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2009 Pandemic Influenza A (H1N1) Virus Infection in Pediatric Oncology and Hematopoietic Stem Cell Transplantation Patients

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Abstract

Background—Pediatric oncology and hematopoietic stem cell transplantation (HSCT) patients are at high risk for influenza infection and its associated complications. Little is known about infection with novel 2009 influenza A (H1N1) in this population.

Procedure—Prospective laboratory surveillance identified all children with positive influenza test results from 4/27/09–12/5/09. 2009 H1N1 infection was confirmed by PCR subtyping; cases in which subtyping was not performed were considered probable. Medical records of all pediatric oncology and HSCT cases were reviewed.

Results—Thirty children with cancer or HSCT had laboratory-confirmed influenza A. Patients with ALL (18), CNS tumors (4), CML (1), Ewing sarcoma (1), Hodgkin lymphoma (1), LCH (1), severe aplastic anemia (1), and HSCT (3), had confirmed (5) and probable (25) H1N1 by rapid (22; 73%), DFA (4; 13%), or RVP (4; 13%) assays. Most frequent presenting signs and symptoms were fever (93%; median 38.6°C), cough (97%), and rhinorrhea (83%). Ten patients required hospitalization for a median of 5 days, most commonly for fever and neutropenia (8). Imaging demonstrated lower respiratory tract involvement in 3 patients. There were no concomitant bacteremias; one patient had rhinovirus co-infection. Three patients required ICU care; 1 developed ARDS, multi-organ failure, and died after 5 days. Chemotherapy was delayed in 5 patients. Oseltamivir was administered to 28 patients; 1 patient developed an oseltamivir-resistant strain and was treated with zanamivir.

Conclusions—2009 influenza A H1N1 infection in children with cancer and HSCT is mild in most patients, but can lead to serious complications.

Keywords

H1N1 influenza; cancer; pediatrics

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Introduction

The burden of seasonal influenza A in the general pediatric population has been well described as an important cause of hospitalization, morbidity, and mortality in the United States.[1-3] Children with compromised immunity from underlying malignancy and chemotherapy or other immunosuppressive therapies are at increased risk for severe influenza illness and its associated complications.[4,5] Respiratory viral infections have contributed substantially to the morbidity and mortality described in pediatric hematopoietic stem cell transplantation (HSCT) recipients.[6] Influenza data in non-transplanted pediatric oncology patients is limited to a few case series during the last 30 years using a variety of viral diagnostic testing methods and diverse chemotherapeutic regimens, limiting comparisons. [7-10] However, all underscore the prolonged duration of influenza infection and increased morbidity risk in children with malignancies.

The Centers for Disease Control and Prevention (CDC) has estimated that 34-67 million people in the United States have been infected with the 2009 pandemic influenza A (H1N1) virus since it was first reported in April 2009.[11] Preliminary data suggest that clinical manifestations of 2009 influenza A (H1N1) and seasonal influenza are similar in affected individuals. However, younger patients and those with underlying medical conditions such as immunosuppression, may be disproportionately affected, have higher hospitalization rates, and increased risk for progression to severe disease. [12-15] Herein, we describe the clinical course, outcomes, and complications of pediatric patients with malignancies, receiving chemotherapy, or hematopoietic stem cell transplantation recipients evaluated at our institution with probable and confirmed 2009 pandemic influenza A (H1N1) infection (2009 H1N1).

Patients and Methods

Study Population

This retrospective cohort study was approved by the Institutional Review Board of the University of Texas Southwestern Medical Center and Children's Medical Center (CMC). All children evaluated for an influenza-like illness (ILI) at CMC Dallas and Legacy sites from April 27 to December 5, 2009 with laboratory-confirmed influenza A were identified by review of CMC laboratory reports of viral testing performed in both ambulatory and inpatient settings. This was compared with the oncology database of patients followed in the Children's Center for Cancer and Blood Disorders (CCBD). From 600 active CCBD patients, subjects ≤ 21 years of age with an oncologic diagnosis, severe aplastic anemia, or HSCT recipients who were receiving or had received immunosuppressive therapy within the previous 12 months were included. Patients with sickle cell disease, thalassemia, autoimmune neutropenia, or other non-malignant hematologic diagnoses were excluded. The medical records of each subject were reviewed and pertinent demographic data (age, gender, ethnicity, school/daycare attendance, number of household members), clinical data including type of malignancy, phase of therapy, dates of chemotherapy and corticosteroid therapy, delay in chemotherapy, presenting signs and symptoms, laboratory test results, therapies provided, and outcomes were recorded.

