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Clinical and Demographic Characteristics of Seasonal Influenza in Pediatric Patients with Cancer

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Abstract

Background—Changes in oncology care and the diagnosis and management of influenza over the past several decades may have altered the epidemiology and outcomes of influenza in pediatric oncology patients.

Methods—The clinical features and outcomes of 102 pediatric patients undergoing cancer therapy during 107 episodes of influenza between January 2002 and April 2009 were retrospectively ascertained.

Results—Median age at the time of influenza was 7.2 years [interquartile range (IQR) 3.8–11.2 years]; 46% of patients were male. Nineteen patients (18%) were recipients of hematopoietic stem cell transplants (HSCT). Patients' median absolute neutrophil and lymphocyte counts were 1300/μL (IQR 500–2967/μL) and 360/μL (IQR 180–836/μL), respectively. Twelve patients (11%) had co-infections with influenza and one or more other respiratory pathogens. Influenza prompted patients' hospitalization during 64% of episodes, and 75% received antiviral therapy. Complications occurred in 30% of infections and serious complications occurred in 7%. Three patients died, but no deaths were directly attributable to influenza. Most patients had delays in cancer therapy; the median delay was 5 days. Neutropenia, concurrent infection, increasing age and having received HSCT increased the risk of serious complications.

Conclusions—Advances in the management of pediatric cancer and influenza have not altered the epidemiology and outcome of influenza in oncology patients. Clinical features identify subgroups of patients with influenza who are at risk for poor outcomes and those with a good prognosis.

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Conflicts of Interest
The other authors have no conflicts of interest or funding to disclose.

Keywords

pediatric; influenza; cancer; immunocompromised host

INTRODUCTION

The last comprehensive review of the epidemiology and clinical characteristics of influenza infection in pediatric oncology patients was published over 2 decades ago in 1989.[1] This, and subsequent studies of smaller numbers of pediatric oncology patients suggest that these children, relative to those who are healthy, experience more prolonged symptoms and high rates of hospitalization and complications.[1–6] Case-fatality rates have ranged from 0–5%. Pediatric oncology care has changed considerably since the 1980s. Many cancer treatment regimens are more intensive than those used in the past, and hematopoietic stem cell transplantation (HSCT) is more widely used.[7] It is plausible that such advances might further predispose patients to influenza infection or to greater morbidity and poorer outcomes than those reported in the past. On the other hand, some risk-stratified therapies may be less immunosuppressive than traditional regimens and place patients at lower risk for adverse outcomes.

As therapy for pediatric cancer has evolved, so have strategies for the diagnosis, prevention and treatment of influenza and its complications. Diagnostic tests for influenza that were introduced in the last two decades may have better (e.g. nucleic acid amplification tests) or poorer (e.g. point-of-care tests) sensitivity relative to the “gold standard” of viral culture.[8] The choice of diagnostic tests may, therefore, alter the proportion of influenza cases that are detected and the subsequent management of patients with these infections. Anti-influenza drugs such as the neuraminidase inhibitors oseltamivir and zanamivir are widely available, safe, and clinically efficacious in preventing influenza and in preventing the progression of influenza to serious disease in highly immunocompromised patients.[9–11] Annual seasonal influenza vaccine is increasingly recommended to members of the general public, health care providers, household contacts of immunocompromised persons, and patients themselves, although adherence to these recommendations has been less than ideal.[12] The recently introduced cold-adapted intranasal influenza vaccines evoke local mucosal immunity and provide greater cross-protection than traditional inactivated vaccine formulations in healthy persons.[13] Finally, supportive therapy, including prompt antibiotic administration for fever and neutropenia and intensive care for pediatric oncology patients has improved in tandem with progress in the treatment and prevention of influenza. These developments may have moderated the number and severity of infections.

We reviewed the epidemiology, clinical features, and outcomes of recent cases of laboratory-confirmed influenza in pediatric patients undergoing cancer therapy at St. Jude Children’s Research Hospital (St. Jude) to examine how these factors may have been affected by changes in pediatric oncology and in the prevention and management of influenza. We also attempted to identify risk factors associated with serious influenza morbidity and mortality.

MATERIALS AND METHODS

Study population

St. Jude provides comprehensive care for pediatric patients with cancer and immunodeficiency diseases. All clinical and laboratory data related to influenza and other acute illnesses is monitored. Children and young adults aged 0–21 years with influenza infection confirmed by direct immunofluorescence assay, polymerase chain reaction (PCR),

or respiratory viral culture between January 1, 2002 and March 31, 2009 were identified by reviewing diagnostic microbiology laboratory results (PCR became available in 2004). Patients who had received cancer therapy within the 3 months preceding influenza infection were included in the study, as we sought to include only significantly immunocompromised patients in the analysis. The study was approved by the St. Jude Institutional Review Board; informed consent was waived.

