The critically ill child with novel H1N1 influenza A: A case series

Justin L. Lockman, MD; William A. Fischer, MD; Trish M. Perl, MD, MSc; Alexandra Valsamakis, MD, PhD; David G. Nichols, MD

**Objective:** To describe the presentation, course, and outcome of critically ill children with novel H1N1 influenza disease.

**Design:** Retrospective case series.

**Setting:** Pediatric intensive care unit in an urban tertiary academic center.

**Patients:** Thirteen consecutive patients admitted between June 2009 and August 2009 and known or subsequently found to be infected with novel H1N1 influenza A.

**Interventions:** None.

**Measurements and Main Results:** Clinical, laboratory, and radiographic data were reviewed. The patients were predominantly male (62%), aged 5 months to 21 yrs, and most (92%) had known risk factors for severe disease. Direct fluorescent antibody testing had a high false-negative rate (82%) and delayed treatment in some cases. The respiratory illness presented clinically with both bronchoconstriction and alveolar consolidation to varying degrees. Bacterial superinfection occurred frequently (23%). Forty-six percent of patients required mechanical ventilation and 23% required inotropic support for hypotension. None of the patients in this series required extracorporeal membrane oxygenation. Intensive care unit length of stay did not differ between an early (within 48 hrs) oseltamivir treatment group (length of stay, 4.2 ± 4.4 days) vs. a late treatment group (length of stay, 6.8 ± 8.8 days). All patients survived to hospital discharge.

**Conclusions:** Underlying chronic illness (especially respiratory illness) seems associated with critical novel H1N1 influenza disease in children. Respiratory manifestations are highly variable among patients and within a single patient involving both bronchoconstriction and alveolar disease. Therapies must be individualized and rapidly adjusted. The duration of critical illness was not different between early and late treatment groups. Whether this is reflective of sample size or indicative of the importance of therapeutic intervention at any time early during infection in critically ill patients is unclear. Bacterial superinfection was more common than previously reported for seasonal influenza A. Moderate novel H1N1 influenza disease, including respiratory failure and hypotension, had 100% survival in our series. (Pediatr Crit Care Med 2010; 11:000–000)

**Key Words:** influenza, human; influenza A virus, H1N1 subtype; intensive care units, pediatric; critical illness; mechanical ventilation; superinfection

From the Departments of Anesthesiology and Critical Care Medicine (JLL, WAF, DGN), Pediatrics (DGN), Medicine (TMP), and Pathology (AV), The Johns Hopkins University School of Medicine, Baltimore, MD.

We thank Alicia Budd in Hospital Epidemiology and Infection Control at The Johns Hopkins Hospital whose efforts tracking the patients of H1N1 during the emerging pandemic were invaluable in the identification of patients for this manuscript.

The authors have not disclosed any potential conflicts of interest. The authors have no potential conflicts of interest to disclose.

For information regarding this article, E-mail: dnichols@jhmi.edu

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DOI: 10.1097/PCC.0b013e3181cedae

**MATERIALS AND METHODS**

**Setting and Case Identification**

The Johns Hopkins Hospital Children's Center is a regional Children's Hospital that serves Maryland and the surrounding area. The 26-bed PICU cares for >1300 children annually with an average length of stay of 5.7 days. Hospital Epidemiology and Infection Control monitors health care-associated infections and epidemiologically significant organisms for The Johns Hopkins Hospital Children's Center, using a system that combines administrative, microbiological, radiologic, and other data sources to produce reports (TheraDoc, Inc., Salt Lake City, UT). Because of an active respiratory virus prevention program, systematic surveillance and prevention planning includes prospective tracking of influenza. All patients admitted to The Johns Hopkins Hospital Children's Center during respiratory season (including the present pandemic) are tested for respiratory virus infection. Nasopharyngeal aspirates are tested, using direct fluorescent antibody (DFA) for influenza A, influenza B, respiratory syncytial virus, human metapneumovirus, adenovirus, and parainfluenza virus types 1–3. All residual specimens were stored at −80°C. Shell vials (R-Mix Too, Diagnostic Hybrids Inc., Athens, OH) and tube cultures (rhesus monkey kidney and A549 cells, Diagnostic Hybrids, Inc.) were inoculated in parallel with DFA. Shell vials were stained at 48 hrs for all viruses detected by DFA, except human metapneumovirus. Tube cultures were examined daily for 7 days, then weekly for an additional 2 wks until cytopathic effect was observed. All samples from inpatient patients identified as influenza A by DFA, shell vial, or tube culture were sent to the Maryland Department of Health and Men-
vomiting, and diarrhea. Hemoglobin was rent fever, cough, dyspnea, lethargy, several days after discharge with recur-