Diagnostic Testing

The study period began April 27, 2009, when the first case of 2009 H1N1 infection was reported in Dallas County and ended December 5, 2009. Two waves of 2009 H1N1 infections occurred during this time. During the first wave (April 27-June 30, 2009), 2009 H1N1 co-circulated with other community respiratory viruses and accounted for a minority of respiratory viral infections. The last seasonal influenza A (H3N2) infection occurred on

May 27, 2009. During the second wave (August 30–November 16, 2009), 2009 H1N1 was the predominant respiratory virus and the only strain of influenza circulating, with a maximum of 50% of all rapid influenza A tests performed being positive at the peak of the outbreak on September 27, 2009.

On April 26, 2009, the hospital implemented a viral testing algorithm for ambulatory and hospitalized patients with an ILI (Figure I). Clinician's evaluating patients at the initial point-of-care ordered viral testing. Viral testing by PCR was performed on hospitalized patients who developed a new respiratory illness.

Nasopharyngeal (NP) swab or bronchoalveolar lavage (BAL) specimens obtained from pediatric oncology patients with an ILI were tested in the clinical virology laboratory. NP swabs were collected per hospital protocol: a sterile nylon swab (Copan Flocked™ swab) was inserted into the nostril, retracted against the posterior wall of the nasopharynx with rotating movements for 2–4 seconds, and transported in sterile M4-viral transport medium on ice to the virology laboratory for processing. Samples were tested using a rapid influenza (rapid influenza) assay (Directigen™ EZ Flu A+B, Becton Dickinson, Sparks, MD), Direct Fluorescent Antibody (DFA) assay (D³ Ultra™ Respiratory Virus Screening and ID Kit, Diagnostic Hybrids, Athens, OH), or by Respiratory Viral Panel PCR (RVP). From April 27 to August 17, 2009, the RVP tests were performed at a commercial laboratory using the ID-Tag Respiratory Viral Panel™ (Luminex Diagnostics, Toronto, Canada); from August 18 to December 5, 2009, RVP assays were performed in the CMC virology laboratory using the Eragen MultiCode®-PLx Respiratory Panel System (Eragen Biosciences, Madison, WI). Confirmatory viral subtyping of available specimens from patients with laboratory-confirmed influenza A infection was done using the real-time reverse transcriptase-polymerase chain reaction (rRT-PCR) protocol recommended by the CDC. Subtyping was performed at Dallas County Health and Human Services until November 5, 2009 when Children's Medical Center instituted rRT-PCR subtype testing. Subtyping was not performed on all positive specimens obtained from ambulatory patients after September 7, 2009 since 99% of the influenza A that was subtyped was 2009 H1N1. Confirmed 2009 H1N1 cases were defined as influenza A positive specimens that were PCR-subtyped as 2009 H1N1. Probable cases were defined as any positive influenza A that was not submitted for subtyping. One specimen from a study subject was sent to the Centers for Disease Control and Prevention (CDC) for comprehensive antiviral resistance testing. Monovalent 2009 H1N1 vaccination became available on November 4, 2009.

Data Analysis

Descriptive statistics were summarized with medians and ranges (minimum and maximum) or frequencies and percentage calculations. Statistical comparisons were made using the Wilcoxon Rank Sum test for continuous variables and Fisher's Exact test for categorical variables. Analyses were performed using SigmaStat version 3.0 (SPSS, Chicago, IL).