Demographic data and clinical findings from the time of onset of symptoms of influenza until death or the complete resolution of acute illness were abstracted from medical records. Laboratory test results obtained within 48 hours of the diagnosis of influenza are reported.

Definitions

Influenza was considered to be nosocomially acquired if the illness began 4 or more days after hospitalization. Influenza-related complications were defined as any adverse clinical event occurring within 14 days after the onset of influenza; respiratory failure, clinically significant hypotension, shock, and acute respiratory distress syndrome were defined as severe complications. Pneumonia was defined as an acute respiratory illness associated with a new or increased pulmonary infiltrate. A co–pathogen was defined as a pathogenic bacterium, fungus, or virus isolated from a respiratory specimen obtained within 14 days of the onset of influenza symptoms. A concurrent infection was defined as the isolation of a pathogenic microorganism from any body site within 14 days of the onset of influenza. Influenza-attributable death was defined as death due to respiratory failure for which no other potential cause was identified.[14] Influenza was considered to have contributed to death if there was clinical or laboratory evidence of persistent or progressive influenza infection at the time of death.[11]

Neutropenia and lymphopenia were defined as an absolute neutrophil count (ANC) ≤1,000/μL and an absolute lymphocyte count (ALC) ≤300/μL, respectively. Hepatic transaminases were considered elevated if serum aspartate aminotransferase (AST) or alanine aminotransferase (ALT) activity exceeded the upper limit of normal for age. Influenza A viruses were not routinely subtyped during the study period.

Statistical analysis

Only the first episode of influenza in a season was included in the analysis. Data were analyzed by using the Stata 9.0 software package (Stata, College Station, TX). Demographic and clinical characteristics were compared by using the *t*, Chi-square, Kruskal-Wallis, Fisher's exact or *t* tests or analysis of variance (ANOVA), as appropriate. *P* values <0.05 (2-tailed test) were considered statistically significant. Risk factors for adverse outcomes were identified by univariate and multivariate logistic regression, and odds ratios (OR) and 95% confidence intervals (CI) were reported. Final models were based on backward elimination of variables with a predetermined cutoff of $P \leq 0.1$ in univariate analyses.

RESULTS

Demographic and clinical characteristics

During the study period, 174 of the 4,201 pediatric patients with cancer treated at St. Jude had influenza; the average frequency was 5.7 infections/1,000 patients/year. One hundred two patients met the inclusion criteria; most others diagnosed with influenza during the study period had not received cancer therapy during the preceding 3 months. Four patients had more than one influenza episode (one patient had three episodes, three patients had two), for a total of 107 distinct influenza episodes. Between 2 and 26 infections were diagnosed per year, with the largest number of cases reported in the month of February.

Information on receipt of influenza vaccine was available for 55 patients; 31 (56%) had been vaccinated during the current season.

Table 1 lists demographic, clinical, and laboratory characteristics of subjects. Patients contracted influenza at a median age of 7.2 years. More episodes (54%) were diagnosed in females. Of the 69 patients with hematological malignancies, 61 (88%) had leukemia and 8 had lymphomas (4 Hodgkin lymphoma, 4 non-Hodgkin lymphoma). A total of 10 (15%) of patients with hematological malignancies were receiving induction chemotherapy and 52 (75%) were in remission. Nineteen patients (18%) had undergone HSCT, a median of 83 days (range, 1–457 days) before the diagnosis of influenza. Most episodes (103, 96%) occurred in outpatients; 66 patients were hospitalized. Four patients (4%) had nosocomially-acquired influenza.

Most infections (65%) were caused by influenza A viruses. The most common symptoms of influenza were fever, cough and coryza (Table 1). Notably, 92% of patients had fever, including 97% of patients with hematological malignancies, but only 79% of patients who had undergone HSCT. Clinical symptoms were similar across patients with different cancer diagnoses. Myalgia was more frequent in patients with influenza B than in those with influenza A (27% vs. 4%, P=0.001), but there were no other notable differences in the clinical manifestations of influenza A and B infection. Patients' median ANC was 1,300/μL (range 0–14,100/μL), and the median ALC was 360/μL (range 0–5,280/μL). Hepatic transaminases were elevated in 56 (62%) patients; in 29 (27%) of these, values were more than twice the upper limit for age. Differences in laboratory values across cancer categories were driven by the greater incidence of neutropenia, lymphopenia and AST elevations in patients with hematological malignancies.