vented to the emergency department for pain management and antimicrobials chest radiography. Respiratory and blood 
sion. No abnormalities were noted on 

patients was verified and supplemented by medical record review with a standardized data abstraction form. Demographic data, past 

patients were considered to have clinical evidence of pulmonary bacterial superinfection if they developed new radiographic find- 
ings consistent with bacterial pneumonia, such as lobar consolidation plus recurrent fever, dyspnea, tachypnea, increased or purulent 

secretions (3) after initial clinical improve-

ment. Patients were considered to have evidence of bronchospasm if they clinically demon-

strated wheezing or improvement with β-agonist therapy. Patients treated with osel-

tamivir were divided into early and late treat-

ment groups based on timing of therapy rela-
tive to symptom onset (>48 hrs or ≥48 hrs, respectively). 

Data are presented as mean ± sd, where 

appropriate. Analysis of variance was used to 
determine statistical significance of differences between early and late treatment 
groups. A p < .05 was considered significant.

RESULTS

Illustrative Cases

Patient 1

A 17-yr-old female with known sickle cell anemia, hypertension secondary to 
sickle cell nephropathy, and asthma pre-

sented to our emergency department with fever, hypoxia, dyspnea, and chest 
pain after a routine outpatient transfu-

sion. No abnormalities were noted on 

chest radiography. Respiratory and blood 
cultures were obtained. She was admitted 

for pain management and antimicrobials and was discharged home 48 hrs later after 

clinical improvement. The patient returned to the emergency department several days after discharge with recur-

rent fever, cough, dyspnea, lethargy, vomiting, and diarrhea. Hemoglobin was noted to be 4.7 g/dL and a repeat chest 

radiograph demonstrated a left upper-lobe consolidation consistent with acute chest syndrome. The patient was admitted to the PICU. The DFA for influenza was negative, and she improved clinically after double-volume exchange transfusion and initiation of bilevel positive airway pressure ventilation and antibacterial therapy. However, ongoing low-grade hemolysis was suspected due to decreasing hemoglobin levels and mild hematuria. On day 3, she developed severe dyspnea and was intubated for respiratory failure. Chest radiography showed diffuse alveolar infiltrates consistent with acute respiratory distress syndrome. Intravenous corticoste-

roids were added to bronchodilator therapy and antibacterial coverage was broadened. The patient subsequently developed oligo-

uric renal failure and hypotension requiring inotropic therapy, and she continued to have unexplained high fever and broncho-

spasm. On day 10 of illness and day 5 after obtaining the nasopharyngeal aspirates on admission, influenza A (nH1N1 influenza) was isolated from tube culture and oseltamivir therapy was begun via nasogastric tube. Her course was notable for paroxysms of severe cough with hypoxia requiring neuromuscular blockade in addition to deep sedation/anaesthesia while intubated. Renal function ultimately recovered to baseline without renal replacement ther-

apy. She remained intubated for a total of 14 days and remained in the intensive care unit for a total of 26 days. On hospital day 32, the patient was transferred to a rehabilita-

tion hospital and was subsequently dis-

charged. She continues outpatient transfu-

sion therapy and is neurologically intact.