Results

Laboratory diagnosis of Influenza A

All study patients presented during the second wave of the pandemic. Thirty children with malignancies or HSCT recipients had laboratory-confirmed influenza A, representing 1.5% of all patients and 5% of active oncology and HSCT patients who underwent viral testing for ILI at CMC during the study period (Figure I). All patients had nasopharyngeal swabs obtained for viral testing; one child also had a bronchoalveolar lavage sample (BAL) submitted. Eleven patients had more than one diagnostic viral test performed during their influenza illness; there were 7 discordant results (Table I). Confirmation of H1N1 subtype

by rRT-PCR was performed on available samples from 5 hospitalized patients. The overall nosocomial rate of H1N1 infection was 3%; none occurred in oncology or HSCT patients.

Patient population

Demographic and clinical characteristics of the 30 study patients are presented in Table II. Twenty-four patients (80%) were receiving chemotherapy at the time of influenza diagnosis. Of the children with ALL, 14 were receiving maintenance chemotherapy, 3 interim maintenance, and 1 delayed intensification. Nine patients were receiving corticosteroids per routine maintenance chemotherapy regimen, 1 patient with severe idiopathic aplastic anemia required immunosuppressive therapy, and 2 HSCT patients were receiving tacrolimus.

Clinical manifestations

Study patients presented to the CMC emergency department (20; 67%), CCBD clinic (8; 26%), or referred from an outside hospital or clinic (2; 7%) for evaluation. The most common symptoms were fever (n=28; 93%), cough (n=29; 97%), rhinorrhea (n=25; 83%). Sore throat (n=6; 20%), headache (n=5; 17%), and myalgias (n=2; 7%) were infrequent. Patients reported decreased oral intake (n=12; 40%) and gastrointestinal symptoms such as vomiting (n=5; 17%), diarrhea (n=4; 13%), abdominal pain and nausea (n=3 each; 10%).

Thirteen (43%) subjects reported having close exposure to someone with an influenza-like illness: 10 in same-household contacts and 3 at school. Eleven patients had sought medical evaluation in the 7 days before their documented influenza illness. At the time of influenza diagnosis, 7 patients were receiving antibiotic therapy for presumed bacterial infections, 1 was receiving oseltamivir, and 1 was receiving oral steroid therapy for an asthma exacerbation.

After initial evaluation, 10 (33%) patients required hospitalization and 20 patients were treated as outpatients. No outpatient had an abnormal pulmonary examination. Five hospitalized patients had abnormal lung examinations with wheezing, rales, or decreased air entry. Differences between hospitalized patients and those managed as outpatients are shown in Table II. The most frequently documented reason for hospitalization was fever and neutropenia (ANC < 500 thousand/mm³; n=8, 80%). Two outpatients also had documented neutropenia; one was afebrile and the other was not receiving chemotherapy and did not have a central vascular catheter. Hospitalized subjects had fevers that peaked within 24 hours of admission [range 0-3 days] and lasted for a median of 1 day [range 1-9 days]. Median length of hospitalization was 5.5 days [range 2-19]. Three patients required admission to the pediatric intensive care unit (PICU) for 4 days [range 3-6]. There was one death.

Other diagnostic testing

Complete blood counts were obtained in 29 patients. Hospitalized patients had significantly greater neutropenia and lymphopenia than outpatients (Table II). Chest radiographs were obtained in 15 patients (7 inpatients, 8 outpatients). Signs of lower respiratory tract infection (LRTI) were found on imaging in 3 (10% of all subjects); all 3 had abnormalities on initial pulmonary auscultation and were hospitalized with lobar pneumonia (1), diffuse bilateral airspace disease (1), and multilobar pneumonia (1) confirmed by computed tomography (CT). The patient with lobar pneumonia had documented rhinovirus co-infection, but did not require oxygen or have a more severe clinical course. Two patients with pneumonia had neutropenia. All patients with fever and neutropenia had blood cultures performed (9 inpatients and 14 outpatients) and all were sterile. One outpatient was hospitalized 8 days after her influenza illness with fever, neutropenia, and *S. pneumoniae* bacteremia. Upon re-

admission, her influenza symptoms had resolved and a DFA, RVP, and chest x-ray performed 11 days post influenza diagnosis were all negative.

