Published in final edited form as:
Crit Care Med. 2012 May ; 40(5): 1487–1498. doi:10.1097/CCM.0b013e3182416f23.

Critical Illness from 2009 Pandemic Influenza A (H1N1) Virus and Bacterial Co-Infection in the United States

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Abstract

Objective—The contribution of bacterial co-infection to critical illness associated with 2009 influenza A (H1N1) [pH1N1] virus infection remains uncertain. The objective of this study was to determine if bacterial co-infection increased the morbidity and mortality of pH1N1.

Design—Retrospective and Prospective cohort study

Setting—35 adult U.S. intensive care units over the course of one year

Patients—683 critically ill adults with confirmed or probable pH1N1

Interventions—None

Measurements and Main Results—A confirmed or probable case was defined as a positive pH1N1 test result or positive test for influenza A that was otherwise not subtyped. Bacterial co-infection was defined as documented bacteremia or any presumed bacterial pneumonia with or without positive respiratory tract culture within 72 hours of ICU admission. The mean age was 45±16 years, mean BMI 32.5±11.1 kg/m^2, and mean APACHE II score 21±9, with 76% having at least one co-morbidity. Of 207 (30.3%) patients with bacterial co-infection on ICU admission, 154

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The authors have not disclosed any potential conflicts of interest.

had positive cultures with *Staphylococcus aureus* (n=57) and *Streptococcus pneumoniae* (n=19) the most commonly identified pathogens. Bacterial co-infected patients were more likely to present with shock (21 vs. 10%; P=0.0001), require mechanical ventilation at the time of ICU admission (63 vs. 52%; P=0.005) and have longer duration of ICU care (median 7 vs. 6 days; P=0.05). Hospital mortality was 23%; 31% in bacterial co-infected patients and 21% in patients without co-infection (P=0.002). Immunosuppression (RR 1.57; 95% CI 1.20–2.06; P=0.0009) and *Staphylococcus aureus* at admission (RR 2.82; 95% CI: 1.76–4.51; P<0.0001) were independently associated with increased mortality.

Conclusions—Among ICU patients with pH1N1, bacterial co-infection diagnosed within 72 hours of admission, especially with *Staphylococcus aureus*, was associated with significantly higher morbidity and mortality.

Keywords

Pandemic H1N1 Influenza; Bacterial Co-infection; Critical Illness; Mortality

INTRODUCTION

Early reports from Mexico and Canada suggested that 2009 influenza A (H1N1) [pH1N1] virus infection could cause profound organ dysfunction in young adults, beyond that typically seen during annual influenza epidemics (1,2). Early in the pandemic, 21–48% mortality was reported for ICU patients (1,3–7), with young adults comprising the majority of fatal cases (8–10). The major severe organ dysfunction associated with pH1N1 infection leading to adult intensive care unit (ICU) admission is rapidly progressive pneumonitis resulting in respiratory failure, acute respiratory distress syndrome (ARDS), and refractory hypoxemia (11). Postmortem findings consistently demonstrate diffuse alveolar damage with hyaline membrane formation (8,9). Other clinical complications include acute renal dysfunction requiring renal replacement therapy (RRT), vasopressor-dependent shock, myositis/rhabdomyolysis, encephalitis, myocarditis, and secondary invasive bacterial infection (1,5–7,11–13). As in previous influenza pandemics, the frequency of bacterial infection was high, ranging from 20–32% of all critically ill patients (1,6,7) and 26–38% of fatal cases (8,9). The contribution of bacterial co-infection in the development of shock, multisystem organ failure, and death versus pH1N1 viral infection alone remains uncertain.

Several early case series have reported on the epidemiology and general disease course of pH1N1 associated critical illness (1,2,7,12,14,15). Small numbers of patients, lack of reliable laboratory confirmation of cases, and narrowly-focused physiologic data in these reports, however, has resulted in remaining knowledge gaps (16). In this study, we describe the clinical features, risk factors for mortality, and outcomes of critically ill pH1N1 patients with and without bacterial co-infection admitted to ARDS Network hospital ICUs across North America during the pandemic to test the hypothesis that bacterial co-infection increased the morbidity and mortality of pH1N1.

MATERIALS AND METHODS

Setting and Participants

This one-year multicenter observational cohort study, coordinated with a parallel study in pediatric ICUs (17), included patients 13 years and older with suspected, probable, or confirmed seasonal influenza or pH1N1 admitted to 35 ARDS Network hospital adult ICUs from April 15, 2009 through April 15, 2010. Sites and the Clinical Coordinating Center obtained local Institutional Review Board (IRB) and waiver of consent approvals between September 22, 2009 and March 23, 2010. From the day of local IRB approval, the records of

all subsequent ICU admissions were prospectively screened for patients with influenza-like illness (ILI) treated empirically with antivirals for influenza and all confirmed seasonal and pH1N1 influenza virus infections (Appendix Figure 1). A ***confirmed*** case was defined as a positive test result for pH1N1 using reverse transcriptase-polymerase chain reaction (RT-PCR) or viral culture. A ***probable*** case was defined as positive diagnostic test for influenza A (RT-PCR, viral culture, rapid diagnostic test, or immunofluorescence) that was otherwise not subtyped. Sites also retrospectively identified all confirmed and probable adult pH1N1 ICU admissions which occurred between April 15, 2009 and the date of IRB approval.

Data Collection

Baseline demographic information, clinical presentation, and hospital course were recorded in a web-based secure electronic case report form (REDCap (18)). Patients with HIV infection, active hematologic malignancies, bone marrow or organ transplants, and those who received systemic corticosteroids at a dose of 20mg or more of prednisone equivalent per day for any duration within 6 months of ICU admission were considered immunosuppressed. Shock was defined as being treated with vasopressors.

Date, source of sample, and result of all available influenza diagnostic tests were recorded. Baseline vital signs, vasopressor dose, PaO_2/FiO_2 (P/F) and SaO_2/FiO_2 (S/F) were the first values obtained in the ICU unless these measurements were available from transport or emergency department documentation. Data for days 3, 7, and 14 were recorded as close to 08:00 as possible. Diagnosis of encephalitis was confirmed by magnetic resonance imaging, elevated protein in the CSF, or neurology consultation. Venous thromboembolism required radiographic confirmation. Cause of death was classified by the clinicians as primary respiratory, cardiovascular, multiorgan failure, neurological, or other.

Bacterial Co-Infections

Bacterial co-infection was defined as any patient with presumed bacterial pneumonia within 72 hours of ICU admission documented in their medical record even if cultures were negative or any patient with a positive blood culture in the first 72 hours. In patients with presumed bacterial pneumonia, positive and negative bacterial culture results from expectorated sputum, or lower respiratory tract (endotracheal or bronchoalveolar lavage) specimens were collected. Positive blood cultures in the first 72 hours were also collected.

Statistical Analysis

Proportions were compared with chi-square testing. Continuous variables are listed as means with standard deviations or medians with interquartile ranges and compared using independent samples t-testing or Wilcoxon-Rank Sum testing. The primary analysis compared patients with bacterial co-infection to those without co-infection. Results from influenza diagnostic testing were compared according to type of test and location of specimen. RT-PCR results from lower and upper respiratory tract sources were compared if the tests were done within 3 days of each other.