Respiratory co-pathogens were identified in 12 patients (11%), most frequently in HSCT recipients (26%). These included adenovirus (n=4, identified by PCR of blood or isolated from nasopharyngeal secretions), cytomegalovirus (CMV) (n=3, identified by PCR of blood or isolated from nasopharyngeal secretions), respiratory syncytial virus (RSV) (n=2, identified by PCR of nasopharyngeal secretions), human parainfluenza virus 2 or 3 (n= 3, identified by PCR of or isolation from nasopharyngeal secretions) and *Aspergillus fumigatus* (n=1, isolated from a tracheal aspirate); 1 patient had simultaneous influenza, human parainfluenza virus, and adenovirus infection. Non-respiratory concurrent infections, present in an additional 6 patients, included bacteremia (n=3, including *Pseudomonas aeruginosa*, *Enterococcus faecalis* and *Staphylococcus epidermidis*), oral candidiasis (n=2), and disseminated aspergillosis (n=1).

Treatment and outcome

Anti-influenza therapy was prescribed to 80 patients (75%) for a median duration of 5 days (range 3–22 days). The median time between the onset of influenza symptoms and initiation of antiviral therapy was 3 days. The majority of patients (86%) also received concomitant antibacterial and/or antifungal therapy. Sixty-four percent of the patients were hospitalized for management of influenza. Table 2 describes treatment and outcome according to number of episodes.

Radiological studies were obtained for 62 patients. HSCT recipients were more likely than others to have had radiological studies (79% vs. 53%, P=0.013). Patients who had radiological tests were febrile and had cough more frequently than others, and their mean ANC was lower than that of others, but these differences were not statistically significant. Nineteen patients (31%) who had radiological studies were found to have pneumonia.

Complications occurred in 32 (30%) of the 107 episodes of influenza (Table 2). Severe complications included hypotension (n=4) and respiratory failure (n=4). Infectious complications other than pneumonia included acute otitis media (n=5), *Candida* mucositis (n=2), acute bacterial sinusitis (n=4), myocarditis (n=1), bacterial pharyngitis (n=1) and disseminated aspergillosis.

Three patients died during influenza infection, but no deaths were directly attributable to influenza. Influenza was judged to have contributed to mortality in only one case. All patients who died had undergone HSCT (2–185 days before influenza onset), and all had influenza A infection, pneumonia, other serious complications, and respiratory co-pathogens. A 12-year-old girl with acute lymphoblastic leukemia (ALL) who had undergone haploidentical HSCT 6 months previously was admitted with *Enterobacter cloacae* bacteremia. She experienced progressive respiratory failure, and *Aspergillus fumigatus* and influenza A virus were isolated from tracheal secretions collected on the 15th day of hospitalization. She expired 30 days after admission. Influenza infection was judged to have possibly contributed to her death. A 13-year-old girl with acute myelogenous leukemia developed new pulmonary infiltrates and hypotension on day 3 after haploidentical HSCT. Influenza A virus and adenovirus were isolated from bronchoalveolar lavage fluid obtained on the 17th hospital day. Her hospital course was further complicated by human parainfluenza 2 virus pneumonia and CMV and Epstein-Barr virus viremias. She died on day 167 of hospitalization. A 15-year-old boy with ALL experienced mental status alteration, hypotension, and respiratory distress on day 2 after allogeneic HSCT. Influenza A virus was isolated from nasopharyngeal lavage fluid collected 8 days later, but follow-up cultures after an additional 5 days were negative for influenza virus. Acute graft-versus-host disease, concurrent CMV and RSV pneumonia, and persistent candidemia complicated his hospital course. He died on the 109th day of hospitalization.

Sixty-three patients (62%) had a delay in cancer therapy due to influenza infection (median delay, 10 days, range 1–26 days). Influenza infection also caused delays in HSCT (n=1) and elective surgery or diagnostic procedures (n=5), and it prolonged the hospitalization of 2 patients who acquired influenza nosocomially.

Risk factors for adverse outcomes

Logistic regression was used to analyze the influence of demographic and clinical characteristics (age, sex, race, cancer diagnosis, vaccination status and fever) and laboratory results (neutropenia, lymphopenia and elevated hepatic transaminases) on the risk of hospitalization for influenza. Hospitalization for influenza was significantly associated with fever [OR 12.1, 95% confidence interval (CI) 1.39–118.36; P=0.001] and having an ANC of <1000 (OR 4.16, 95% CI 1.85–11.07; P=0.024) in both univariate and multivariate analyses, but not with any other demographic, clinical, or laboratory characteristics.

