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ORIGINAL ARTICLE

Predictors of Mortality in Hospitalized Children with Pandemic H1N1 Influenza 2009 in Pune, India

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Abstract
Objective To analyse the factors associated with increased mortality among Indian Children with H1N1.
Methods Data were abstracted from available hospital records of children less than 12 y of age, who were admitted to Sassoon General Hospital in Pune, India, with confirmed pandemic 2009 H1N1 influenza infection from August 2009 through January 2010. Logistic regression analysis was used to identify clinical characteristics associated with mortality.

Results Of 775 pediatric cases admitted with Influenza Like Illness (ILI), 92 (11.8%) had confirmed H1N1 influenza infection. The median age of HIN1 cases was 2.5 y; 13 (14%) had an associated co-morbid condition. Median duration of symptoms was 4 d (interquartile range (IQR), 3–7 d). All 92 H1N1 cases received oseltamivir and empiric antimicrobials on admission. Intensive care unit (ICU) admission was required for 88 (96%) children, and 20 (23%) required mechanical ventilation.Fifteen children (16%) died; mortality was associated with presence of diffuse alveolar infiltrate on admission chest radiography (odds ratio (OR) 45, 95%CI :5.4–370; $p<0.001$), use of corticosteroids in ARDS in children who required mechanical ventilation (OR 8.12, 95%CI: 2.44–27.05; $p=0.001$), SpO_2 <80% on admission (OR 32.8, 95% CI: 5.8–185.5; $p<0.001$) and presence of ARDS (OR 345.3, 95% CI :33.5–3564.1; $p<0.001$). Necropsy from all children who died showed 9 (60%) had ARDS pattern and necrotizing pneumonitis, diffuse hemorrhage and interstitial pneumonia ($n=4$ each, 27%) with gram positive organisms consistent with severe viral and bacterial co-infection.
Conclusions Hypoxia, ARDS and use of corticosteroids in children with ARDS who were mechanically ventilated were the factors associated with increased odds of mortality. Necropsy also suggested bacterial co-infection as a risk factor.

Keywords Pandemic 2009 H1N1 virus · Mortality · Children

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Introduction

On 11 May 2009, the first Indian case of H1N1 was confirmed. Subsequently, one of India's largest documented H1N1 outbreaks occurred in Pune, with the first pediatric

case reported in July 2009. Subsequently, Sassoon General Hospital (SGH), Pune established a separate isolation ward and ICU for suspected H1N1 patients.

To date, data on the current pandemic suggests that children under 18 y of age represent almost half of all 2009 H1N1 influenza cases, with many having at least one underlying medical condition, particularly asthma [1–4]. In published reports, the majority of hospitalized children received antivirals; however, they appear to have significant mortality [5]. A recent publication reported that factors independently associated with in-hospital mortality in adults and children were, requirement for invasive ventilation at intensive care unit (ICU) admission, older age and presence of any co-existing conditions [6].

Understanding the factors associated with increase morbidity and mortality among Indian children with H1N1 could identify opportunities to prevent deaths due to present and future influenza pandemics in India. Therefore, the authors analyzed the factors associated with mortality, among children admitted to the largest public hospital in Pune, during the H1N1 pandemic.

Material and Methods

Sassoon General Hospitals (SGH)-Byramjee Jeejeebhoy Medical College (BJMC) is a large Maharashtra Government tertiary care public and teaching hospital, which serves Pune city (city with population of approximately 4 million) and surrounding peri-urban and rural areas. Available hospital records were retrospectively reviewed for children with PCR-confirmed 2009 H1N1 infection, who were less than 12 y of age on admission to SGH and were admitted between 7 August 2009 and 31 January 2010 to the pediatric swine flu isolation ICU and ward. Children were admitted to ICU if they had severe respiratory distress or hemodynamic instability requiring continuous monitoring and ICU care. Pathological specimens from children who died were reviewed for histopathological changes and secondary bacterial infections by gram staining.

Clinical and demographic data were extracted from available hospital records, using a standardized case report form (CRF). The CRF's were quality assured for completeness and accuracy and were entered *via* single data entry in a MS Access database.