SAS version 9.2 (SAS Institute, Cary, N.C. USA) was used for descriptive, bivariate, and multivariable analyses. Patients with presumed bacterial co-infection but no positive cultures from blood or respiratory secretions were excluded in a sensitivity analysis. These sensitivity analyses compared demographics, clinical characteristics, ICU course, and clinical outcomes in patients without co-infection with the subset of co-infected patients who had positive cultures (i.e. excluding those with presumed bacterial co-infection but no positive cultures from blood or respiratory secretions). Because these sensitivity analyses demonstrated no differences when patients with presumed bacterial co-infections without positive cultures were excluded, only the analyses with all 207 patients with presumed

bacterial co-infection are reported in the manuscript. A comparison of co-infected patients with and without positive cultures is included in the appendix. Bivariate analyses used chi-square and Fisher's exact tests to examine the association between baseline clinical factors and 60-day mortality. Clinical factors such as demographics, ICU admission clinical conditions, including co-morbidities and co-infections, and ICU course were chosen *a priori*. Factors demonstrating a significant unadjusted association with 60-day mortality ($P \leq 0.10$) were included in subsequent multivariable analyses. The final multivariable model using SAS's PROC GENMOD (19) contained all independent predictors of mortality ($P < 0.05$). Adjusted risk estimates are reported with 95% confidence limits. Kaplan-Meier curves were utilized to demonstrate survival and ventilator-dependent time.

RESULTS

Data from 683 patients with confirmed or probable pH1N1 were obtained from 35 participating hospitals. Of these, 424 (62.1%) were *confirmed* and 259 (37.9%) were *probable* cases. Most patients were in the ICU between September and December 2009, with almost half during October and November (Figure 1a).

Demographics

Patients ranged from 13–92 years old with a mean age of 45 ± 16 years old (Figure 1b). Slightly less than half were male (Table 1). Most patients were obese with mean body mass index (BMI) of 32.5 ± 11.1 kg/m^2; 52% had a BMI ≥30 kg/m^2 and 32% had a BMI ≥35 kg/m^2. Comorbid conditions were present in 519 (76%) patients; diabetes and underlying lung disease were the most common (Table 1). Immunosuppression was present in 170 (24.9%) patients with human immunodeficiency virus (HIV) infection the cause in 11% of these cases. Baseline demographics were similar between patients with and without bacterial co-infection on admission with the exception that those with bacterial co-infection were less likely to have diabetes (Table 1).

Presentation

Presenting symptoms did not differ significantly between patients with and without presumed bacterial co-infection (Table 2). On average, patients with and without presumed bacterial co-infection presented to the hospital (5.2 ± 4.9 vs. 5.0 ± 4.5 days; P=0.66) and ICU (5.8 ± 5.3 vs. 5.8 ± 4.5 days; P=0.94) within a similar timeframe after onset of symptoms.

On admission, the cohort had an average APACHE II score of 21 ± 9 and a Sequential Organ Failure Assessment (SOFA) score of 7.0 ± 3.5. Respiratory and central nervous system dysfunction were the most prevalent (Table 1). Co-infected patients had higher APACHE (P=0.008) and SOFA scores (P<0.001) compared to those without infection (Table 1).

Respiratory failure and/or lower respiratory tract infection was the most common reason for ICU admission. Shock was present in 90 (13.2%) patients at ICU admission, with 35 receiving high doses of vasopressors (i.e. norepinephrine > 0.1 mcg/kg/min). Myositis was common on admission, with 27.5% of patients presenting with a CPK above 500 U/L. Renal dysfunction was also seen with 18 (2.8%) patients receiving RRT for acute renal failure on ICU admission.

Most patients (n=486, 71.2%) had pulmonary infiltrates on chest radiographs with an average of 2.6 quadrants involved whether or not there was a bacterial co-infection. On the day of ICU admission, more patients with co-infections received mechanical ventilation than those without (63 vs. 52%; P=0.005) and a third of both groups received non-invasive

ventilation. The mean admission P/F was 151 ± 114 and the mean S/F was 157 ± 124 (Table 3).

Influenza Diagnostic Testing

On average, 2.2 ± 1.4 tests for influenza were recorded per patient. RT-PCR was performed most often (1.2 ± 0.9 PCR tests/patient) followed by rapid influenza antigen testing (0.4 ± 0.6/patient), viral culture (0.3 ± 0.7/patient) and direct fluorescent antibody staining (DFA) (0.3 ± 0.7/patient). For confirmed cases, both rapid influenza antigen tests and DFA had low sensitivity (29% and 24% respectively) compared to RT-PCR. Fifty-two patients had RT-PCR results from both lower and respiratory tract specimens collected within a three day period. Fifty-five percent of the lower tract specimens were positive for pH1N1 by RT-PCR compared to 38% of upper tract specimens.

Bacterial Co-Infections

Within 72 hours of ICU admission, 207 (30.3%) pH1N1 cases had a presumed bacterial co-infection. Of these, 84 (40.6%) had bacteria identified from sputum or lower respiratory specimens, 50 (24.2%) had bacteremia, 20 (9.7%) had both positive respiratory tract cultures and bacteremia, and 53 had presumed bacterial pneumonia with negative (n=52) or no (n=1) cultures (Table 2). Sensitivity analysis excluding these 53 patients with presumed bacterial co-infection but without any positive cultures demonstrated no difference in demographics (appendix Table 1), clinical presentation (appendix table 2), ICU clinical course (appendix table 3), or outcomes (appendix table 4). A similar proportion of the 53 patients presumed to have bacterial co-infection but without any positive cultures presented in shock (11.2%) as the 154 with positive bacterial cultures of blood or sputum (13.6%).

Patients with presumed bacterial co-infections presented with similar temperatures, leukocyte counts, and P/ F ratios as those without co-infections. Shock was present on admission in 21.3% of patients with compared to 10% of patients without bacterial co-infection (P=0.0002). *Staphylococcus aureus* was the most common pathogen with bacteremia in 23 cases. *Streptococcus pneumoniae* was identified in 17 patients; 10 with bacteremia. Four patients had group A *Streptococcus* in lower respiratory tract specimens on admission, with two patients also bacteremic. *Staphylococcus aureus* and *Pseudomonas* species were the most common pathogens identified in respiratory secretions after 72 hours from patients presenting without bacterial co-infections. Sixteen patients (6.3% of those with bacterial infections) had parapneumonic effusions or empyemas requiring drainage via thoracostomy tube or surgery.

Clinical Course

The median ICU length of stay was 5 days (IQR 2–11) (mean 9.3 ± 8.6). Patients without a bacterial co-infection had a shorter ICU length of stay (median 6; IQR 2–13; mean 8.8 ± 8.3 days) than co-infected patients (median 7; IQR 3–13; mean 10.4 ± 9.1 days; P=0.05).

The majority of patients were mechanically ventilated during their ICU stay (n=478, 66%), with an average duration of 10.5 days (Figure 2). Mechanical ventilation was more common in patients who presented with a bacterial co-infection (74 vs. 63%, P=0.008) (Table 4). 231 (33.8%) patients received non-invasive positive pressure ventilation, 175 (76%) of whom eventually were mechanically ventilated. Over three-fourths of patients still in the ICU on day 7 (n=355) were receiving mechanical ventilation as were 87% still in the ICU on day 14 (n=200)(Table 3). Thirteen percent of patients underwent tracheostomy.