Radiographically confirmed pneumonia was associated with female sex (OR 3.20, 95% CI 1.04–9.84; P=0.042) and concurrent infection (OR 4.63, 95% CI 1.38–15.54, P=0.013) in univariate analyses, but the incidence of pneumonia did not vary according to race, cancer diagnosis, age or the presence of neutropenia, lymphopenia or the presence of concurrent respiratory pathogens. None of these risk factors was statistically significant in a multivariate analysis.

Serious complications were more common in older patients (OR 1.18 per year of age, 95% CI 1.26–24.87; P=0.013), recipients of HSCT (OR 5.6, 95% CI 1.26–24.87; P=0.024), patients who were neutropenic (OR 4.54, 95% CI 0.87–23.65, P=0.072) and those with concurrent infections (OR 11.03, 95% CI 2.35–51.72; P=0.002).

DISCUSSION

A surprising finding of this study is that the morbidity and mortality associated with influenza is very similar to that observed in previous retrospective and prospective studies of pediatric oncology patients carried out in our own and other institutions over the past three decades. Feldman and Webster reported in 1977 that the symptoms of influenza in pediatric oncology patients at St. Jude were similar to those in healthy children, but that these persisted about twice as long, 14 days. The median duration of symptoms in the current study was comparable to that study (15 days), slightly longer than that reported by other investigators.[1, 2] In view of the degree of immunosupression among patients in this study (42% had an ANC <1000/μL, 37% had an ALC <300/μL, and 17% were HSCT recipients), it is notable that no mortality was directly attributable to influenza infection. Previously reported case-fatality rates in the general pediatric oncology population have ranged from 0% to 5%.[1–6, 16, 18] Most of these studies were relatively small and did not distinguish between influenza-attributable and all-cause mortality. All patients who died in this study had undergone HSCT, a finding consistent with previous reports of higher influenza mortality rates in transplant recipients at our own and other institutions.[5, 17] We also observed a comparatively low rate (7%) of respiratory failure and shock in the current series. Tasian et al noted that 4/24 patients with influenza (17%) required intubation and mechanical ventilation, and Kersun et al reported that 4/42 children (10%) were admitted to the intensive care unit.[2, 5] Only the latter study included HSCT recipients. Surprisingly, no severe or necrotizing secondary bacterial pneumonia was confirmed microbiologically in patients in this study and no patient had a delayed respiratory deterioration consistent with such an infection. It seems plausible that the prompt use of broad-spectrum antibacterial and antiviral agents (92% and 80% of neutropenic patients received antibacterial and antiviral therapy, respectively) may have prevented or moderated the course of synergistic bacterial pneumonia. Alternatively, immunocompromised patients may be less capable of mounting vigorous inflammatory responses to pulmonary infections and be at lower risk of lung damage and the adverse outcomes that may complicate pro-inflammatory responses.[21]

Although low mortality rates and low rates of serious complications were observed in this series, the morbidity associated with influenza was substantial. A large majority (80%) of patients was hospitalized due to influenza; this rate is much higher than in previous reports (0%–20%).[1, 2, 6] One possible explanation is that the decision to hospitalize patients may have reflected their underlying clinical condition, rather than the severity of their respiratory symptoms. Ninety-eight percent of our hospitalized patients were febrile, and 59% were both febrile and neutropenic; these clinical findings are commonly used to identify oncology patients at high risk of serious infection. Our institutional policy is to hospitalize all patients with fever and neutropenia. Leukemia patients were more likely to be hospitalized because of influenza than were solid tumor patients or HSCT recipients, and they had the lowest ANC of any patient group and the highest incidence of febrile neutropenia (52%).

Although more patients were hospitalized in this series than in previous reports, the risk of other complications does not appear to be significantly increased. Pneumonia was reported in 17% of pediatric oncology patients with influenza A in one prospective study[1] and in 0%–47% of hospitalized patients in retrospective studies[2, 3, 6], comparable to the 30% in this report. Notably, viral and fungal respiratory co-pathogens were identified in many patients with pneumonia and may have contributed to lower respiratory tract disease. As in previous reports, patients with cancer experienced postponement of cancer treatment, surgery, diagnostic procedures, and hospital discharge.[1, 2, 6] These delays are inconvenient, necessitate additional monitoring, and place patients at risk of adverse cancer outcomes.[22]