Patient 2

A 21-yr-old female with a history of congenital human immunodeficiency vi-

rus infection complicated by encephalo-

pathy (with paraplegia), lymphocytic inter-

stitial pneumonitis, and poor compliance with medical therapy presented with 2 
days of fever, tachypnea, pharyngitis, and cough. Absolute CD4 count on admission was 470/mm3. She was admitted to the PICU for management of hypoxia, dyspnea, and hypotension requiring transient vaso-

pressor therapy. Antimicrobial therapy, including oseltamivir, was initiated despite negative DFA results because chest radiogra-

phy demonstrated increased bilateral perihilar markings consistent with viral in-

fection compared to a previous study. Within 24 hrs, the patient had returned to 

her baseline respiratory condition and was 
downgraded to a noncritical hospital bed. Shell vial culture was negative, but tube culture grew influenza A (nH1N1 influ-

enza) at 3 days; the patient completed a 5-day course of oseltamivir.

Patient 3

A 14-yr-old female with congenital cyto-

megalovirus infection and associated cere-

bral palsy, mental retardation, obstructive 

sleep apnea (requiring overnight continu-

ous positive airway pressure), and gastro-

tomy tube dependence was admitted with increased frequency of emesis. After admi-

mission, she developed progressive respiratory distress requiring intubation and transfer to the PICU for mechanical ventilation. Na-

sopharyngeal aspirates was sent due to the 
decline in respiratory status and the DFA 

was positive for influenza A (nH1N1 influ-

enza). Oseltamivir therapy was initiated (approximately 24 hrs after onset of initial 
symptoms). The patient required invasive mechanical ventilation for 7 days and re-

mained in the PICU for 16 days. Because 

airway instrumentation occurred before the suspicion of viral illness, the patient 

was not appropriately isolated and multiple staff members on the inpatient floor, the 

rapid response team, and the ICU team 

were exposed to influenza.

Summary Results for the Entire Series

Between June 1, 2009 and August 7, 2009, we diagnosed 140 patients <264 

months (22 yrs) of age with nH1N1 in-

fection at The Johns Hopkins Hospital; 13 

(9.3%) required admission to the PICU 

(three patients, aged 20 –21 yrs, were ad-

mitted to adult ICUs). All patients were 

acquired in the community. The median 

age was 114 months (range, 5–263 months), with a male predominance (62% 

male) (Table 1). Almost all patients had underlying comorbid illness and risk fac-

tors for complications of influenza, of 

which asthma was most prevalent (85%) 

followed by neuromuscular disease (38%). 

Based on the Pediatric Risk of Mortality III 
score (4.5 ± 4.36), the severity of illness at 

admission to the PICU was mild to moder-

ate (4). DFA proved highly insensitive with 

a 62% false-negative rate. DFA detected 

only 38% of cases; an additional 38% of 
cases were detected at 48 hrs by shell vial. Twenty-three percent of cases were de-

ected only by tube culture. The mean 
times to diagnosis of all samples requiring 

shell vial or tube culture were 5.3 (± 2.8)
days and 2.4 (±1.2) days from symptom onset and PICU admission, respectively. The mean times to diagnosis of samples requiring tube culture were 7.3 (±3.1) days and 3.3 (±1.5) days from symptom onset and PICU admission, respectively.

Laboratory data were consistent with viral infections. The average admission total leukocyte count was in the normal range (8724 ± 4439/mm³); some patients presented with leukenopia or leukocytosis (Table 2). Lymphopenia was common with the mean lymphocyte count of 1473 (±1110)/mm³ at admission. Hepatic transaminase enzymes and renal function tests were normal or mildly elevated during the PICU stay.

Twenty-three percent (3 of 13 patients) of the study population presented with normal chest radiography and never developed any abnormality on chest radiography. Some patients with radiographic abnormalities on admission had multiple types of abnormalities. Of patients with abnormal admission chest radiographs, 60% (6 of 10) demonstrated increased interstitial markings consistent with viral disease, whereas 30% (3 of 10) revealed diffuse alveolar infiltrates and 40% (4 of 10) had findings consistent with hyperinflation. Thirty-one percent (4 of 13) of all patients already had evidence of lobar consolidation on chest radiography at PICU admission and one patient (8%) had a pleural effusion at admission. Peak radiographic findings occurred at 4.6 (±3.4) days after admission and consisted of diffuse alveolar infiltrates in 70% (7 of 10) of patients with abnormal chest radiographs.