The respiratory system represented the most common and persistent organ dysfunction (Table 3). At least one “rescue therapy” was used in 119 (17.4%) patients; inhaled nitric

oxide or epoprostenol (10.4%), high frequency ventilation (8.1%), prone ventilation (5.3%), or extracorporeal membrane oxygenation (ECMO) (3.5%) (Table 4). Of the 119, 49 (41.2%) received more than one form of rescue therapy.

Cardiovascular dysfunction was also common and prolonged with 211 (30.9%) patients experiencing shock at some time and 20% of those in the ICU on day 3 in shock, 18% on day 7, and 21% on day 14. Patients without a bacterial co-infection had a high incidence of shock, with 17%, 20%, and 24% of those still residing in the ICU receiving vasopressors on days 3, 7, and 14, respectively. Overall, 14% of patients received new RRT for acute renal failure. Venous thromboembolism was confirmed in 9% of patients. Seizure, myocarditis, and encephalitis were rare, occurring in 2%, 1% and 1% of patients, respectively.

Treatment

Only 51 (7%) patients received antiviral treatment for influenza prior to ICU admission. Although low, a higher proportion of patients presenting after September 1, 2009 had antiviral treatment initiated before ICU admission compared with those presenting earlier in the pandemic (8.5% vs. 3.2%; P=0.04). Neuraminidase inhibitors were administered to nearly all patients while in the ICU. Ninety-three percent received oseltamivir for 5 (IQR 3–7) days, with 66% and 28% receiving 75 mg and 150 mg twice daily, respectively. About 4% of patients were treated with intravenous peramivir and 2% received inhaled zanamivir. Amantadine or rimantadine were used in 50 (7.3%) patients in combination with a neuraminidase inhibitor.

Survival

All-cause 28-day and 60-day hospital mortality were 21.8% and 23.4%, respectively (Table 4). Ten percent of deaths occurred after ICU day 28 (Figure 2). Mortality was 31% in those who presented with bacterial co-infection compared to 21% in those without (P=0.002). Respiratory and multi-organ failure were the most common primary causes of death, regardless of bacterial infection status, accounting for 43% and 37% of deaths, respectively. Only 5% of patients died of primary cardiovascular failure.

In multivariable analysis, age (RR 1.01/yr; 95%CI 1.00–1.02) and immunosuppression (RR 1.57; 95%CI 1.20–2.06) were both independently associated with higher mortality (Appendix Table 1). Previously healthy patients experienced lower mortality (RR 0.58; 95%CI 0.38–0.89) compared to patients with comorbidities. Shock at presentation, (RR 2.09; 95%CI: 1.44–3.03) and baseline oxygenation (i.e. P/F or S/F) (RR 0.99; 95%CI: 0.99–1.00) were both independent predictors of mortality. BMI was not independently associated with mortality. Although bacterial infection was not independently associated with mortality (RR 1.43; 95% CI: 0.95–2.14), co-infection with methicillin-sensitive *Staphylococcus aureus* at admission was independently associated with increased mortality (RR 2.82; 95% CI: 1.76–4.51; P<0.0001).

DISCUSSION

Critical illness with pH1N1 in this adult ICU cohort occurred predominantly in young, obese adults with a high prevalence of co-morbidities. The disease was typically characterized by acute hypoxemic respiratory failure from a rapidly progressive pneumonitis. Bacterial co-infection, especially with *Staphylococcal aureus*, was associated with a significant increment in morbidity and mortality, but our findings suggest that infection with pH1N1 virus and the resulting host response can also cause severe respiratory failure, shock, and multiorgan failure without apparent bacterial co-infection. The disease progressed rapidly to critical illness in patients both with and without presumed bacterial co-infection. Very few subjects

received antiviral therapy prior to admission, suggesting a potential missed treatment opportunity.

The prevalence of bacterial co-infection while similar to that previously reported for pH1N1 and a commonly collected pediatric cohort (8,9,17), but higher than that seen in Spanish ICUs which required positive cultures (20). Bacteremia was common, occurring in 34% of those suspected of having a bacterial co-infection, most of which had presumed pneumonia. As others have reported, *Staphylococcus aureus* and *Streptococcus pneumoniae* were the most common respiratory isolates (8,9,17,20). Co-infection on admission was associated with a higher severity of illness, increased incidence and severity of shock, and greater likelihood of requiring mechanical ventilation (20). Furthermore, in unadjusted analyses bacterial co-infection was associated with higher mortality and longer duration of mechanical ventilation (20), possibly suggesting early empiric antimicrobial treatment may improve clinical outcomes.

Substantial controversy persists over the cause of mortality during the 1918 pandemic, with recent analyses of the historical record supporting the conclusion that the virus caused a mild illness that enabled colonizing strains of bacteria to cause lethal pneumonia (21). However, morbidity and mortality from pH1N1-associated critical illness cannot be attributed only to bacterial co-infections as 7% of patients without bacterial co-infection were in shock at presentation with 10% on vasopressors at ICU admission, 17% were on vasopressors on ICU day 3, 63% received mechanical ventilation during their ICU stay, and 20% died prior to hospital discharge.

The hypoxemic respiratory failure seen with pH1N1 critical illness appeared more severe than in patients with both other influenza viruses and other etiologies of lung injury (22,23). Patients received prolonged mechanical ventilation and nearly one in 5 received at least one “rescue therapy”, rates slightly higher than those reported in studies of patients with non-H1N1 ARDS (24). Respiratory failure was the most common cause of death which differs from other etiologies of acute lung injury where most patients die from multisystem organ failure (25). This observation may be explained in part by the tropism of pH1N1 virus for both the upper (i.e. tracheobronchitis) and lower airways and alveolar epithelium (8,9). Furthermore, the replication of pH1N1 virus is prolonged in the lower respiratory tract in critically ill patients and an exuberant local immune response in previously healthy young adults are additional possible explanations for severe lung injury (5,8,26). These factors may explain why diagnostic testing of lower airway specimens result in better sensitivity and specificity than upper airway samples. Our data confirm previous reports (27–29) of low sensitivity and specificity of rapid antigen tests and direct immunofluorescence assays for pH1N1 in critically ill individuals, especially in specimens from upper airways, and confirm the need for repeat testing, preferably from bronchoalveolar lavage or other lower airway sampling technique, if initial results are negative during a pandemic.

Immunosuppression was associated with more severe illness and a 60% higher risk of mortality: an incremental risk also found in the pediatric cohort (17) and similar to receiving high dose vasopressors on admission. Other studies have identified chronic co-morbidities (congestive cardiac failure, diabetes, underlying lung disease, morbid obesity), and pregnancy as risk factors for ICU admission with pH1N1 (3,14,30–32). In our cohort, none of these factors, including obesity or underlying lung disease, were independently associated with death, although similar to a previous study (6), baseline P/F or S/F levels were independently associated with mortality. Like our counterpart pediatric cohort (17), we found *Staphylococcus aureus* co-infection at admission, rather than pneumococcal pneumonia, as the organism associated with increased mortality (6). However, our

association was with methicillin sensitive (MSSA) strains as opposed to our pediatric cohort which found an association with methicillin resistant *Staphylococcus aureus* (MRSA).

