Original Article

Comparison of ICU and non-ICU patients infected with the 2009 H1N1 influenza virus in a Florida Children's Hospital between April and December 2009

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Abstract. We conducted a retrospective comparative review of children ≤ 21 years of age infected with the 2009 H1N1 influenza virus hospitalized between April and December 2009 in northeast Florida, United States. Patients admitted to the Pediatric Intensive Care Unit (PICU) and general medical ward were compared based on patient demographics, chronic medical conditions, complications, co-infections, length of stay and outcome. Of the 119 hospitalized children, 25 (21%) were admitted to the PICU and 94 (79%) were admitted to the general medical ward. Overall, there were 63 (53%) male and 54 (45%) African-American. Mean age was 6.4 years with 52 (44%) patients < 5 years of age. Fever was seen in 114 (96%) patients and 60 (50%) patients had respiratory distress of varying severity. More than 70% of patients had at least one chronic medical condition, with the three most common being pulmonary, immunosuppression and neurodevelopmental conditions. The incidence of microbiologically-proven co-infections and mortality rate were 6.7% and 0.8%, respectively. Patients stayed at the hospital for an average of 4.3 days. Our analysis demonstrated that patients in the PICU had a statistically significant higher rate of chronic medical conditions, complications and longer lengths of stay compared to patients admitted to the general medical ward.

Key words: H1N1, influenza, pandemic flu

1. Introduction

The 2009 H1N1 influenza virus identified in the United States in April 2009 rapidly spread to other countries leading the World Health Organization to declare a state of pandemic in June 2009. (1,2) Not previously seen in humans, 2009 H1N1 virus' genetic uniqueness (quadruple reassortant virus), rapidity of spread, off-influenza season activity, unexpected impact on young adults and increase in influenza-associated morbidity and mortality in children are only some of the reasons why it is distinct from seasonal influenza. (3-6) In addition, rapid influenza antigen tests were deemed to have low sensitivity in detecting 2009 H1N1 virus. (7,8) Real time reverse transcriptase polymerase chain reaction (RT-PCR) assay played a more prominent role because of its higher sensitivity and specificity in detecting the 2009 H1N1 virus. Most studies done were early on in the outbreak and described a brief period of the 2009 H1N1 activity. We conducted a retrospective study to compare children admitted to the Pediatric Intensive Care Unit (PICU) and to the general medical ward (GMW) in northeast Florida, United States from the time H1N1 was first reported in April to December 2009 when H1N1 activity started to wane.

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2. Materials and methods

This retrospective comparative analysis was conducted at Wolfson Children's Hospital (WCH), a regional pediatric referral hospital serving northeast Florida and southeast Georgia, United States, with a catchment area of 3 million. WCH has 192 beds including 20 PICU beds with 8,000-9,000 hospital and more than 1,200 PICU annual admissions. In the initial months of the outbreak, our institution used rapid antigen test (BinaxNOW® Influenza A & B, Inverness Medical, Waltham, MA). However, we experienced high false positive rates (42%, data not shown; no reflex testing done on antigen negative specimen) prompting us to stop using the rapid antigen test. By July 22, 2009, we were routinely using real time reverse transcription polymerase chain reaction (RT-PCR) assay (ProFlu+, Prodesse Inc., Waukesha, WI) or viral culture in detecting influenza A. Specimens were concurrently tested for influenza B.