Eighty-five percent (11 of 13 patients) of patients with nH1N1 received antiviral therapy (Table 3); all treated patients received standard-dose oseltamivir. Among those treated, 45% (5 patients) were treated within 48 hrs of initial symptom onset (early treatment group) and 55% (6 patients) were treated after >48 hrs of symptom onset (late treatment group). Forty-six percent (6 of 13 patients) of the entire study population received mechanical ventilation, four patients via endotracheal tube and two patients by noninvasive methods (e.g., bilevel positive airway pressure). Consistent with the radiographic prevalence of increased interstitial markings and hyperinflation, a majority of patients (77%) also presented with leukopenia or leukocytosis (Table 3).
had symptoms of bronchospasm that were alleviated with β-agonist therapy. More than half of patients received adjuvant therapies for bronchoconstriction, including therapeutic magnesium and/or systemic corticosteroids. Three patients (23%) required inotropic therapy for hypotension; echocardiography for two of these patients demonstrated normal left ventricular function. The third patient did not undergo echocardiography due to limited duration of vasopressor therapy. No patient required renal replacement therapy or extracorporeal support.

Twenty-three percent (3 of 13 patients) of patients in this case series were treated for a suspected bacterial superinfection on the basis of clinical and radiographic findings (Table 3). None of the bacterial cultures obtained from patients grew.

Patient outcomes were divided into subgroups based on early treatment or late treatment (Table 4). ICU length of stay was 4.2 (±6.6; median, 1.0) days and 6.8 (±8.8; median, 3.5) days for the early and late treatment groups, respectively. Duration of mechanical ventilation for the early treatment group was 4.0 ± 4.2 days compared with the late treatment group duration of 7.8 ± 6.5 days. The differences in ICU length of stay and duration of mechanical ventilation were not statistically significant between those who were part of the early or late treatment groups. All patients survived through hospital discharge.

**DISCUSSION**

The nH1N1 disease has primarily impacted young people, including children. The major findings from this series are: 1) underlying chronic illness (especially respiratory illness) seems associated with critical nH1N1 influenza disease in children. 2) The respiratory illness is highly variable from patient to patient and within a single patient involving bronchoconstriction and alveolar consolidation. Respiratory support and sedation therapies must be individualized and rapidly adjusted. 3) Diagnosis and treatment were often delayed, reflecting initial inexperience with nH1N1 disease during the start of the pandemic. 4) The duration of critical illness was not different between early and late treatment groups although our patient numbers are small. 5) Bacterial superinfection occurred in one quarter of patients, more commonly than previously reported. 6) Moderate nH1N1 influenza disease, including respiratory failure and hypotension, had 100% survival in our series.

**Association With Underlying Chronic Illness**

The CDC has described underlying conditions that, for seasonal influenza disease, place patients at increased risk for complications (5). This series confirms the significant vulnerability of patients with comorbidities for nH1N1 influenza infection. Ninety-two percent of patients admitted to our ICU with nH1N1 influenza disease were previously known to have one of these high-risk conditions (Table 1), whereas only one patient was admitted with no significant past history of disease. As this pandemic continues, additional data will likely emerge to better define high-risk groups for nH1N1 influenza; however, our data support the use of high-risk groups as defined in seasonal influenza outbreaks as preliminary risk factors for critical illness in nH1N1 disease.

**Delayed Diagnosis and Prevention of Disease**

A surprising aspect of this series was the variability of symptomatology among the most severely affected children. Both clinically and radiographically, our patients displayed features of alveolar consolidation/acute respiratory distress syndrome and reversible obstructive lung disease (bronchoconstriction). This combination proved a particular challenge in critical care management.