Despite data from observational studies reporting less severe illness and survival benefit with early neuraminidase inhibitor treatment (3,12,32,33), only 7% of patients in this study received antivirals prior to ICU admission, and therefore we were unable to assess the impact of early oseltamivir treatment on outcomes. The reason for this is unknown, but possible explanations include unaccounted factors leading to delayed presentation or delay in or no antiviral treatment, failure to consider the diagnosis of pH1N1 despite an on-going influenza pandemic, insensitive initial diagnostic tests, and rapid disease progression. Although antiviral treatment prior to ICU admission increased late in the pandemic, utilization remained below 10%.

This study is subject to several limitations. First, similar to the pediatric cohort (17), 38% of the patients tested positive for influenza A without subtyping and were included in this cohort as probable pH1N1 cases. It is likely that these cases were pH1N1 cases since 99% of influenza A virus strains tested during the study period were identified as pH1N1 virus (34). Second, this was a survey of clinical characteristics and practice and we did not standardize the diagnostic approach to bacterial co-infection but relied on a clinical diagnosis by the treating ICU physicians, even if respiratory cultures were negative. Thus we may have overestimated the proportion of pH1N1 virus-infected patients with bacterial co-infection. Sensitivity analysis demonstrates that patients presumed to have bacterial co-infection on ICU admission but without positive cultures were not sicker, and in fact, may have been slightly less ill with lower severity of illness scores, less shock and less mechanical ventilation on admission compared to the patients in the co-infection cohort with positive cultures. However, it is still possible that the sicker patients were more likely presumed to have bacterial pneumonia or were subject to more extensive testing, potentially confounding the association between bacterial co-infection and increased severity of illness and introducing potential bias in the difference in outcomes. Furthermore, most patients in this study had neither a clinical suspicion nor positive cultures for bacteria yet were critically ill with multisystem organ failure. Thus, these findings support a role for pH1N1 infection per se in the genesis of a syndrome most clinicians associate with bacterial infections. In addition, administration of broad-spectrum antibiotics and the unknown sensitivity and specificity of bacterial cultures of blood and respiratory specimens for identifying the etiology of pneumonia may confound negative culture results, potentially underestimating certain co-infections like *Streptococcus pneumoniae* which have been identified with greater frequency in other studies (6). In addition, unknown specificity of respiratory specimen culture results in identifying the etiology of pneumonia also may have resulted in an overestimation of the incidence of bacterial co-infection. Further, we did not collect time to or appropriateness of antibiotics which also likely plays a key role in clinical outcomes. Finally, since our study was limited to patients admitted to ICUs, the associations found between co-infections and morbidity and mortality may not be generalizable to non-critically ill populations.

CONCLUSION

Although pH1N1 influenza virus caused severe respiratory and multiorgan failure and death without apparent bacterial co-infection, co-infection, especially with *Staphylococcus aureus* was associated with a significant increase in morbidity and mortality among ICU patients. Despite the pH1N1 pandemic being declared over, pH1N1 virus continues to circulate worldwide, and antigenic drift is expected. Changes in viral characteristics are unpredictable, but we speculate circulating strains of pH1N1 virus will continue to cause critical and fatal multi-organ system complications, with or without invasive bacterial co-

infection. Accordingly, prevention efforts, including vaccination, encouragement of symptomatic patients to seek early medical care, especially those at high-risk for influenza complications, and early neuraminidase inhibitor treatment, may help prevent progression to critical illness. While we will never know if immunization and early and more widespread use of empiric antiviral therapy would have improved outcomes, our findings suggest that antiviral therapy should be considered for patients with comorbidities and even healthy subjects with severe symptoms during a pandemic. Initial negative influenza test results do not exclude influenza virus infection, and multiple specimens from different respiratory sites may be needed for confirmation, preferably by RT-PCR. Furthermore, for severely ill patients, empiric neuraminidase inhibitor treatment and antibiotic therapy with *Staphylococcus aureus* and MRSA coverage should be considered in the treatment plan and initiated as soon as possible (35).

Acknowledgments

Andrea L. Harabin, PhD, NHLBI

Funding Source: NHLBI N01-HR-56179

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention

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Appendix

Appendix Table 1

Baseline demographics by infection status

	Culture Confirmed Clinical Bacterial Coinfection (72hrs) (n = 154)	All Presumed Bacterial Coinfection (72 hrs) (n = 207)
Age (SD)	45.4 ± 16.2	45.1 ± 16.7
Body mass index (SD), kg/m^2	32.7 ± 12.2	32.3 ± 11.6
Male, %	49	47
Hispanic, %	19	16
Race, %		
White	70	70
Black	20	21
Asian	5	4
Other	1	1
Not Reported	3	4
Comorbidities, %		
Healthy prior to admission	25	26
Diabetes	25	22
Asthma	18	19
Chronic obstructive pulmonary disease	16	14
Congestive heart failure	12	13
Coronary artery disease	7	7
Chronic renal insufficiency	5	6
End-stage renal disease (chronic dialysis)	4	5
Immunosuppressed	23	24
Obese (i.e. body mass index ≥30)	50	50
Morbidly obese (i.e. body mass index ≥40)	14	11
Pregnancy	2	1
Tobacco Use		
Current	32	30
Past	13	14
Pre-intensive care unit admission location (%)		
Emergency department	54	50
Hospital floor	18	20
Referring intensive care unit	15	17
Home	1	0.5
Other/unknown	13	12
Acute Physiology and Chronic	24.1 ± 9.0	23.1 ± 9.3

	Culture Confirmed Clinical Bacterial Coinfection (72hrs) (n = 154)	**All Presumed Bacterial Coinfection (72 hrs) (n = 207)**
Health Evaluation II (SD)		
Total Sequential Organ Failure Assessment (SD)	7.1 ± 3.6	6.9 ± 3.7
Respiratory component	2.8 ± 1.1	2.7 ± 1.1
Cardiovascular	0.9 ± 1.5	0.8 ± 1.4
Nervous system	1.9 ± 1.7	1.7 ± 1.7
Coagulation	0.5 ± 0.8	0.6 ± 0.9
Renal	0.8 ± 1.1	0.8 ± 1.1
Liver	0.4 ± 0.8	0.4 ± 0.8
Preamission medicines, %		
Aspirin	15	14
Nonsteroidal anti-inflammatory drugs	16	17
Statin	11	12
Influenza antivirals	6	8
Corticosteroids	14	14

Sensitivity analysis comparing co-infection group limited to only patients with documented positive cultures from blood or respiratory secretions to all presumed bacterial coinfected patients.