Therapeutics

In the 10 hospitalized patients, 3 required admission to the PICU for vasopressor support of persistent hypotension (2), mechanical ventilation for respiratory failure (1), and hypotension and respiratory distress requiring supplemental high-flow oxygen (1). Four patients required supplemental oxygen therapy for a median of 3 days [3-9] via nasal cannula (2), high-flow delivery (1), and mechanical ventilation (1). All hospitalized patients received empiric antibiotic therapy on admission and for a median of 4 days [2-17]. Two patients in the PICU and 2 outpatient HSCT recipients received immunoglobulin infusions. Scheduled chemotherapy was delayed in 5 hospitalized children (17%) during their influenza illness for a median of 19 days [range 5-20]. Of the 20 subjects managed as outpatients, one received intravenous fluids for vomiting and mild dehydration and 13 subjects received a dose of ceftriaxone before discharge from the emergency department.

Twenty-eight patients were treated with oseltamivir at an average dose of 2.2 mg/kg/dose twice daily for 5 days. In hospitalized patients, the median time from admission to initiation of appropriate antiviral therapy was 1 day [range 0-4]. Eighteen (60%) children (7 inpatients) had already received their seasonal influenza vaccination prior to their 2009 H1N1 influenza illness. Eleven (37%) patients received H1N1 influenza vaccination after their acute influenza illness.

Complications

Patient 1: A 10-year-old female with pre-B ALL receiving maintenance chemotherapy had laboratory-confirmed influenza A shedding for more than 4 weeks. She had received two separate 5-day courses of oseltamivir for influenza exposure and positive rapid influenza testing. She was hospitalized with fever, rales, and leukopenia (ANC 500, ALC 40). Her NP rapid influenza assay was again positive, imaging revealed bilateral multilobar infiltrates, and oseltamivir was prescribed. Her respiratory status and hypoxia worsened despite oseltamivir therapy and she was transferred to the PICU for 6 days. Influenza subtyping confirmed the virus to be 2009 H1N1. The patient defervesced within 48 hours of starting zanamivir and completed 5 days of therapy, with negative results on repeat RVP testing. She required prolonged hospitalization (19 days), supplemental oxygen therapy for 9 days, and 14 days of antimicrobial therapy for a suspected superimposed bacterial pneumonia. Pyrosequencing of virus in nasopharyngeal specimens obtained on admission confirmed the presence of a H275Y mutation in the neuraminidase protein conferring oseltamivir resistance.

Patient 2: A 16-month-old female with history of total resection of a pilocytic astrocytoma complicated by vocal cord paralysis requiring a tracheostomy in the previous 7 months, presented to the emergency department with a 3 day history of fever, increased tracheal secretions, poor feeding, and somnolence. She had been receiving oral corticosteroids and antibiotics. She was lethargic with poor respiratory effort, hypoxia, and shock. A chest x-ray demonstrated diffuse bilateral airspace disease with near total opacification of the right lung. Within 4 hours, the child required high frequency oscillating ventilation with inhalational nitric oxide, vasopressor support, veno-venous extracorporeal membrane oxygenation, and continuous veno-venous hemofiltration. A nasopharyngeal aspirate was positive for influenza A by DFA testing and oseltamivir therapy was started. BAL showed abundant neutrophils and was concerning for pulmonary hemorrhage; BAL cultures were negative for bacteria, fungi, and mycobacteria, and RVP was negative. Viral subtyping later confirmed

the isolate to be 2009 H1N1. On the fourth hospital day, the patient developed cerebellar hemorrhages with herniation, support was withdrawn, and the patient died.

Discussion

Children served as sentinel cases in the emergence of the pandemic 2009 influenza A (H1N1) virus in the US that has resulted from the reassortment of gene segments from both the triple reassortant swine-origin virus and the Eurasian influenza A (H1N1) swine virus. [16,17] Recently published 2009 H1N1 reports indicate that young children and those with underlying immunodeficiencies may be at greater risk of hospitalization, influenza-associated complications, and mortality.[18,19] We describe our institutional experience with 2009 H1N1 infections in pediatric patients with malignancies, receiving chemotherapy, and hematopoietic stem cell transplantation recipients.