The following data were collected: demographic characteristics like age, gender and location of residence; clinical characteristics on admission including duration of symptoms, co-morbid illnesses; clinical findings at presentation; and hospital course including use of antibiotics, corticosteroids and antiviral drugs, requirement of bubble continuous positive airway pressure (CPAP)or mechanical ventilation, presence of co-infections, laboratory and radiologic findings. The primary outcome of the study was in-hospital mortality. Necropsy data were available and included in the analysis for all children who died. Tissue sections of lung and liver were formalin fixed, paraffin embedded and hematoxylin and eosin stained. Gram staining of lung tissue blocks was also performed on all lung necropsy specimens. No personal patient identifiers were extracted on the CRF's.

All children admitted with ILI, underwent nasopharyngeal (NP) aspirate or swab specimen collection for the presence of H1N1 specific viral nucleic acid on the day of hospitalization. Influenza-like illness was defined by the documentation of fever (temperature >100°F), and/or cough or sore throat, with any of the following symptoms: myalgia or arthralgia, respiratory distress, or vomiting or diarrhea.

Patient specimens were analyzed at the National Institute of Virology (NIV), a World Health organization (WHO)-certified national reference virology laboratory in Pune, India within 24 h of collection. Reverse-transcriptase PCR assay was performed according to the protocol recommended by the U.S. Centers for Disease Control and Prevention (CDC) [7]. For the purposes of this analysis, a child was defined as infected with 2009 H1N1 influenza based on laboratory confirmation of the presence of H1N1 specific viral nucleic acid in nasopharyngeal specimen collected on hospitalization.

The study was reviewed and approved by the ethics committee of SGH and the institutional review board (IRB) of the Johns Hopkins University School of Medicine.

Data Analysis

An epidemic curve of children presenting to the hospital with ILI, and among those with PCR confirmed 2009 H1N1was created. Demographic and clinical characteristics, on admission and in hospital, were summarized as a whole and also stratified by age categories less than 1 y, 1–5 y and more than 5 y. Categorical variables were summarized using frequencies, and non-normal continuous variables using medians and IQR. Categorical and continuous data across age categories were compared at 5% level of significance, using a Fisher's exact test and nonparametric analysis of variance (Kruskal-Wallis test) respectively. The primary outcome of the study was mortality defined as in hospital death. Logistic regression was used to identify risk factors for mortality. All analysis was done using STATA software version 9.1.

Results

Between 7 August 2009 and 31 January 2010, a total of 1219 patients with ILI were admitted to the H1N1 ward and

ICU, of which 775 (64%) were children <12 y old. Ninety-two children (12%) had PCR-confirmed 2009 H1N1 influenza infection. Epidemic curve shown in Fig. 1, suggests an initial peak in late August and September (wk 4–8). Subsequently, there was a waxing and waning in the number of cases followed by another mild increase in the number of H1N1cases beginning in November 2009 and continuing through January 2010.

Among the 92 H1N1-confirmed cases, 43 (47%) were males and the median age was 2.5 y (IQR 1.3–6), with 16 (17%) cases less than 1 y of age. Thirteen (14%) cases had a confirmed H1N1 positive contact. Table 1 shows the demographic and clinical characteristics including signs and symptoms on admission and in-hospital, stratified by age. An underlying co-morbid condition was noted in 13 (14%) of H1N1 cases: congenital heart disease (n=6), asthma (n=4), diaphragmatic hernia (n=1), seizure disorder (n=1) and gastroesphageal reflux disease (n=1). Co-infections were noted in 13 (14%) of H1N1 cases: HIV (n=4), dengue (n=4), tuberculosis (n=2), malaria (n=2) and typhoid (n=1). Nutritional assessment at admission revealed that 96% of the H1N1 cases had adequate nutrition and 4% had moderate acute malnutrition as per 2006 WHO growth standards [8].

All H1N1 cases received the antiviral drug oseltamivir on admission at the dosage recommended by the CDC [9]. The median time from illness onset to initiation of oseltamivir was 3 d and 14 (15%) children received oseltamivir within 48 h of symptom onset. Two (2%) had received oseltamivir prior to admission. On admission, all children who were subsequently confirmed to have H1N1 were also empirically started on broad spectrum antibiotics (3rd generation cephalosporin), and 13 (14%) received vancomycin, although all children had received antibiotics prior to admission by an outside provider.