In our case series, the severe bronchospasm was treated with intravenous magnesium sulfate, systemic corticosteroids, and short-acting β-agonist therapy in 54%, 54%, and 77% of patients, respectively. The most severely affected patients also experienced intense coughing spells during invasive mechanical ventilation requiring both anesthetic doses of sedative hypnotic agents and (in three patients) persistent neuromuscular blockade. Given that management strategies for bronchospasm and acute respiratory distress syndrome are not well aligned, mechanical ventilation and management of critically ill children with nH1N1 infection proved to be challenging. When the composite picture included alveolar consolidation, hypoxemia, and bronchospasm, we utilized a strategy of high positive end-expiratory pressure, low tidal volume, and low ventilator breath frequency to maintain protective low lung volumes at the same time prolonging the expiratory phase to allow alveolar emptying and prevent air trapping. However, the management of these patients should be individualized and regularly reassessed and rapidly adjusted to reflect the heterogeneous and labile nature of the lung involvement.
The importance of detailed hospital disaster plans and staff preparedness cannot be underestimated. As demonstrated by patient 3, delayed diagnosis and failure to anticipate the possibility of an influenza-related etiology for symptoms will lead to unnecessary staff exposure. We subsequently determined that our rapid response team would carry personal protective equipment to all off-unit events where intubation or other high-risk procedures may take place. Note that this practice is also not without risk, as it involves a delay in care as personal protective equipment is applied and decreased efficiency of communication when members of the team are subjected to the noise and isolation of a Powered Air-Purifying Respiratory device. As noted by Aziz, it is essential for hospitals to prepare for pandemic influenza with written (and rehearsed) disaster policies (8).

There are few data regarding preventive chemoprophylaxis in the ICU; however, Oliveira et al recommended routine chemoprophylaxis with neuraminidase inhibitors for all adult ICU patients on a daily basis from the start of an outbreak (confirmed case in an ICU patient) until approximately 1 wk after the end of the outbreak (9). Current CDC recommendations suggest antiviral chemoprophylaxis with neuraminidase inhibitors should be reserved for those patients with likely nH1N1 exposure who are at high risk for complications (5). In accordance with this, we have adopted a strategy of heightened surveillance to identify symptomatic patients, early isolation, and treatment of patients with unexplained fever or other symptoms (before diagnostic testing results). However, we have not used chemoprophylaxis routinely for asymptomatic, unexposed ICU patients during either seasonal influenza outbreaks or the present pandemic. This practice is based on our prior experience with seasonal influenza disease. Of note, both the CDC recommendations and our hospital and PICU policies regarding the diagnosis, isolation, and management of patients infected with nH1N1 influenza have evolved throughout the pandemic and are expected to continue to change as new data become apparent.

Effect of Early Antiviral Treatment

Aoki et al demonstrated that early treatment with neuraminidase inhibitor therapy has the greatest effect on symptom duration and severity in a healthy population. Although 48 hrs is the most frequently recommended interval for therapy, the authors demonstrated that treatment as early as 12 hrs after symptom onset had greater effects than treatment at 48 hrs (10). Eighty-five percent of our patients were treated; all those treated received the neuraminidase inhibitor oseltamivir, which has demonstrated efficacy in decreasing viral shedding and the duration of mild symptoms in uncomplicated seasonal influenza (11). Reasons for failure to treat included significant delay in diagnosis with spontaneous resolution of symptoms. However, patient 1 illustrates the risks of delayed treatment, especially in patients with significant comorbidities. Patient outcomes (Table 4) are divided into subgroups of early treatment (oseltamivir administered within 48 hrs of symptom onset) and late treatment (oseltamivir administered after 48 hrs of symptoms). The reasons for delayed treatment include delayed presentation and delayed diagnosis. Although not statistically significant, we are limited in our conclusions because we had a small number of patients. Still, we did note trends toward shorter ICU stays, shorter duration of mechanical ventilation, and shorter interval between oseltamivir and extubation (as a surrogate for clinical improvement) in the early treatment group. We report these findings because there is a paucity of data about the use of antiviral agents for severe influenza disease in critically ill patients, and there are even fewer data in children.