Population-based studies of the epidemiology and outcomes of influenza infection in patients with cancer have been described in adults, but not in children. [7] The incidence and outcome of viral infections among children with cancer is variable and is likely determined in part by the intensity and duration of immune suppression. Similar to descriptions of seasonal influenza in both immunocompetent and immunocompromised hosts, our patients presented most frequently with upper respiratory symptoms and fever. However, they also had diarrhea and vomiting which have been reported more frequently with 2009 H1N1 infections compared with seasonal influenza, particularly in children. [19] The sicker patients in our cohort also had vascular instability that required intravenous fluids.

Unlike published reports that demonstrate 15% concurrent bacteremia in children with cancer and seasonal influenza [10], our cohort had none. The only bacteremia in our cohort occurred after resolution of the influenza infection. Co-infections with viral pathogens have been reported in up to 24% of patients with seasonal and 19% of patients with 2009 H1N1. [5,18] One patient with rhinovirus co-infection had a mild clinical course with no sequelae despite having lymphopenia and an abnormal chest x-ray. However, only 8 (27%) of our patients underwent PCR testing for other viral pathogens, so viral co-infections may have been more frequent, but not detected.

Viral infections have been reported to occur more commonly in leukemic children during maintenance chemotherapy, one of the least immunosuppressive phases.[20] This finding was seen in our cohort of patients as well and could be explained by the fact that a larger number of patients are receiving maintenance therapy (lasting 2-3 years) at any one time compared with other shorter chemotherapy phases. Also, children receiving maintenance chemotherapy are in school or daycare more often, thereby increasing their exposure to possible sick contacts. Seventeen percent of our population had delays in their chemotherapeutic regimens similar to what has been described in children with seasonal influenza infection. [8,10] To what extent influenza virus caused further leukocyte suppression and what impact temporary delays in chemotherapy have on outcomes are unknown.

Our patients presented a median of 1 day into their influenza illness, most commonly with fever. Caregivers are educated about the importance of prompt evaluation of fever in children with cancer. Yet despite seeking care early, 5 patients already had findings of LRTI on physical examination or imaging. A significant risk factor for progression to LRTI is profound lymphopenia and is also associated with additional morbidity and mortality. [21-24] An ALC < 1000 thousand/mm³ was found in 9 hospitalized patients versus 14 outpatients. Five hospitalized children with lymphopenia had findings consistent with LRTI; 2 with radiological evidence of pneumonia had a median ALC of 83 thousand/mm³. In a

recent analysis of patients with 2009 H1N1 infection, those who had received previous antimicrobial agents and corticosteroids were more likely to require hospitalization, ICU care, and die. [19] In our cohort, 23% had received antibiotics in addition to those used as prophylaxis and 33% received corticosteroids. There was no difference in the number or severity of illness of hospitalized versus ambulatory patients receiving corticosteroids, the dose (all receiving protocol dose of dexamethasone 6 mg/m²/day for 5 days), or in the time since last corticosteroid dose before influenza illness. The 3 HSCT patients with 2009 H1N1, all > 6 months post transplantation, were treated as outpatients, with no LRTI or complications.

The majority of our patients were diagnosed by rapid influenza testing assays, following our hospital's testing algorithm. In our laboratory, the sensitivity of the rapid influenza assay compared to PCR for 2009 H1N1 was 72%. [25] Performance of all rapid assays by trained technologists in the clinical microbiology laboratory and higher viral loads in children and immunocompromised hosts may explain the increased sensitivity of the rapid assays in our patients compared with published data in adults.[26-29] Furthermore, some children were receiving systemic corticosteroid therapy, which has been shown to prolong detection of viral RNA in specimens from hospitalized patients with seasonal influenza. [30] Two patients with positive rapid tests had negative RVP results and may represent false-positive assays (Table I). However, patient 21 had fever, ILI, and a household contact with confirmed 2009 H1N1 and patient 6 had fever and hypoxia requiring supplemental oxygen, thus both were treated with oseltamivir. In contrast to previous studies that showed a strong correlation between seasonal influenza detection by DFA and PCR methods [31], five (16%) of our patients had negative results on DFA testing, but were positive for influenza A by RVP. DFA methodology appears to be less sensitive for detection of 2009 H1N1 than for seasonal influenza.[26] RT-PCR testing methods offer the advantage of detecting viral co-infections and differentiating among influenza strains with distinct antiviral susceptibilities co-circulating during the same season.