Patients were identified by reviewing records of the Virology Laboratory and Infection Control and Hospital Epidemiology Department which used Theradoc Tracking System (TheraDoc, Inc., Salt Lake City, UT). Review of charts and laboratory records was performed for patients $\leq$ 21 years of age with confirmed and/or presumed 2009 H1N1 infection admitted between April 1, 2009 and December 31, 2009. Patients with presumed H1N1 infection were those in whom nasopharyngeal wash or swab specimen was positive for influenza A detected by RT-PCR or by viral culture. Since epidemiologic surveillance during the study period indicated that the only influenza A strain circulating in the community in our region was H1N1, we assumed that any test positive for influenza A was H1N1, as recommended by the Centers for Disease Control and Prevention (CDC). In contrast to presumed cases, those with confirmed 2009 H1N1 infection were those who had positive RT-PCR or viral culture with subsequent specific H1N1 testing using CDC protocol done at the Florida Department of Health. All laboratory tests performed and management decisions were at the discretion of the physician of record for the patient. We excluded patients (N = 28) who had a positive rapid antigen result but did not have the more reliable testing with either RT-PCR or viral culture. Information obtained included demographic, clinical, laboratory and radiographic data. Length of stay (LOS) for patients admitted to the PICU included PICU LOS as well as LOS in the GMW, when applicable. Co-infections were defined as infections present on admission. Infections acquired 2 or more days after admission were considered nosocomial. Body mass index (BMI) was defined as those whose BMI were $\geq$ 95th percentile for age based on CDC growth chart. Information about chronic medical conditions (CMC) was gathered from medical records and included pulmonary diseases, neurodevelopmental conditions, metabolic conditions, cardiac disease, hematologic conditions and immunosuppression from primary and secondary causes.

Statistical analyses and modeling were done using SAS 9.1 software. Categorical comparisons, such as comparing race, medical conditions or complications between PICU with GMW patients and confirmed with presumed H1N1 infection were done using Chi-square tests or Fisher's tests. Means were compared using two sample t-tests. Logistic regression analysis was performed to assess the role of the time to treatment in the likelihood of PICU admission. Approval from the Institutional Review Board (IRB) was obtained.

3. Results

There were 308 patients $\leq$ 21 years of age infected with the 2009 H1N1 virus from April 1 to December 31, 2009. One hundred thirty-two (42.9%) patients were hospitalized -- 13 to the adult hospital and 119 to Wolfson Children's Hospital. The first case of 2009 H1N1 infection confirmed by the CDC protocol in our region was on April 30, 2009 and the first admissions were in June 2009. The total number of H1N1 infections and admissions to the GMW peaked in September whereas admissions to PICU peaked in October (Figure 1).

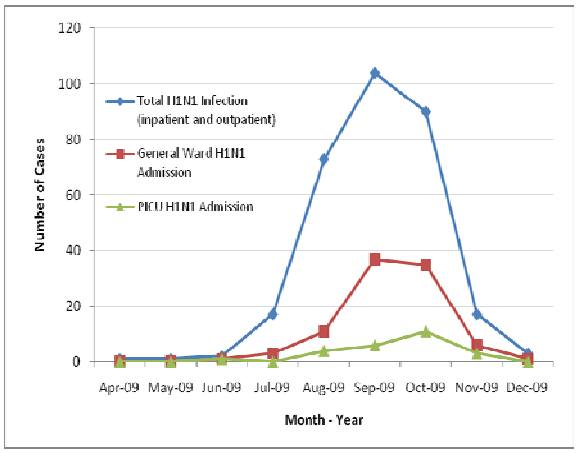

Fig. 1. Total 2009 H1N1infections, General Ward and PICU admissions.