All patients in this study who died had undergone HSCT and had pneumonia and serious complications. All also had respiratory co-pathogens, which in most cases were likely to have directly caused or significantly contributed to mortality. Several previous studies of influenza in pediatric oncology and HSCT patients have identified lymphopenia at the time of diagnosis as a risk factor for hospitalization, progression to pneumonia, and other influenza-related complications. [4, 10, 23] Like Kersun et al, we found no relationship between lymphopenia and adverse outcomes but, in contrast to their results, we found neutropenia to be a risk factor for serious complications.[24] We observed no pneumonia, serious complications, or death in patients with solid tumors and no serious complications or death occurred in patients with leukemia or lymphoma who were not neutropenic. Notably, vaccination against current seasonal influenza viruses was not associated with better outcomes. However, this observation is subject to selection bias; first, we do not know how many vaccinated patients were protected from clinically significant infection and, second, the effectiveness of vaccine is influenced by the timing of its administration relative to the onset of influenza symptoms. Prior receipt of influenza vaccine, the patient's age, the timing of immunization and the concordance of circulating influenza strains with those strains included in the vaccine also influence the protective efficacy of vaccines against influenza.[25]

Among healthy children, the annual frequency of seasonal influenza is estimated to be as high as 24%.[1] In previous studies of pediatric oncology patients, influenza has been diagnosed in 2% to 21% of patients per year.[1, 4, 5, 15–18] Fewer than 1% of pediatric oncology patients in our study had laboratory-confirmed influenza each year. Because patients with respiratory symptoms were not routinely tested for viral infections at our institution, the true infection rate is likely to be higher than the rate we observed. Another explanation for the low observed rate of influenza infection, however, is that St. Jude has fewer patients at any one time than do many medical centers and provides lodging to many patients during their treatment. Parents and patients are encouraged to avoid contact with crowds and with persons exhibiting symptoms of illness, and patients' school and social activities may be restricted. Uptake of seasonal influenza vaccination among healthcare providers has also exceeded 80% annually since 2004.[19, 20] These factors may reduce patients' exposure to influenza in the health care setting and community. It is possible that diagnostic tests were preferentially performed on patients who had more severe symptoms or who were perceived to be at higher risk of severe influenza infection or its complications and that reported cases reflect the severe end of the disease spectrum.

Influenza-attributable mortality among children and young adults with cancer has remained relatively stable in the past several decades, but influenza continues to cause considerable morbidity. The ability to identify patients at high risk of serious complications of influenza (those who are neutropenic, have concurrent respiratory infections or who have undergone HSCT) may facilitate a risk-adapted approach to management - aggressive treatment and supportive care for those at high risk of serious disease while minimizing the duration of hospitalization and therapeutic interruptions in low-risk patients in whom other serious illnesses have been excluded. Enhancing preventative strategies for high-risk populations could also potentially reduce the morbidity of influenza. Although annual influenza vaccination has been demonstrated as safe and efficacious in the childhood oncology population, Porter et al and Crawford et al found that only 65–69% of North American and Australasian pediatric oncologists, respectively, routinely recommend influenza vaccination for their patients in the United States, a rate similar to that described in patients with influenza in our study.[26, 27] The reasons for this may include lack of knowledge and misconceptions among both patients and physicians about the immunogenicity and potential benefits of the vaccine in pediatric oncology patients. Antiviral prophylaxis is not commonly used, for example, but may be effective for patients in whom vaccine is contraindicated or unlikely to be immunogenic. An uncontrolled trial of oseltamivir prophylaxis in a pediatric

cancer center suggested that the agent protected against laboratory-confirmed seasonal influenza; the drug was also effective and well tolerated in HSCT recipients.[28] Further study is needed to determine whether this approach would be practical over time, as the rapid emergence of drug-resistant variants has been described in oncology and non-oncology patients receiving oseltamivir prophylaxis.[29, 30]

This study demonstrated that advances in the treatment of pediatric cancer and in the diagnosis and treatment of influenza have had little impact on the severity of influenza in pediatric cancer patients. In fact, the low prevalence of influenza and lack of directly attributable influenza-related deaths, in light of a more intensively treated population may suggest that, if anything, risk is lower and outcomes may be better. A larger proportion of patients who underwent HSCT experienced serious complications during their episode of influenza than did those in other groups and the only deaths in this study occurred in transplant recipients. A greater proportion of patients with neutropenia and a greater proportion of patients who had concurrent infections developed serious complications than patients who did not have these comorbidities. Risk-adapted management plans may reduce the burden of influenza in this population but prospective studies are needed to confirm our findings and identify the optimal strategies.