Appendix Table 2

Clinical presentations

	Culture Confirmed Clinical Bacterial Coinfection (72 hrs) (n = 154)	All Presumed Bacterial Coinfection (72 hrs) (n = 207)
Symptoms, %		
Cough	71	72
Dyspnea	71	74
Fever	71	73
Myalgias	31	31
Vomiting	22	20
Nausea	22	22
Diarrhea	18	19
Altered mental status	10	10
Reason for intensive care unit admission, %		
Lower respiratory tract disease	55	59
Respiratory failure	61	61
Shock	14	13
Central nervous system symptoms	1	1
Cardiac arrest	4	4
Bacterial coinfection[a] (%)	154 (100%)	207 (100%)
Respiratory culture positive (%)	104 (68%)	104 (50%)
Staphylococcus aureus (MRSA) (%)	29 (19%)	29 (14%)
Staphylococcus aureus (MSSA) (%)	18 (12%)	18 (9%)
Streptococcus pneumoniae (%)	17 (11%)	17 (8%)
Group A Streptococcus (%)	4 (3%)	4 (2%)
Bacteremia within 72 hours[b] (%)	70 (45%)	70 (34%)
Staphylococcus aureus (MRSA) (%)	15 (10%)	15 (7%)
Staphylococcus aureus (MSSA) (%)	8 (5%)	8 (4%)
Streptococcus pneumoniae (%)	10 (6%)	10 (5%)
Duration of symptoms to hospitalization (SD), days	5.3 ± 5.1	5.2 ± 4.9
Duration of symptoms to intensive care unit admission (SD), days	5.6 ± 5.1	5.8 ± 5.3
Temperature (SD), °C	38.0 ± 5.0	37.8 ± 4.4
Glasgow Coma Scale	9.9 ± 5.0	10.4 ± 4.8
Systolic blood pressure (SD), mm Hg	119 ± 30	121 ± 30
Vasopressors at admission, %	23	21

	Culture Confirmed Clinical Bacterial Coinfection (72 hrs) (n = 154)	All Presumed Bacterial Coinfection (72 hrs) (n = 207)
Mechanical ventilation at admission, %	69	63
Noninvasive positive pressure ventilation on admission, %	36	34
Creatinine (SD), mg/dL	1.6 ± 1.7	1.7 ± 1.7
Total bilirubin (SD), mg/dL	1.1 ± 1.4	1.1 ± 1.9
Creatine phosphokinase (SD), U/L	906 ± 1478	770 ± 1317
White blood cell count (SD), $\times 10^3/mm^3$	11.9 ± 10.3	11.4 ± 10.3
Lymphopenia, %[c]	17	15
Platelets (SD), $\times 10^9/L$	196 ± 102	193 ± 102

MRSA, methicillin-resistant *Staphylococcus aureus;* MSSA, methicilin-sensitive *S. aureus;*

Sensitivity analysis with coinfection group limited to only patients with documented positive cultures from blood or respiratory secretions to all presumed bacterial coinfected patients.

[b] The 48 patients in the no coinfection group had positive cultures from respiratory secretions collected after 72 hrs in the ICU;

[b] defined as positive blood culture within 72 hrs of admission;

[c] absolute lymphocyte count < $1000/mm^3$.

Appendix Table 3

Intensive care unit clinical course

	Culture Confirmed Clinical Bacterial Coinfection (72 hrs) (n = 154)	All Presumed Bacterial Coinfection (72 hrs) (n = 207)
Number still in intensive care unit		
Baseline	154	207
Day 3	131	176
Day 7	92	121
Day 14	53	67
% on mechanical ventilation		
Baseline	69	63
Day 3	79	73
Day 7	83	81
Day 14	85	84
Ventilator parameters		
Positive end-expiratory pressure (SD), cm H_2O		
Day 3	11.8 ± 6.3	12.3 ± 6.9
Day 7	12.2 ± 6.8	12.1 ± 6.7
Day 14	12.0 ± 7.4	12.1 ± 7.2
Pao_2 /Fio_2 (SD)		
Baseline	153 ± 119	154 ± 119
Day 3	152 ± 103	154 ± 99
Day 7	152 ± 110	177 ± 125
Day 14	165 ± 97	169 ± 96
Spo_2/Fio_2 (SD)		
Baseline	154 ± 123	145 ± 116
Day 3	169 ± 106	176 ± 107
Day 7	183 ± 98	181 ± 92
Day 14	166 ± 88	180 ± 88
% on dialysis		
Day 3	10	11
Day 7	11	13
Day 14	15	15
% on vasopressors		
Baseline	23	21
Day 3	25	27
Day 7	12	15
Day 14	15	15

	Culture Confirmed Clinical Bacterial Coinfection (72 hrs) (n = 154)	**All Presumed Bacterial Coinfection (72 hrs) (n = 207)**
Creatinine (SD), mg/dL		
Baseline	1.6 ± 1.7	1.7 ± 1.7
Day 3	1.6 ± 1.5	1.7 ± 1.5
Day 7	1.6 ± 2.1	1.6 ± 1.9
Day 14	1.7 ± 1.8	1.6 ± 1.7
Total bilirubin (SD), mg/dL		
Baseline	1.1 ± 1.4	1.1 ± 1.9
Day 3	1.4 ± 1.8	1.3 ± 1.8
Day 7	1.4 ± 2.2	1.8 ± 3.7
Day 14	1.8 ± 3.6	2.8 ± 6.1
Platelets (SD), $\times 10^3/mm^3$		
Baseline	196 ± 102	193 ± 102
Day 3	178 ± 100	173 ± 97
Day 7	248 ± 127	248 ± 136
Day 14	305 ± 199	297 ± 198
Total Sequential Organ Failure Assessment score (SD)		
Baseline	7.1 ± 3.6	6.9 ± 3.7
Day 3	7.8 ± 4.0	7.7 ± 4.2
Day 7	7.2 ± 3.0	7.1 ± 3.2
Day 14	7.3 ± 3.8	7.4 ± 3.7

Sensitivity analysis with coinfection group limited to only patients with documented positive cultures from blood or respiratory secretions to all presumed bacterial coinfected patients.

Appendix Table 4

Clinical outcomes

	Culture Confirmed Clinical Bacterial Coinfection (72 hrs) (n = 154)	All Presumed Bacterial Coinfection (72 hrs) (n = 207)
Twenty-eight-day mortality, %	31	29
Sixty-day hospital mortality, %	32	31
Ventilator days (to day 28) (SD)	13.7 ± 11.9	13.0 ± 12.0
Intensive care unit days (to day 28) (SD)	10.8 ± 9.3	10.4 ± 9.1
Ever ventilated, %	79	74
Any rescue ventilation, %	23	23
Nitric oxide or inhaled epoprostenol, %	15	14
Extracorporeal membrane oxygenation, %	5	5
High frequency ventilation, %	12	11
Prone ventilation, %	10	10
Ever on vasopressors, %	40	39
Ever on dialysis, %	19	20
Development of pulmonary embolism/venous thromboembolic disease, %	11	10
Tracheostomy, %	18	17

Sensitivity analysis with coinfection group limited to only patients with documented positive cultures from blood or respiratory secretions to all presumed bacterial coinfected patients.