Table 1. Hospitalized patients and comparison of patients in PICU and GMW*

VARIABLES	HOSPITALIZED (N = 119)	PICU (N = 25)	GMW (N = 94)	PICU vs GMW
Age, Mean, year	6.4 (R 0.04 – 20, med 6)	7.6 (R 0.5-20, med 8)	6.1 (R 0.04-18, med 5.4)	p = 0.183
Male	63 (52.9%)	13 (52%)	50 (53.2%)	p = 0.916
AA:Caucasian: Others	54:51:14	12:10:3	42:41:11	p = 0.947
Medical condition	162 (1.36/patient)	46 (1.84/patient)	119 (1.23/patient)	p = 0.0219
Pulmonary	57 (47.9%)	16 (64%)	41 (43.6%)	p = 0.069
Immunosuppression	26 (21.8%)	3 (12%)	23 (24.5%)	p = 0.276
Neurodevelopmental	21 (17.6%)	8 (32%)	13 (13.8%)	p = 0.034
Metabolic	18 (15.1%)	9 (36%)	9 (9.6%)	p = 0.001
Obesity	16 (13.4%)	5 (20%)	11 (11.7%)	p = 0.079
Hematologic	16 (13.4%)	2 (8%)	14 (14.9%)	p = 0.518
Cardiac	8 (6.7%)	3 (12%)	5 (5.3%)	p = 0.36
Co-infections on admission	8 (6.7%)	2 (8%)	6 (6.4%)	p = 0.673
Complications	79 (0.66/patient)	31 (1.24/patient)	48 (0.51/patient)	p < 0.0001
Respiratory distress	60 (50.4%)	23 (92%)	37 (39.4%)	p < 0.001
Seizure	11 (9.2%)	2 (8%)	9 (9.6%)	p = 0.99
Hepatitis	5 (4.2%)	3 (12%)	2 (2.1%)	p = 0.061
Coagulopathy	2 (1.7%)	2 (8%)	0 (0%)	p = 0.042
Renal Failure	1 (0.8%)	1 (4%)	0 (0%)	p = 0.21
Therapy, Mean, days from onset	3.6 (N=93, R 0-10, med 3)	3.4 (N=23, R 2-10, med 3)	3.7 (N=70, R 0-8, med 3)	p = 0.731
Length of Stay, Mean, days	4.30 (R 1–42, med 2)	10 (R 2-42, med 5)	2.78 (R 1-7, med 2)	p = 0.0018
Expired	1 (0.8%)	1 (4%)	0 (0%)	p = 0.21

*PICU = Pediatric Intensive Care Unit, GMW = General Medical Ward, R = range, med = median, AA = African-American

Of the 119 patients admitted to the children's hospital, 94 (79%) were admitted to the GMW and 25 (21%) were to the PICU. Influenza A infection was determined by RT-PCR in 113 patients and by viral culture in 6 patients. Only 15 patients were confirmed to have H1N1 infection using the CDC protocol. Overall (Table 1), there were 63 (53%) male, 54 (45%) African-American and 51 (43%) Caucasian. Mean age was 6.4 years with 52 (44%) patients < 5 years of age. Shown in Table 2 is the age distribution of patients with 2009 H1N1 influenza.

Patients were admitted within 2.97 days (range 0 – 7, median 2) of symptom onset and almost all of them presented with fever (114, 96%). Respiratory distress of varying severity was seen in 60 (50%) patients with 13 (10.9%) patients in the PICU requiring mechanical ventilation. Three of them required extracorporeal membrane oxygenation (ECMO). Average LOS for all patients was 4.3 days (range 1-42, median 2). 85 (71%) patients had at least one CMC with pulmonary disease (primarily asthma) being the most common in both groups (Table 1).

Table 2. Age distribution among PICU and GMW patients*

Age	PICU	GMW
< 1 month	0	3
≥ 1 month - < 6 month	0	8
≥ 6 month - < 1year	3	7
≥ 1 year < 5 year	6	25
≥ 5 year	16	51

*PICU = Pediatric Intensive Care Unit, GMW = General Medical Ward

Twenty-one of the 52 patients (40.4%) less than 5 years of age had no CMC.