Antiviral treatment was initiated promptly in 93% of patients. Oseltamivir for treatment of seasonal influenza infection has been shown to decrease the risk of complications in children with chronic medical conditions.[32] The optimal dose and duration of antiviral therapy in immunocompromised pediatric patients is not well established. Pandemic 2009 H1N1 is universally susceptible to zanamivir, but increasing numbers of cases of oseltamivir resistant strains have been reported among immunocompromised hosts receiving treatment and in the setting of chemoprophylaxis. [12,33-35] Lack of clinical improvement, worsening disease, or prolonged viral shedding should prompt evaluation for antiviral resistance. The H275Y mutation in the neuraminidase protein documented to have occurred in our patient's influenza isolate has been associated with oseltamivir resistance of both seasonal H1N1 and 2009 pandemic influenza A H1N1 viruses. [36]

Influenza prevention is a cornerstone in the care of children with malignancies. Hospital policy was to initiate droplet and contact precautions for isolation based on signs and symptoms, before viral test results were known. Hospitalized patients who developed a new fever and ILI symptoms were tested by RVP. Isolation precautions were continued until the patient was asymptomatic and results of two consecutive viral tests were negative. We also enforced hand hygiene, screened visitors for signs of respiratory illness, and limited the number of visitors to 2 per patient during the 2009 H1N1 pandemic. These practices were likely effective in preventing hospital-acquired infection among our high-risk population. The American Academy of Pediatrics [37] and CDC recommend trivalent inactivated seasonal influenza vaccination for immunocompromised children, although the data regarding clinical efficacy is not conclusive and vaccination practices vary nationwide. [38-41] By November, 60% of our cohort had already received their seasonal influenza

vaccination. Early in the pandemic, there were no recommendations to defer H1N1 monovalent vaccination after natural infection. Later, vaccine deferral was offered as an option in cases of RT-PCR confirmed 2009 H1N1 infection; 37% of our patients opted to receive the vaccine after their 2009 H1N1 illness.

Limitations of this study are its small size, single center site, and retrospective nature. Although a testing algorithm was in place, the actual test performed varied by location (ambulatory vs. inpatient) and resources. Samples were not always available to confirm proven 2009 H1N1 by rRT-PCR in all study patients. Since all our patients presented with fever and ILI during the second wave of the pandemic when there was a high prevalence of 2009 H1N1 in our community, the positive predictive value of the rapid assays in this setting would be higher.

We have shown that 2009 H1N1 illness was mild in most, but can be severe in children with cancer. Based on the extent of immunosuppression, a systematic approach to testing for possible viral etiologies using sensitive molecular testing such as PCR in conjunction with bacterial and fungal diagnostic testing in febrile pediatric oncology patients is warranted. Prompt institution of appropriate therapies, continued surveillance, and consistent implementation of preventive practices are essential components of care. Further studies that assess the safety, effectiveness, pharmacodynamics, and pharmacokinetics of antivirals are needed to determine the optimal therapeutic management of the pediatric patient with malignancy and influenza infection.