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References

1. Kempe A, Hall CB, MacDonald NE, et al. Influenza in children with cancer. J Pediatr. 1989; 115:33–39. [PubMed: 2738793]
2. Tasian SK, Park JR, Martin ET, Englund JA. Influenza-associated morbidity in children with cancer. Pediatr Blood Cancer. 2008; 50:983–987. [PubMed: 18240170]
3. Mendoza Sanchez MC, Ruiz-Contreras J, Vivanco JL, et al. Respiratory virus infections in children with cancer or HIV infection. J Pediatr Hematol Oncol. 2006; 28:154–159. [PubMed: 16679938]
4. Koskenvuo M, Mottonen M, Rahiala J, et al. Respiratory viral infections in children with leukemia. Pediatr Infect Dis J. 2008; 27:974–980. [PubMed: 18833026]
5. Kersun LS, Coffin SE, Leckerman KH, Ingram M, Reilly AF. Community acquired influenza requiring hospitalization: vaccine status is unrelated to morbidity in children with cancer. Pediatr Blood Cancer. 2010; 54:79–82. [PubMed: 19743304]
6. Feldman S, Webster RG, Sugg M. Influenza in children and young adults with cancer: 20 cases. Cancer. 1977; 39:350–353. [PubMed: 576210]
7. Pui CH, Carroll WL, Meshinchi S, Arceci RJ. Biology, risk stratification, and therapy of pediatric acute leukemias: an update. J Clin Oncol. 2011; 29:551–565. [PubMed: 21220611]
8. McGeer AJ. Diagnostic testing or empirical therapy for patients hospitalized with suspected influenza: what to do? Clin Infect Dis. 2009; 48 (Suppl 1):S14–19. [PubMed: 19067610]
9. Flore AE, Fry A, Shay D, et al. Antiviral agents for the treatment and chemoprophylaxis of influenza - recommendations of the Advisor Committee on Immunization Practices (ACIP). MMWR Recomm Rep. 2011; 60:1–24.
10. Nichols WG, Guthrie KA, Corey L, Boeckh M. Influenza infections after hematopoietic stem cell transplantation: risk factors, mortality, and the effect of antiviral therapy. Clin Infect Dis. 2004; 39:1300–1306. [PubMed: 15494906]