Appendix Table 5

Bivariate and multivariable analyses for mortality

Bivariate Analysis	Odds Ratio	95% Confidence Interval for Odds Ratio		*p*
		Lower	Upper	
High dose vasopressors at baseline	2.32	1.62	3.31	<.001
Immunosuppression	2.24	1.46	3.45	.002
Cirrhosis	2.12	1.31	3.44	.01
Days of symptoms prior to admission, day	1.74	1.01	3.01	.033
Suspected any bacterial coinfection	1.67	0.77	3.60	.24
Corticosteroids at baseline	1.43	1.03	1.97	.04
Low dose vasopressors at baseline	1.31	0.85	2.03	.24
Coinfection with MSSA	1.31	0.83	2.07	.27
Male gender	1.28	0.98	1.66	.07
Coinfection with *Staphylococcus pneumoniae*	0.97	0.41	2.31	.95
Hispanic ethnicity	0.91	0.60	1.36	.63
Diabetes	0.90	0.66	1.24	.52
African American race	0.89	0.63	1.25	.49
Coinfection with MRSA	0.88	0.43	1.81	.72
Chronic lung disease	0.81	0.61	1.09	.16
Previously healthy	0.62	0.41	0.94	.02
Pregnancy	0.58	0.20	1.67	.28
New acute renal replacement therapy (chronic dialysis patients excluded) at admission	0.50	0.20	1.27	.11
Multivariable Analysis	**Odds Ratio**	**95% Confidence Interval for Odds Ratio**		***p***
		Lower	**Upper**	
Bacterial coinfection with MSSA	2.82	1.76	4.52	<.0001
High dose vasopressors at intensive care unit admission	2.09	1.44	3.03	<.0001
Immunosuppression	1.57	1.20	2.06	.001
Other bacterial confection	1.43	0.95	2.14	.084
Age, yrs	1.01	1.00	1.02	.02
Pao_2 /FIo_2 or Spo_2/FIo_2	0.99	0.99	1.00	<.0001
Chronic lung disease	0.76	0.58	1.02	.064
Healthy	0.58	0.38	0.89	.013

MRSA, methicillin-resistant *Staphylococcus aureus;* MSSA, methicilin-sensitive *S. aureus.*

High dose vasopressors ≥15 μg/min norepinephrine or equivalent. Days of symptoms prior to admission is reported per day.

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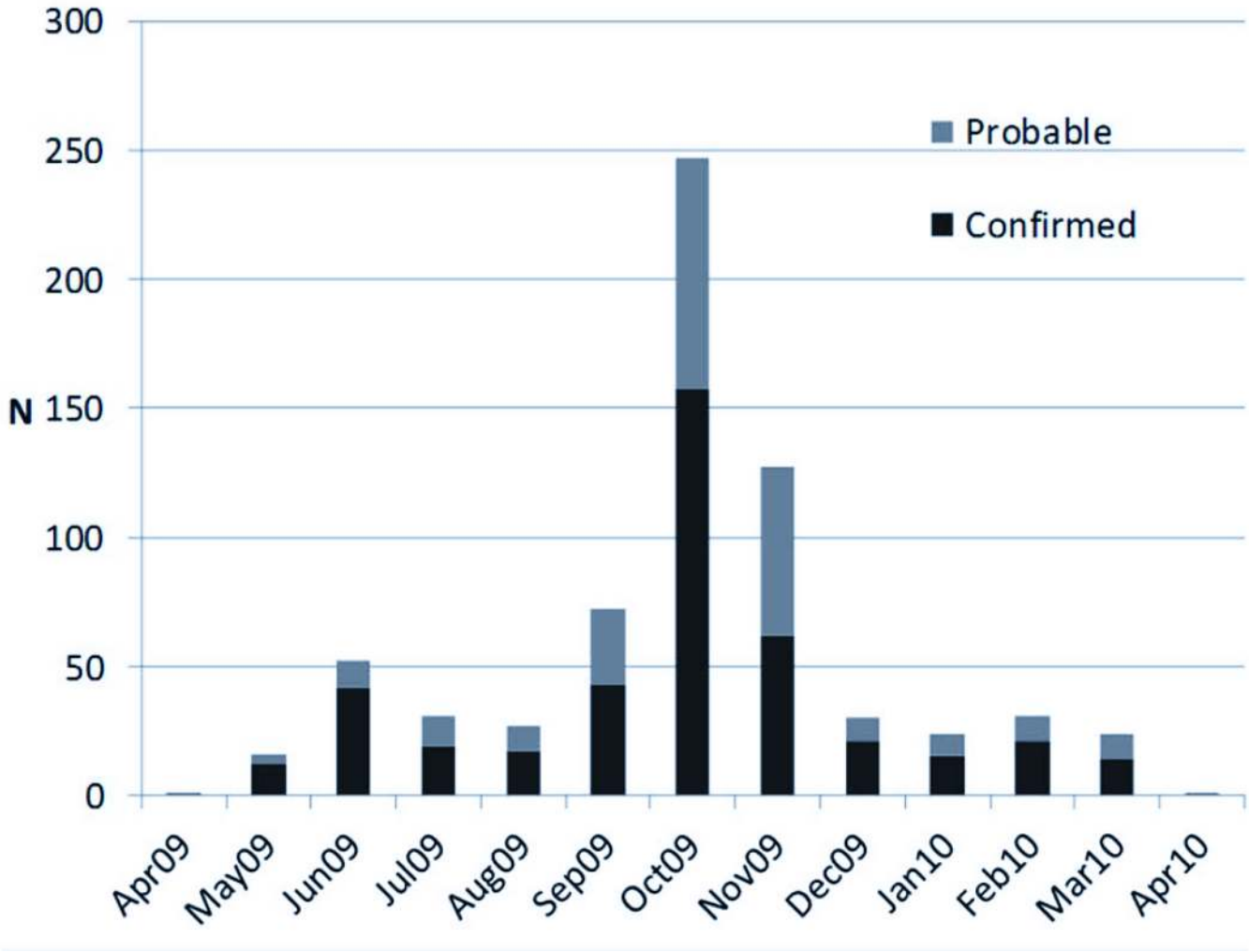