On admission, blood cultures were done in 79 (66.4%), urine cultures in 32 (26.9%), respiratory syncytial virus (RSV) PCR in 62 (52.1%) and Mycoplasma IgM serology in 46 (38.7%) patients. Of the 8 patients with microbiologically-proven bacterial and viral co-infections on admission (Table 1), 2 were in the PICU and 6 were on the GMW. Co-infections in PICU included *Enterococcus faecalis* bacteremia in a 6-month old girl and RSV infection in a 4 year old child while co-infections on the GMW consisted of *Escherichia coli* urinary tract infection in 2 neonates, non-typeable *Haemophilus influenzae* and *Streptococcus pneumoniae* conjunctivitis in a neonate, oxacillin-resistant *Staphylococcus aureus* sinusitis in a patient with cystic fibrosis, oxacillin-sensitive *Staphylococcus aureus* neck abscess in a 7 month old patient and Enterovirus meningitis in a 2 month old girl. Mycoplasma IgM was positive in 11 patients. A patient in the PICU developed nosocomial *Candida albicans* urosepsis and *Staphylococcus epidermidis* sepsis. None of the patients tested positive for influenza B virus.

Of the 96 patients who had chest radiographs done on admission, 52 patients (PICU 17, GMW 35) were found to have abnormal findings.

Abnormalities reported included coarse interstitial markings, peribronchial thickening, hyperinflation, atelectasis, consolidation, pleural effusion, pneumomediastinum, subcutaneous emphysema, pneumothorax and lung collapse.

Aside from respiratory distress, complications noted included seizure, renal failure necessitating hemodialysis, hepatitis (transient) and coagulopathy necessitating transfusion of blood products (Table 1).

Ninety-eight (82%) patients (including all 25 patients in PICU) were treated with antivirals, oseltamivir being the most commonly used drug, usually given for 5 days. Combined rimantadine and zanamivir therapy was used in one patient in the PICU. Information on the timing of treatment initiation was available for 93 (78.2%) patients. Thirty-six patients (38.7%) received treatment early (≤ 2 days); 28 (30.1%) received intermediate treatment (> 2 and < 5 days); and 29 (31.2%) received late treatment (≥ 5 days). The mean time to treatment initiation was 3.42 days (range 2 to 10 days) among PICU patients and it was 3.6 days (range from 0 to 8 days) among GMW patients. Eleven of the 25 patients in PICU were treated within 48 hours. Logistic regression analysis showed that the likelihood of PICU admission increased among patients treated within the first 5 days of treatment and then decreased after the fifth day (linear component p = 0.02, quadratic component p = 0.04).

Although only 6 patients had microbiologically-proven bacterial infections, 82 (69%) patients (PICU 23, GMW 59) received at least 1 dose of antibiotics. Azithromycin was given for 5 days in 15 (12.6%) patients (7 PICU, 8 GMW), and at-least 10 day course of other antibiotics as empiric treatment for bacterial pneumonia was given to 20 (16.8%) patients.

Twenty-one patients were not treated with antivirals, all of them were admitted to the GMW. For this group of patients who did not receive antiviral therapy, the mean age was 5.5 years (range 2 weeks to 18 years, median 4 years), 8 patients were ≤ 6 months, 12 were male, 12 had at least 1 underlying CMC and patients presented with a mean of 3.68 days from onset of symptoms (N = 19, range 0-7, median 4 days). Despite the lack of anti-viral therapy, these patients did well in the hospital and were subsequently sent home.

Only one patient in this review expired. This patient was admitted to the PICU with underlying hypoplastic left heart syndrome.

Comparison of the patients in PICU and GMW in terms of demography, CMC, complications, co-infections on admission, therapy, length of stay and outcome are shown in Table 1. Patients in PICU had significantly longer LOS, higher rate of CMC and complications. Metabolic and neurodevelopmental conditions, respiratory distress and coagulopathy were statistically more likely among patients in the PICU. Analysis of only the PICU patients, comparing the confirmed and presumed H1N1 cases in the PICU showed no significant difference except for LOS. Total

hospital and PICU LOS was 11.6 ($p = 0.007$) and 6.1 ($p = 0.022$) days longer for confirmed H1N1 infection, respectively.

4. Discussion

The United States national data show that H1N1 pandemic activity peaked in spring and fall of 2009 and has since then declined with many states showing low activity by mid-December 2009. (5) Most previous reports involved patients seen early in the outbreak while this study presents our overall experience from April through December.