Our experience supports the CDC advisory of immediate, presumptive treatment of critically ill children with a history suggestive of nH1N1 influenza disease (regardless of duration of symptoms) because the risk/benefit ratio for these patients is likely in favor of therapy. DFA has a high false-negative rate and definitive culture diagnosis takes several days. Although widespread resistance to neuraminidase inhibitors among seasonal H1N1 influenza A has occurred (including rare reports of nH1N1 isolates) (12), the nH1N1 influenza virus seems to still be largely sensitive to oseltamivir (13). Whitley et al suggested that oral dosing to children >12 months results in cost-effective reduction of disease burden and viral shedding (14). Oseltamivir is only approved for use in patients ≥12 months of age, but during this pandemic the U.S. Food and Drug Administration approved an Emergency Use Authorization for treatment of influenza infection in patients <12 months old. Oseltamivir is not available in a parenteral formulation; we were able to treat four of our patients (including patients 1 and 3) via nasogastric or gastrostomy tube. This practice is supported by a pharmacokinetic study of nasogastric administration of oseltamivir to adults demonstrating good absorption and extensive metabolism to the active metabolite, oseltamivir carboxylate, even in critically ill patients with severe influenza (15). The Food and Drug Administration recently approved intravenous peramivir for compassionate use, although there are very limited data for its use in pediatric patients.

The CDC has recommended peramivir in unresponsive or deteriorating patients or in patients unable or unlikely to absorb oseltamivir. Intravenous peramivir can be obtained through the CDC at http://emergency.cdc.gov/1Nantivirals.

Bacterial Superinfection

A key component of severe influenza management involves surveillance for and early treatment of bacterial superinfection. Reed et al found that, among children hospitalized with seasonal influenza disease, 15% had culture-proven bacterial infection (16). The most common organism among those cases was *Staphylococcus aureus* (including methicillin-resistance in >40% of *S. aureus* isolates). Patients with bacterial infection were also more likely to require critical care and had a higher patient fatality than other children with influenza. In our series, 23% of our nH1N1 influenza-infected patients developed clinical and radiographic evidence of bacterial superinfection, although none of our patients had positive bacterial respiratory cultures (3). Enhanced morbidity and mortality with influenza-related bacterial infection may be due to increased viral replication and pathogenicity caused by proteolytic activation of hemagglutinin (17). Seasonal influenza A has also been reported to downregulate neutrophil function (18), which would theoretically provide a more hospitable milieu for bacterial infection. Critically ill children with nH1N1 influenza disease deserve extreme vigilance for bacterial superinfection.

Survival

All 13 patients in this case series survived until discharge. This finding contrasts with a report by Li et al revealing a mortality rate of 18.5% in a cohort of more severely compromised critically ill adult patients (Acute Physiology and
Chronic Health Evaluation III scores of 82 ± 20 in nonsurvivors) with seasonal influenza A infection (19). The comparison between our data and those by Li et al. should be interpreted cautiously because of the younger age group, the early stage of a new pandemic, and the less severe illness in our cohort. None of our patients required renal replacement therapy or extracorporeal support. Regardless, we report that, in this series of 13 children in our PICU, 12 of whom had known high-risk conditions for severe influenza disease, mortality was 0%.

CONCLUSIONS

This series illustrates the presentation of critical nH1N1 influenza disease in the PICU. The pediatric intensivist must be prepared for hemodynamic instability and highly individualized ventilator management, depending on whether bronchospasm or alveolar consolidation predominates. Significant sedation and even neuromuscular blockade may be necessary to manage paroxysms of severe coughing. All patients including those presenting with mild-moderate cardiovascular, respiratory, and hematologic dysfunction as well as bacterial superinfection survived. The duration of critical illness was not different between early and late treatment groups. Whether this is reflective of sample size or indicative of the importance of therapeutic intervention at any time early during infection in critically ill patients is unclear. The effect of early antiviral therapy on critically ill pediatric patients with influenza infection (nH1N1 or seasonal) is an area for future larger studies. In the meantime, practitioners are advised to have a high index of suspicion and to consider presumptive treatment of all critically ill patients, regardless of duration of symptoms until definitive diagnostic testing is available. Additional epidemiologic studies in children are desperately needed to guide surveillance practices and infection prevention and control strategies for emerging pathogens, such as nH1N1 influenza.

REFERENCES