Bacterial co-infections isolated from blood cultures and/or endotracheal aspirates were identified in 15 (16%) children; gram-negative infections included *Acinetobacter baumanii* (n=4), *Pseudomonas aeruginosa* (n=3), *Citrobacter freundii* (n=1) and *Escherichia coli* (n=1), and gram positive infections included coagulase-negative *Staphylococci* spp. (n=3) and methicillin resistant *Staphylococcus aureus* (n=3). The most common clinical complications observed were acute respiratory distress syndrome (ARDS) (n=17, 18%), empyema (n=5, 5%), and encephalitis (n=4, 4%).

Eighty-eight (96%) H1N1 cases required ICU care. All received oxygen therapy on admission. Thirty six (39%) required ventilatory support on admission; 16 (44%) received non invasive ventilation (nasal bubble CPAP) and 20 (56%) received mechanical ventilation. Among ICU admitted cases, the median time from symptoms onset to initiation of oseltamivir was 2 d (range, 0–3 d). A short course of corticosteroids was administered to 21 (24%) children.

Among 88 ICU-admitted cases, 15 (16%) died, of which 7 (47%) died within the first 48 h of hospital admission. All children (n=16) who received non-invasive ventilation (bubble CPAP) survived. The median age of children who died was 6 y (IQR, 2–6.4 y) and the median time from onset of symptoms to death was 8 d (IQR, 5–11 d). The median duration of hospital stay among those who died was 1 d (IQR, 1–4 d). Among those who survived and were on mechanical ventilation, the median duration of hospital stay was significantly higher than those who died (11 d *vs.* 1 d, p 0.02). The duration of symptoms before admission was significantly lower in those who survived on assisted ventilation compared to those who died (median 3 d *vs.* 6 d, 95% CI :0.49–32.4; p 0.06).

Mortality was associated with SpO_2 <80% at admission (OR 32.8, 95%CI: 5.8–185.5; p<0.001); presence of diffuse alveolar infiltrate (DAI) on admission (OR 45, 95%CI:5.4–370.0; p<0.001) and presence of ARDS on admission (OR 345, 95%CI: 33.5–3564; p<0.001) (Table 2). There was a strong trend with late presentation to hospital

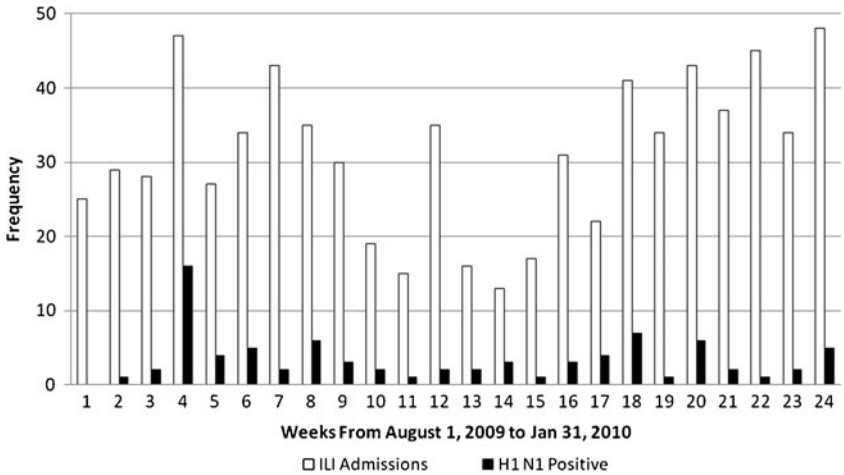

Fig. 1 Children with Influenza-like Illness (ILI) <12 y of age admitted to SGH and among those who were PCR confirmed H1N1 infected: August 2009–January 2010

Table 1 Demographic and clinical characteristics of hospitalized children, less than 12 y of age, with PCR-confirmed 2009 H1N1 influenza infection in Pune, India