In our institution, about one of every three children testing positive for influenza A was admitted to the hospital and of those, one in five to the PICU. Although a large proportion of our patients were admitted to the PICU (21%), the mortality and incidence of microbiologically-proven bacterial and viral co-infections was low, 0.8% and 6.7%, respectively. In general, our patients had moderately severe illness. Patients in the PICU had higher rates of CMC and complications when compared to the patients admitted to the GMW and not unexpectedly, had longer LOS.

Similar to other reports in hospitalized patients with 2009 H1N1 infection and seasonal influenza, majority of our patients (71%) had at least one CMC with pulmonary condition being the most common. (6,9-13) Although the proportion of chronic pulmonary conditions was comparable between GMW and PICU patients, respiratory distress was more common among those patients admitted to the PICU ($p < 0.001$). This is not unexpected since patients with respiratory distress from any cause are more likely to be admitted to the PICU. Half of the PICU patients (13 of 25) required mechanical ventilation. This prominence of pulmonary dysfunction as both risk factor and complication among H1N1 infected patients, particularly critically ill patients, has been reported by others. (6,14-15)

Many of our patients were treated with antivirals and among those whose timing of treatment was known ($N = 93$), antiviral medications were started past 48 hours in majority of them mainly because they presented more than 48 hours from symptom onset. No statistical difference was noted between patients in PICU and GMW although logistic regression analysis showed that those patients treated within the first 5 days of illness with antivirals had higher likelihood of admission to PICU, possibly indicating they were clinically worse and sought medical attention earlier. Treatment within 48 hours of illness has been shown to be most effective. (16) The CDC recommends treating patients who have severe, progressive illness or those who are hospitalized. (17) This recommendation was not followed in 21 (17.6%) hospitalized patients indicating that in some hospitalized patients the illness was not severe enough and that patients were hospitalized perhaps for monitoring and a concern for the potential for rapid deterioration.

There were few microbiologically confirmed co-infections and nosocomial infections in our patients. A high incidence of viral co-infections (almost 20%) and bacteria (43-45%) has been reported. (9,18-19) Despite the low number of co-infections, 69% of the patients received at least one dose of antibiotics and 29% completed at least 5 days of treatment of antibiotics as empiric treatment for pneumonia. Possible reasons for this may include difficulty in differentiating bacterial versus viral pneumonia based on radiographic findings and concerns for secondary bacterial complications since the majority of influenza-associated fatalities has been thought to result from secondary bacterial complications.

There are several limitations to this study. First, only 12.6% of the cases were confirmed 2009 H1N1 by the CDC protocol. This was primarily because of the retrospective nature of the study and lack of a standard protocol to confirm all influenza A cases to be H1N1 or not. We believe the assumption was acceptable for several reasons: we only included patients whose influenza A infection was diagnosed by reliable tests (RT-PCR and viral culture), H1N1 was the only reported circulating strain in our region and our subset statistical analysis showed that our confirmed and presumed H1N1 infections were comparable except for LOS. Second weakness of the study was the lack of objective clinical scoring to determine severity of the disease among patients admitted to the PICU. Third, as has also been seen in other series, H1N1 has a wide range of symptoms and severity therefore it is difficult to ascertain as to the extent of its contribution in the patient's illness. (6,10) Most of the patients were sent home before completion of antiviral therapy precluding further follow up of their course on and off treatment.

In the 9 months of the H1N1 pandemic from April to December 2009, close to 40% of infected patients <21 years of age with influenza were hospitalized and heavy utilization of hospital resources and antimicrobials was seen despite

mild to moderate severity of illness in the patients in our series. In preparing for any future influenza pandemic, considerations should include education on early recognition and triaging of illnesses as well as timely and appropriate use of antivirals and antibiotics. Use of vaccines in preventing infection particularly in children with underlying CMC should remain the mainstay for dealing with influenza epidemics.

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