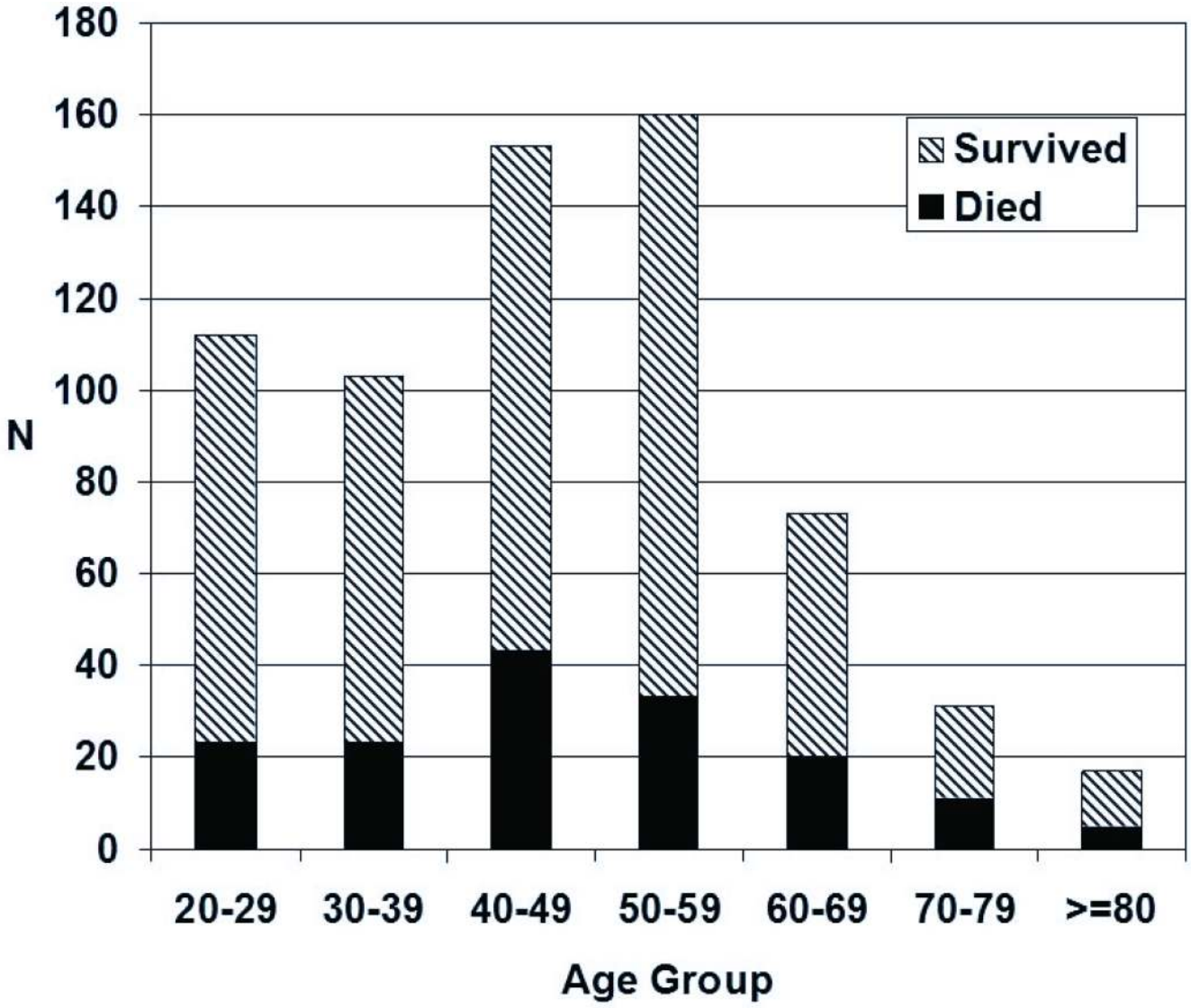

Figure 1.

a. Timing of pH1N1 Cases. Number of influenza cases by testing result by month.

b. pH1N1 Cases by Decades of Age. Number of cases by decade of age, divided into survivors and non-survivors.

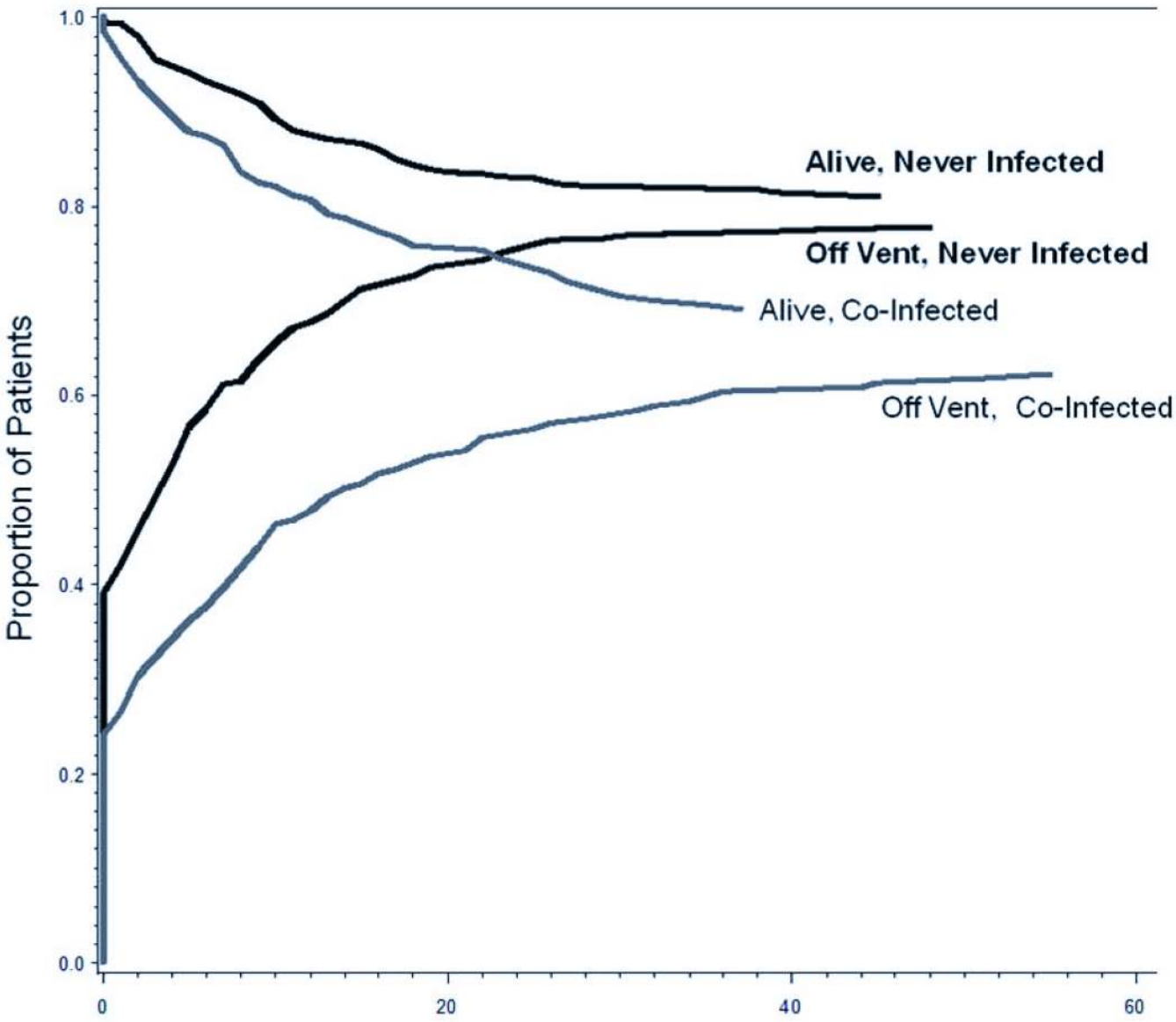

Figure 2. Funnel Plot of Survival and Ventilator Days in pH1N1 Patients with and without Bacterial Co-Infection

The top and bottom black lines represent survival and liberation from mechanical ventilation, respectively, in patients with pH1N1 and no co-infection. The top and bottom gray lines represent the same thing in patients with pH1N1 and bacterial co-infection. Patients still on the ventilator are censored at time of death for liberation from mechanical ventilation plots.