Characteristics	Overall	Age			*P*
	N=92	<1 Y *N*=16	1–5 Y *N*=43	≥5 Y *N*=33	
Male Gender	43 (47%)	11 (69%)	21 (49%)	11 (33%)	0.06
Underlying Co-morbidity	13 (14%)	2(6%)	7 (16%)	4 (18%)	0.59
Asthma	4 (4%)	0	2 (5%)	2 (6%)	0.62
Congenital Heart Disease	6 (7%)	1 (6%)	3 (7%)	2 (6%)	0.99
Diaphragmatic hernia	1	0	1 (2%)	0	>0.95
Seizure disorder	1	0	1 (2%)	0	>0.95
GERD	1	1 (6%)	0	0	0.16
Clinical Symptoms and Signs on Admission					
Duration of any symptoms					
Median (IQR) days	4 (3–7)	5 (2.5–7.5)	4 (3–7)	5 (3–7)	0.70
Fever	88 (96%)	13 (81%)	43 (100%)	32 (97%)	0.006
Cough	88 (96%)	14 (88%)	42 (97%)	32 (97%)	0.21
Shortness of breath	44 (48%)	5 (31%)	23 (53%)	16 (48%)	0.31
Rhinorrhea	21 (23%)	4 (25%)	10 (23%)	7 (21%)	0.95
Sore throat	15 (16%)	1 (6%)	5 (12%)	9 (27%)	0.09
Diarrhea	8 (9%)	2 (13%)	3 (7%)	3 (9%)	0.80
Nausea/Vomiting	7 (8%)	1 (6%)	2 (5%)	4 (12%)	0.47
Laboratory Abnormalities					
Anemia	42 (46%)	5 (31%)	29 (67%)	8 (24%)	<0.001
Thrombocytopenia	31 (34%)	4 (25%)	16 (37%)	11 (33%)	0.68
Leucopenia	22 (24%)	1 (6%)	10 (23%)	11 (33%)	0.11
Abnormality on Chest X-ray					0.16
Diffuse alveolar infiltrate	12 (13%)	2 (13%)	2 (5%)	8 (24%)	
Multi-lobar infiltrate	60 (65%)	11 (69%)	31 (72%)	18 (55%)	
Uni-lobar Infiltrate	20 (22%)	3 (19%)	10 (23%)	7 (21%)	
In Hospital Course					
Antiviral within 48 h	14 (15%)	4 (25%)	4 (9%)	6 (18%)	0.28
Corticosteroid Use	21 (23%)	3 (19%)	10 (23%)	8 (24%)	0.91
Secondary Bacterial Infection	15 (16%)	2 (13%)	8 (19%)	5 (15%)	0.87
Co-infections	13 (14%)	1 (6%)	7 (16%)	5 (15%)	0.67
HIV	4 (4%)	0	2 (5%)	2 (6%)	0.95
Malaria	2 (2%)	0	2 (5%)	0	0.66
Dengue	4 (4%)	1 (6%)	1 (2%)	2 (6%)	0.51
Typhoid Fever	1 (1%)	0	1 (2%)	0	>0.95
Tuberculosis	2 (2%)	0	1 (2%)	1 (3%)	>0.95
Complications other than death					
Empyema	5 (5%)	0	5 (12%)	0	0.09
ARDS/ALI	17 (18%)	3 (19%)	4 (9%)	10 (30%)	0.07
Encephalitis	4 (4%)	0	1 (2%)	3 (9%)	0.38
Renal Failure[a]	2 (2%)	0	1 (2%)	1 (3%)	0.79
Congestive heart failure	6 (7%)	1 (6%)	2 (5%)	3 (9%)	0.85
ICU Admission	88 (96%)	16 (100%)	42 (98%)	30 (91%)	0.23
Required Ventilation	36 (39%)	8 (50%)	18 (42%)	10 (30%)	0.35
Mechanical Ventilation	20 (56%)	3 (38%)	7 (39%)	10 (100%)	0.002
Bubble CPAP	16 (44%)	5 (62%)	11 (61%)	0	0.001
Death	15 (16%)	1 (6%)	4 (9%)	10 (30%)	0.02

ICU Intensive care unit; *Anemia* Hb less than 10 mg/dl; *Thrombocytopenia* Platelets less than 10^5/dl; *Leucopenia* White blood cells less than 4,000/dl; *GERD* Gastro-esophageal reflux disease; *ARDS/ALI* Acute respiratory distress syndrome/Acute lung injury defined as diffuse alveolar infiltrate along with PaO_2/FiO_2 ratio less than 200 and 300 respectively.

[a] Defined as 50% increase from baseline creatinine.