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Figure 1. Viral diagnostic algorithm and population tested

ILI= influenza-like illness; Rapid = Rapid influenza immunosorbent assay; DFA= Direct Fluorescent Antigen assay; RVP= respiratory viral panel by multiplex PCR; CMC= Children's Medical Center; HSCT= hematopoietic stem cell transplantation

Table 1

Results of viral diagnostic testing

Pt	Initial Positive	Rapid	DFA	RVP	H1N1 Confirmation
1	Rapid	+	-	+	Yes
2	Rapid	+	ND	ND	No
3	Rapid	+	ND	ND	Yes
4	Rapid	+	ND	ND	Yes
5	DFA	ND	+	2	Yes
6	Rapid	+	ND	-	No
7	RVP	-	-	+	Yes
8	RVP	-	-	+	No
9	RVP	ND	-	+	No
10	RVP	ND	-	+	No
11	Rapid	+	ND	ND	No
12	Rapid	+	ND	ND	No
13	Rapid	+	ND	ND	No
14	Rapid	+	-	ND	No
15	Rapid	+	ND	ND	No
16	Rapid	+	ND	ND	No
17	Rapid	+	ND	ND	No
18	Rapid	+	ND	ND	No
19	DFA	ND	+	ND	No
20	Rapid	+	+	ND	No
21	Rapid	+	-	-	No
22	DFA	ND	+	ND	No
23	Rapid	+	ND	ND	No
24	Rapid	+	ND	ND	No
25	Rapid	+	ND	ND	No
26	DFA	ND	+	ND	No
27	Rapid	+	ND	ND	No

Pt	Initial Positive	Rapid	DFA	RVP	H1N1Confirmation
28	Rapid	+	ND	ND	No
29	Rapid	+	+	ND	No
30	Rapid	+	ND	ND	No

Pt = Patient; ND= not done;

¹ Nasopharyngeal specimen;

² Bronchoalveolar lavage specimen Patients with discordant viral testing results are highlighted in gray.

Table II
Characteristics of subjects

	All (n=30)	Inpatient (n=10)	Outpatient (n=20)	Inpatient versus Outpatient p-value [†]
Age (years)	10 [1.4-18]	8 [1.4-15]	10 [3-18]	0.24
Gender (Male:Female)	15:15	4:6	11:9	0.70
Ethnicity (n)				
White	10	3	7	0.55
Black	2	0	2	
Hispanic	13	4	9	
Other	5	3	2	
Cancer type (n)				
ALL ¹	18	8	10	0.24*
CNS ²	4	1	3	
Solid Tumor ³	2	1	1	
HSCT	3	0	3	
Other	3	0	3	
Other high-risk diagnoses (n)				
Asthma	3	2	1	0.69
Diabetes mellitus	1	1	0	
Hypogammaglobulinemia	1	0	1	
GVHD	1	0	1	
Seizure	2	1	1	
Obesity	3	0	3	
Tracheostomy	1	1	0	
Peak temperature at home (° C)	38.6°C [38.2-41]	38.9°C [38.2-39.7]	38.6°C [38-41]	0.28
Fever prodrome before presentation (days)	1 [0-6]	0.5 [0-7]	1 [0-6]	0.36
Recent Steroids (≤ 7 days)	9	3	6	1.0
WBC (thousand/mm ³)	2.7 [0.5-11.9]	0.8 [0.5-11.9]	3.1 [0.6-6.4]	0.004
ALC (thousand/mm ³)	481 [40-2380]	204 [40-2380]	637 [106-2070]	0.01
ANC (thousand/mm ³)	1600 [60-5260]	325 [96-9250]	1920 [60-5260]	0.02
Pneumonia (n)	3	3	0	0.03
Chemotherapy Interrupted (n)**	5	5	0	0.003

n= number; Median [minimum-maximum];

¹ Acute lymphoblastic leukemia (ALL): pre-B cell (16), T-cell (2);

² Central nervous system (CNS) tumors: pilocytic astrocytoma (2), recurrent medulloblastoma, optic glioma;

³ Solid tumors: recurrent Ewing's, Hodgkin's lymphoma; WBC = white blood cell count, ANC = absolute neutrophil count, ALC = absolute lymphocyte count; GVHD = graft-versus-host disease;

* ALL versus all other types combined;

** out of n=24 (9 Inpatients and 15 Outpatients) on chemotherapy.

⁺ Inpatient and Outpatient groups were compared with the Wilcoxon Rank Sum test for continuous variables and the Fisher's Exact test for categorical variables.