n (%)	17 (71)
Relapse, n (%)	2 (8)

Table II
Impact of Influenza Infection Upon Clinical Factors During Influenza-Related Encounters

Impact of influenza infection	Influenza-related clinical encounters (N = 27)	Severe influenza disease requiring respiratory support (N = 4) ^a
Duration of fever, mean days (range)	4.6 (0–16)	8.8 (3–16)
Duration of symptoms, mean days (range)	11.1 (3–27)	18.8 (14–21)
Duration of clinical encounter, median days (range)	7.4 (0–44.9)	24.2 (14.1–44.9)
Inpatient admission, n (%)	18 (67)	4 (100)
Maximum temperature, mean °C (range)	39.2 (36.5–40.6)	39.0 (38.2–40.1)
ANC, mean neutrophils/ μ l (range)	2,269 (0–7,921)	1,450 (64–2,772)
ANC<500/ μ l, n (%)	8 (30)	1 (25)
ALC<1,000/ μ l, n (%)	17 (63)	3 (75)
Oxygen requirement, n (%)	6 (22)	4 (100)
Mechanical ventilation, n (%)	4 (15)	4 (100)
BAL performed, n (%)	4 (15)	4 (100)
Chest radiograph change, n (%)	9 (47) ^b	4 (100)
Bacteremic, n (%)	4 (15) ^c	2 (50)
Antibiotic administered, n (%)	19 (70)	4 (100)
Antiviral administered, n (%)	17 (63)	4 (100)
Chemotherapy delayed, n (%)	8 (40)	4 (100)

^a These four encounters with severe influenza disease are a subset of the total 27 encounters

^b Chest radiographs were obtained for 19 clinical encounters

^c Blood cultures were obtained for 24 clinical encounters.