11. Chemaly RF, Torres HA, Aguilera EA, et al. Neuraminidase inhibitors improve outcome of patients with leukemia and influenza: an observational study. Clin Infect Dis. 2007; 44:964–967. [PubMed: 17342649]
12. Poland GA. The 2009–2010 influenza pandemic: effects on pandemic and seasonal vaccine uptake and lessons learned for seasonal vaccination campaigns. Vaccine. 2010; 28 (Suppl 4):D3–13. [PubMed: 20713258]
13. Belshe RB, Gruber WC, Mendelman PM, et al. Efficacy of vaccination with live attenuated, cold-adapted, trivalent, intranasal influenza virus vaccine against a variant (A/Sydney) not contained in the vaccine. J Pediatr. 2000; 136:168–175. [PubMed: 10657821]
14. Ljungman P, Ward KN, Crooks BN, et al. Respiratory virus infections after stem cell transplantation: a prospective study from the Infectious Diseases Working Party of the European Group for Blood and Marrow Transplantation. Bone Marrow Transplant. 2001; 28:479–484. [PubMed: 11593321]
15. Arola M, Ruuskanen O, Ziegler T, Salmi TT. Respiratory virus infections during anticancer treatment in children. Pediatr Infect Dis J. 1995; 14:690–694. [PubMed: 8532427]
16. Long DR, Craft AW, Kernahan J, et al. Virus infections in childhood malignant disease. Pediatr Hematol Oncol. 1987; 4:283–292. [PubMed: 3152935]
17. Lujan-Zilbermann J, Benaim E, Tong X, et al. Respiratory virus infections in pediatric hematopoietic stem cell transplantation. Clin Infect Dis. 2001; 33:962–968. [PubMed: 11528566]
18. Maltezou HC, Kafetzis DA, Abisaid D, et al. Viral infections in children undergoing hematopoietic stem cell transplant. Pediatr Infect Dis J. 2000; 19:307–312. [PubMed: 10783020]
19. Hakim H, Gaur AH, McCullers JA. Motivating factors for high rates of influenza vaccination among healthcare workers. Vaccine. 2011; 29:5963–5969. [PubMed: 21699950]
20. McCullers JA, Speck KM, Williams BF, Liang H, Mirro J Jr. Increased influenza vaccination of healthcare workers at a pediatric cancer hospital: results of a comprehensive influenza vaccination campaign. Infect Control Hosp Epidemiol. 2006; 27:77–79. [PubMed: 16418993]
21. Smith MW, Schmidt JE, Rehg JE, Orihuela CJ, McCullers JA. Induction of pro- and anti-inflammatory molecules in a mouse model of pneumococcal pneumonia after influenza. Comp Med. 2007; 57:82–89. [PubMed: 17348295]
22. Relling MV, Hancock ML, Boyett JM, Pui CH, Evans WE. Prognostic importance of 6-mercaptopurine dose intensity in acute lymphoblastic leukemia. Blood. 1999; 93:2817–2823. [PubMed: 10216075]
23. Redelman-Sidi G, Sepkowitz KA, Huang CK, et al. 2009 H1N1 influenza infection in cancer patients and hematopoietic stem cell transplant recipients. J Infect. 2010; 60:257–263. [PubMed: 20138188]
24. Kersun LSCS, Leckerman KH, Ingram M, Reilly AF. Community acquired influenza requiring hospitalization: vaccine status is unrelated to morbidity in children with cancer. Pediatr Blood Cancer. 2010; 54:79–82. [PubMed: 19743304]
25. Carr S, Allison KJ, Van De Velde LA, et al. Safety and immunogenicity of live attenuated and inactivated influenza vaccines in children with cancer. J Infect Dis. 2011; 204:1475–1482. [PubMed: 21949042]
26. Porter CC, Poehling KA, Hamilton R, Frangoul H, Cooper WO. Influenza immunization practices among pediatric oncologists. J Pediatr Hematol Oncol. 2003; 25:134–138. [PubMed: 12571465]
27. Crawford NW, Heath JA, Buttery JP. Immunisation practices of paediatric oncologists: an Australasian survey. J Paediatr Child Health. 2007; 43:593–596. [PubMed: 17608646]
28. Chik KWLC, Chan PK, Shing MM, Lee V, Tam JS, Yuen PM. Oseltamivir prophylaxis during the Influenza season in a paediatric cancer centre : prospective observational study. Hong Kong Med J. 2004; 10:103–106. [PubMed: 15075430]
29. Carr S, Ilyushina NA, Franks J, et al. Oseltamivir-resistant influenza A and B viruses pre-and postantiviral therapy in children and young adults with cancer. Pediatr Infect Dis J. 2011; 30:284–288. [PubMed: 21048522]
30. Oseltamivir-resistant 2009 pandemic influenza A (H1N1) virus infection in two summer campers receiving prophylaxis--North Carolina, 2009. MMWR Morb Mortal Wkly Rep. 2009; 58:969–972. [PubMed: 19745803]

Table 1

Demographic, Clinical, and Laboratory Characteristics of 107 Episodes of Seasonal Influenza in 102 Pediatric Patients with Cancer

	Total ***n*** **= 107 episodes**	**Leukemia/Lymphoma** ***n*** **= 69 episodes**	**Solid tumor** ***n*** **= 19 episodes**	**HCST** ***n*** **= 19 episodes**	***P value***[a]
Median age (y)(IQR)	7.2 (3.8–11.2)	7.0 (4.0–9.0)	5.5 (6.4)	11.5 (8.0–15.0)	0.02
Male (%)	49 (46)	38 (66)	11 (58)	9 (47)	0.8
Race (%)					
White	64 (60)	40 (58)	13 (68)	11 (58)	1.0
Black	31 (29)	21 (30)	4 (21)	6 (32)	
Other	12 (11)	8 (12)	2 (11)	2 (11)	
Vaccinated (%)[b]	31 (56)	20 (64)	7 (23)	4 (33)	0.2
Influenza type (%)					
A	70 (65)	40 (58)	14 (74)	16 (84)	0.08
B	37 (35)	29 (42)	5 (63)	3 (16)	
Nosocomial infection (%)[c]	4 (4)	0 (0)	1 (5)	3 (17)	0.005
Symptoms (%)					
Fever	98 (92)	67 (97)	16 (84)	15 (79)	0.01
Cough	102 (95)	67 (97)	17 (89)	18 (95)	0.2
Coryza	88 (82)	58 (84)	16 (84)	14 (74)	0.6
Pharyngitis	23 (22)	18 (26)	1 (5)	4 (21)	0.1
Wheezing	10 (9)	7 (10)	1 (5)	2 (11)	1.0
Myalgia	13 (12)	10 (14)	2 (11)	1 (5)	0.5
Malaise	31 (29)	21 (30)	5 (26)	5 (26)	1.0
Dizziness	3 (3)	1 (1)	1 (5)	1 (5)	0.3
Headache	17 (16)	12 (17)	3 (16)	2 (11)	0.9
Gastrointestinal	34 (32)	17 (10)	9 (47)	8 (42)	0.1
Laboratory results, median (IQR)[d]					
WBC (*n* = 106)	2.0 (1.1–5.0)	1.9 (1.0–3.0)	3.5 (3.1)	4.8 (4.5)	0.001