Table 2 Univariate analysis by logistic regression evaluating the risk factors for mortality

Characteristic	Died *N*=15 (%)	Survived *N*=77 (%)	Odds Ratio	95% CI	*P*
Age					
<1 y	1 (7)	15 (19)	Referent	–	–
1–5 y	4 (27)	39 (51)	1.54	(0.16, 14.90)	0.71
≥5 y	10 (67)	23 (30)	6.52	(0.76, 56.33)	0.09
Male Gender	7 (47)	36 (47)	0.99	(0.33, 3.02)	0.995
Hindu Religion	14 (93)	60 (78)	3.97	(0.49, 32.4)	0.20
Duration of Symptoms					
<72 h	2 (13)	31 (40)	Referent	–	–
≥72 h	13 (87)	46 (60)	4.38	(0.92, 20.78)	0.06
Co-morbidity	4 (27)	9 (12)	2.28	(0.81, 6.45)	0.13
Asthma	1 (7)	3 (4)	1.76	(0.17, 18.2)	0.63
Co-infections	1 (7)	12 (16)	0.43	(0.06, 3.05)	0.36
O_2 Saturation <80%	7 (47)	2 (3)	32.8	(5.8, 185.5)	<0.001
Admission CXR Findings					
Diffuse Alveolar Infiltrate	10 (67)	2 (3)	45	(5.4, 370)	<0.001
Multilobar	3 (20)	57 (74)	0.47	(0.07,3.06)	0.43
Unilobar	2 (13)	18 (23)	Referent	–	–
Corticosteroid Treatment in Ventilated Children	9 (60)	12 (16)	8.12	(2.44, 27.05)	0.001
Antiviral Treatment <48 h of symptom onset	1 (7)	13 (17)	0.35	(0.04, 2.9)	0.33
ARDS/ALI	14 (93)	3 (4)	345.3	(33.5, 3564.1)	<0.001
Bacterial Infection	5 (33)	10 (13)	3.4	(0.95, 11.8)	0.06

‡ *p*-values are based on logistic regression.

DAI Diffuse alveolar infiltrate; *ARDS/ALI* Acute respiratory distress syndrome/acute lung injury, defined as diffuse alveolar infiltrate along with PaO_2/FiO_2 ratio less than 200 and 300 respectively.

(admission to the hospital ≥72 h of symptom onset) being associated with 4-fold increased odds of mortality; however this was not statistically significant (p=0.06).However, late presentation to the hospital combined with need for mechanical ventilation on admission was associated with statistically significant increased risk of mortality (OR 494, 95%CI: 41.7–5848.9; p<0.001).Lastly, there was also a strong trend with the presence of co-morbid condition being associated with an almost 5-fold increased odds of mortality (OR, 4.56, 95%CI: 0.91–23; p=0.07).

Fourteen (15%) children admitted to ICU received oseltamivir within 48 h of symptom onset and survived while one of the children who died, received oseltamivir within 48 h of symptom onset. Pneumonia on admission was seen in all the children and was associated with higher mortality if presented with diffuse alveolar infiltrate. Secondary bacterial infections particularly, nosocomial infection was associated with higher mortality; however this was not statistically significant (OR 3.4, 95% CI: 0.95–11.8; p=0.06).

Necropsy performed on all 15 children who died showed ARDS pattern (n=9) (Fig. 2a), necrotizing pneumonitis (n=4), diffuse hemorrhage (n=4) and interstitial pneumonia (n=4) consistent with severe viral and/or bacterial infection (Table 3). A polymorphonuclear infiltrate was seen in 9 cases (Fig. 2b), suggestive of a secondary bacterial infection. Further gram staining of lung tissue blocks showed presence of gram positive infection in 8 (53%) patients. Liver necropsy revealed varied pathology ranging from fatty changes to sub massive necrosis (data not shown).

Discussion

Since the beginning of the present pandemic in Pune, India, until 31st January 2010;686 adult and 932 pediatric patients with influenza-like illness were screened at various screening centers (unpublished report from NIV, Pune, India) and 12,668 (2%) underwent nasopharyngeal swab testing. Of these, 2487 (20%) were confirmed to have 2009 H1N1 infection and 714 (28.7%) were in the 0–12 y age group. The authors evaluated the risk factors associated with mortality in their setting and found that lower admission O_2 saturation, corticosteroid treatment in children with ARDS requiring mechanical ventilation, diffuse alveolar infiltrate and presence of ARDS was associated with