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	Total ***n*** **= 107 episodes**	**Leukemia/Lymphoma** ***n*** **= 69 episodes**	**Solid tumor** ***n*** **= 19 episodes**	**HCST** ***n*** **= 19 episodes**	***P value***[a]
ANC (*n* = 106)	1300 (500–2967)	900 (300–2000)	1600 (990–4600)	3200 (1400–7700)	0.001
ALC (*n* = 97)	360 (180–836)	331 (194–594)	799 (270–1854)	328 (168–960)	0.2
Concurrent infection (%)	18 (17)	10 (9)	0 (0)	4 (21)	0.03
Co-pathogen identified (%)	12 (11)	6 (9)	1 (5)	5 (26)	0.08

ALC, absolute lymphocyte count (cells/μL); ALT, alanine aminotransferase (units/L); ANC, absolute neutrophil count (cells/μL); AST, aspartate aminotransferase; BUN, blood urea nitrogen (mg/dL); Cr, creatinine (mg/dL); HSCT, hematopoietic stem cell transplant; IQR, interquartile range; WBC, white blood count ($\times 10^3/\mu L$).

[a] Values were compared across cancer diagnoses by the Chi square, Fisher's exact or Kruskal-Wallis tests or ANOVA.

[b] Vaccination data were available for 55 patients.

[c] Nosocomial infection data were available for 106 episodes

[d] Obtained within 48 hours of the diagnosis of influenza; n indicates number of tests performed.

Table 2

Treatment and Outcomes of 107 Seasonal Influenza Episodes in Children with Cancer.

	Overall ***n*** **= 107**	**Leukemia/Lymphoma** ***n*** **= 69 (64)**	**Solid Tumor** ***n*** **= 19 (18)**	**HCST** ***n*** **= 19 (18)**	***P*** [a]
Received antiviral therapy (%)	80 (75)	54 (78)	9 (47)	17 (89)	0.01
Type of antiviral agent (*n* = 80)[b]					
Oseltamivir	73 (91)	52 (96)	7 (78)	14 (82)	
Rimantadine	2 (3)	1 (2)	1 (11)	0	
Amantadine	2 (3)	1 (2)	0	1 (6)	
Oseltamivir + rimantidine	2 (3)	0	1 (11)	1 (6)	
Oseltamivir + amantadine	1 (1)	0	0	0	
Days of antiviral therapy, median (IQR)(*n* = 80)	5 (5–5)	5 (5–5)	5 (4–5)	5 (5–6)	0.2
No. receiving concurrent antibacterial therapy (%)	92 (86)	66 (96)	14 (74)	12 (63)	<0.001
No. of antimicrobials, median (IQR) (*n* = 92)	2 (1–3)	2 (1–3)	2 (1–2)	3 (2–5)	0.08
Days of symptoms, median (IQR)(*n* = 80)	15 (10–21)	15 (10–19)	13 (11–23)	17 (11–37)	0.3
No. hospitalized (%)	66 (64)	46 (67)	10 (53)	10 (53)	0.4
Days of hospitalization, median (IQR) (*n* = 70)	5 (3–8)	4 (3–7)	5 (4–7)	14 (5–29)	0.01
No. deaths (%)	3 (3)	0 (0)	0 (0)	3 (16)	0.01
No. complications (%) (*n* = 106)	32 (30)	21 (30)	2 (11)	9 (47)	0.04
No. pneumonia (%) (*n* = 62)	19 (31)	12 (29)	0 (0)	7 (47)	0.1
No. serious acute complications (%) (*n* = 106)	8 (7)	4 (6)	0 (0)	4 (21)	0.05
No. with delay in chemotherapy (%) (*n* = 102)	63 (62)	59 (86)	3 (17)	1 (7)	<0.001
Days therapy delayed, median (IQR) (*n* = 63)	5 (5–5)	5 (5–5)	5(4–5)	5 (5–6)	0.4

HSCT, hematopoietic stem cell transplant; IQR, interquartile range

[a] Values were compared across cancer diagnoses by the Chi square, Fisher's exact and Kruskall-Wallace test or ANOVA.

[b] n indicates number of episodes for which variable was recorded.