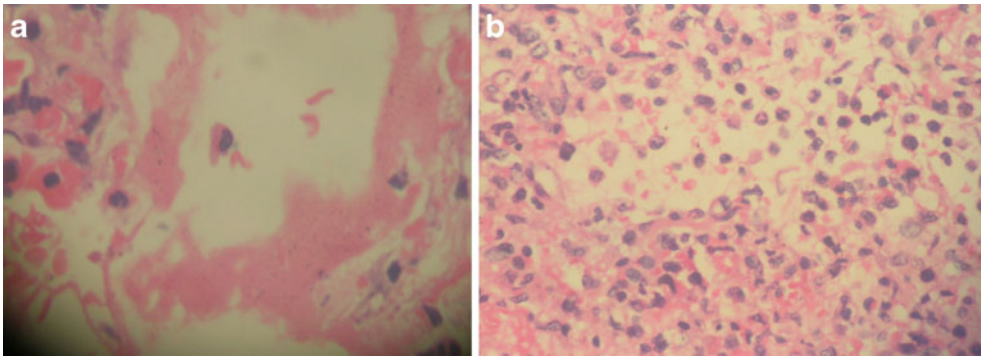

Fig. 2 **a**. Well formed hyaline membrane with some partially atelectatic alveoli with sparse infiltrate of macrophages. **b**. Alveoli filled with dense exudate of polymorphs with scanty mononuclear cell, fibrin deposition, intra alveolar hemorrhage, necrosis of alveolar wall with micro abscess formation and marked congestion of alveolar capillaries

increased mortality in children with pandemic 2009 H1N1 influenza infection. In addition, the authors found a trend towards late presentation to the hospital and bacterial co-infection also being associated with increased risk of mortality (though these were not statistically significant).

The present case series of hospitalized children with 2009 H1N1 influenza infection during the H1N1 India pandemic depicts the severity of illness seen in hospitalized young children. H1N1 infection caused significant pneumonia and ARDS, and resulted in ICU admissions and deaths in 96% and 16% of children, respectively. The reported influenza-like presentations such as fever, cough, sore throat, and myalgia as well as gastrointestinal symptoms in the present setting was comparable to previous reports of H1N1 in children [10–12]. Neurological symptoms and complications such as, altered mentation and seizures along with influenza like symptoms were also noted in the present study and were similar to what has been previously reported [12].

High-income settings have reported obesity in a significant proportion of adults and children with H1N1 infection [1–3]. In contrast, the authors did not find an association between nutritional status and risk of H1N1 illness in the present hospitalized cohort; nutritional assessment in the present center revealed that 96% of those children admitted were neither obese nor undernourished by standard anthropometric measurements.

In contrast to reports from the developed world [1–4] of the current H1N1 pandemic, underlying medical conditions were lower in the present case series. Asthma only accounted for 4% in the present group, whereas in other studies it has been reported to be 12% or higher [1–4]. HIV has been associated with H1N1 in published reports [13] and the authors identified 4% of their children co-infected with HIV, which is higher than the population prevalence of HIV in children in the authors' area (unpublished data). Nevertheless, the presence of a co-morbid condition showed a trend towards increased mortality in the present series.

All children received oseltamivir and empiric antimicrobials on admission to the present center. Although the present data shows that survival and deaths among children who have received oseltamivir within 48 h of symptom onset is not statistically significant, the authors recommend early initiation of oseltamivir under pandemic situation. In spite of receiving antimicrobials prior to admission and upon admission, 16% had confirmed bacterial co-infection during the course of their hospitalization. This included both gram negative and gram positive organisms and is consistent with previous reports [14]. The presence of secondary bacterial infection showed a trend towards increased mortality by 3 fold. Dengue [15] and HIV [16] co-infection with H1N1 has been recently reported, but for the first time, the present case series is reporting co-infections like malaria, tuberculosis and typhoid fever in patients with confirmed 2009 H1N1 infection. However, these co-infections were not associated with increased mortality in the present cohort.

The mortality rate of 16% noted in the present study is consistent with prior reports of current pandemic for children [1–3]. The authors found that lower admission O_2 saturation, diffuse alveolar infiltrate on admission, corticosteroid treatment in children with ARDS requiring mechanical ventilation and presence of ARDS was associated with increased mortality in children with pandemic 2009 H1N1 influenza infection. The fact that mechanical ventilation was required on admission in patients who died, suggests that these children presented late in the course of their illness. Late presentation to the health care system remains a major challenge in influenza pandemics and is frequently associated with poor outcomes, including higher risk of mortality. Mass media and community efforts during a pandemic need to emphasize earlier presentation to health care centers equipped to address pandemic influenza with special care taken to transfer critically ill patients in well equipped ambulances.

Necropsy performed on the children who died demonstrated presence of ARDS pattern, necrotizing pneumonitis, and diffuse alveolar hemorrhage as the probable cause of mortality. The histological findings are similar to that a recent report [17]. The gram staining of lung tissue blocks in the present series revealed that more than half had an underlying gram positive bacterial infection suggestive of

Table 3 Characteristics, including lung necropsy results of 15 children infected with 2009 H1N1 influenza who died

	Age	Sex	Co-morbidity	Duration of Symptoms before Hospitalization	Duration of Hospitalization	Lung Necropsy Gram Stain Findings	Lung Necropsy Pathology Findings
1	3 y	F	Asthma	3 d	1 d	Gram positive cocci in clusters	Necrotizing pneumonitis with micro abscess formation, PMN infiltrates, and hyaline membrane formation
2	7 y	F	None	6 d	3 d	No organisms seen	Hyaline membrane formation
3	9 mo	M	None	8 d	4 d	No organisms seen	Necrotizing pneumonitis with PMN infiltrates
4	15 mo	F	None	6 d	1 h	Gram positive cocci in clusters	Acute hemorrhagic pneumonitis, and PMN infiltrates
5	5 y	F	None	4 d	2 d	Gram positive cocci in chains	Acute hemorrhagic pneumonitis with hyaline membrane, and PMN infiltrates
6	6 y	M	Congenital heart disease	7 d	2 d	No organisms seen	Pulmonary hemorrhage with ARDS
7	6 y	M	None	8 d	1 d	Gram positive cocci in clusters	Interstitial pneumonia, hyaline membrane, and PMN infiltrates
8	2 y	F	None	5 d	1 d	No organisms seen	Necrotizing pneumonia, hyaline membrane, and PMN infiltrates
9	5 y	F	None	4 d	22 h	Gram positive cocci in clusters	Alveoli filled with PMN and fibrin, necrotizing pneumonia, hyaline membrane and alveolar lining necrosis.
10	6.5 y	M	Epilepsy	8 d	11 h	No organisms seen	Focal intra-alveolar hemorrhage, mononuclear cell infiltrates, hyaline membrane and interstitial pneumonia.
11	6.5 y	M	None	2 d	13 d	Gram positive cocci in chains	Mononuclear cell infiltrate, thick alveolar wall with hyaline membrane and early diffuse alveolar damage with patchy pneumonitis.
12	6 y	M	None	6 d	7 d	No organisms seen	Interstitial mononuclear infiltrate, alveoli filled with neutrophils and few macrophages and evidence of viral pneumonitis.
13	11 y	M	Interstitial Lung Disease	4 d	7 d	Gram positive cocci in chains	Diffuse alveolar damage, alveoli with anthracotic pigment, bronchiolar wall necrosis and focal PMN infiltration in interstitium.
14	1.5 y	F	None	4 d	1 d	Gram positive cocci in clusters	Interstitial pneumonitis with mononuclear cell infiltrate and interstitial pneumonitis.
15	8 y	F	Thalassemia Major, Splenectomy	4 d	1 d	No organisms seen	Mononuclear infiltrate, diffuse alveolar damage with thick hyaline membrane and interstitial septate fibrosis.

PMN polymorphonuclear cells

streptococcal and staphylococcal infections. CDC has reported bacterial co-infection in almost one third of all fatal H1N1 cases in United States and majority of these infections were streptococcal and staphylococcal infections [14].

The present study had a potential limitation. Since SGH was the only referral center for critically ill patients with suspected H1N1 infection in Pune, India during the early pandemic, the patients represented the most critically ill children in the community with H1N1 and are not representative of the typical cases of childhood H1N1 in the community.

The authors' experience in India suggests that mortality may be associated with late presentation to tertiary care centers and severe illness at presentation, including severe respiratory distress and ARDS. In addition, secondary bacterial infection may also be clinically significant contributor to mortality. In resource-constrained settings such as the present one, the authors recommend early referral and admission of critically ill children, prompt initiation of empirical oseltamivir and broad spectrum antibiotics in order to have better outcomes.

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Contributions All authors participated in data analysis and manuscript preparation.

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