Table 1

Baseline Demographics by Infection Status

	Clinical Bacterial Co-Infection (72hrs) (n=207)	No Bacterial Co-Infection (N=476)	All (n=683)
Age (s.d)	45.1 ± 16.7	45.1 ± 16.3	45.1 ± 16.4
BMI (s.d) (kg/m^2)	32.3 ± 11.6	32.6 ± 10.9	32.5 ± 11.1
Male (%)	47	44	45
Hispanic (%)	16	14	14
Race (%)			
White	70	66	67
Black	21	24	23
Asian	4	3	3
Other	1	3	2
Not Reported	4	3	4
Comorbidities (%)			
Healthy prior to admission	26	23	24
Diabetes	22	28	26
Asthma	19	22	21
COPD	14	17	16
CHF	13	12	12
CAD	7	5	6
CRI	6	7	6
ESRD (chronic dialysis)	5	5	5
Immunosuppressed	24	26	26
Obese (i.e. BMI ≥30)	50	53	52
Morbidly obese (i.e. BMI ≥40)	11	13	12
Pregnancy	1	2	2
Tobacco Use			
Current	30	29	30
Past	14	15	14
Pre-ICU Admission Location (%)			
Emergency Department	50	54	53
Hospital Floor	20	22	21
Referring ICU	17	12	13
Home	0.5	1	1
Other/Unknown	12	11	12
APACHE II (s.d.)	23.1 ± 9.3	20.5 ± 9.3	21.3 ± 9.4
Total SOFA (s.d.)	6.9 ± 3.7	5.4 ± 3.2	5.9 ± 3.4
Resp Component	2.7 ± 1.1	2.6 ± 1.1	2.6 ± 1.1
Cardiovascular	0.8 ± 1.4	0.4 ± 1.0	0.5 ± 1.1

	Clinical Bacterial Co-Infection (72hrs) (n=207)	**No Bacterial Co-Infection (N=476)**	**All (n=683)**
Nervous system	1.7 ± 1.7	1.21 ± 1.52	1.4 ± 1.6
Coagulation	0.6 ± 0.9	0.48 ± 0.82	0.5 ± 0.8
Renal	0.8 ± 1.1	0.7 ± 1.1	0.7 ± 1.1
Liver	0.4 ± 0.8	0.3 ± 0.6	0.3 ± 0.7
Pre-Admission Meds (%)			
Aspirin	14	15	15
NSAIDS	17	11	13
Statin	12	14	13
Influenza antivirals	8	7	7
Corticosteroids	14	14	14

BMI = Body Mass Index; COPD = Chronic Obstructive Pulmonary Disease; CHF = Congestive Heart Failure; CAD = Coronary Artery Disease; CRI = Chronic Renal Insufficiency; ESRD = End-stage Renal Disease; APACHE II = Acute Physiology and Chronic Health Evaluation II; SOFA = Sequential Organ Failure Assessment; NSAIDs = Non-steroidal Anti-inflammatory Drugs;

Table 2

Clinical Presentations

	Clinical Bacterial Co-Infection (72hrs) (n=207)	No Bacterial Co-Infection (N=476)	All (n=683)
Symptoms (%)			
Cough	72	76	74
Dyspnea	74	76	75
Fever	73	70	71
Myalgias	31	31	31
Vomiting	20	24	23
Nausea	22	25	24
Diarrhea	19	19	19
Altered Mental Status	10	15	14
Reason for ICU Admission (%)			
Lower Resp tract disease	59	53	55
Resp Failure	61	42	47
Shock	13	7	9
CNS symptoms	1	1	1
Cardiac Arrest	4	2	2
Bacterial Co-Infection * (%)	207 (100%)	48 (10%)	255 (37%)
All Cultures Negative/Not Reported (%)	53 (26%)	N/A	53 (8%)
Respiratory Culture Positive (%)	104 (50%)	48 (10%)	152 (22%)
S. aureus (MRSA) (%)	29 (14%)	9 (2%)	38 (6%)
S. aureus (MSSA) (%)	18 (9%)	1 (0.2%)	19 (3%)
S. pneumoniae (%)	17 (8%)	2 (0.4%)	19 (3%)
Group A Strep (%)	4 (2%)	0	4 (0.6%)
Bacteremia within 72 hours ** (%)	70 (34%)	N/A	70 (10%)
S. aureus (MRSA) (%)	15 (7%)	N/A	15 (2%)
S. aureus (MSSA) (%)	8 (4%)	N/A	8 (1%)
S. pneumoniae (%)	10 (5%)	N/A	10 (1%)
Duration of symptoms to hospitalization (s.d) (days)	5.2 ± 4.9	5.0 ± 4.5	5.1 ± 4.6
Duration of symptoms to ICU admission (s.d.) days	5.8 ± 5.3	5.8 ± 4.5	5.8 ± 4.8
Temperature (s.d.) °C	37.8 ± 4.4	37.5 ± 3.2	37.6 ± 3.6
GCS	10.4 ± 4.8	11.9 ± 4.3	11.5 ± 4.5
SBP (s.d.) (mm Hg)	121 ± 30	126 ± 27	124 ± 28
Vasopressors at admission (%)	21	10	13
Mechanical Ventilation at admission (%)	63	52	55
NIPPV on admission (%)	34	32	33

	Clinical Bacterial Co-Infection (72hrs) (n=207)	**No Bacterial Co-Infection (N=476)**	**All (n=683)**
Creatinine (s.d.) (mg/dL)	1.7 ± 1.7	1.6 ± 1.9	1.6 ± 1.8
Total Bilirubin (s.d.) (mg/dL)	1.1 ± 1.9	0.8 ± 1.1	0.9 ± 1.4
CPK (s.d.) (U/L)	770 ± 1317	1192 ± 5836	1069 ± 4960
WBC (s.d.) ($\times 10^3$ / mm^3)	11.4 ± 10.3	12.0 ± 15.6	11.8 ± 14.2
Lymphopenia^ (%)	15	19	18
Platelets (s.d.) ($\times 10^9$ / L)	193 ± 102	203 ± 149	200 ± 136

GCS = Glasgow Coma Scale; SBP = Systolic Blood Pressure; NIPPV = Non-Invasive Positive Pressure Ventilation; CPK = Creatine PhosphoKinase; WBC = White Blood Cell Count;

* the 48 patients in the no co-infection group had positive cultures from respiratory secretions collected after 72 hours in the ICU;

** defined as positive blood culture within 72 hours of admission;

^ absolute lymphocyte count < 1000/mm^3

Table 3

ICU Clinical Course

	Clinical Bacterial Co-Infection (72hrs) (n=207)	No Bacterial Co-Infection (N=476)	All (n=683)
Number still in ICU			
Baseline	207	476	683
Day 3	176	394	570
Day 7	121	234	355
Day 14	67	133	200
% on Mechanical Ventilation			
Baseline	63	52	55
Day 3	73	67	69
Day 7	81	79	80
Day 14	84	88	87
Ventilator Parameters			
PEEP (s.d) (cm H_2O)			
Day 3	12.3 ± 6.9	11.2 ± 6.7	11.6 ± 6.8
Day 7	12.1 ± 6.7	11.7 ± 6.1	11.8 ± 6.3
Day 14	12.1 ± 7.2	10.7 ± 5.8	11.2 ± 6.3
P/F (s.d.)			
Baseline	154 ± 119	150 ± 112	151 ± 114
Day 3	154 ± 99	158 ± 97	157 ± 98
Day 7	177 ± 125	155 ± 88	162 ± 99
Day 14	169 ± 96	155 ± 88	160 ± 90
S/F (s.d.)			
Baseline	145 ± 116	162 ± 128	157 ± 124
Day 3	176 ± 107	189 ± 123	185 ± 119
Day 7	181 ± 92	175 ± 105	177 ± 100
Day 14	180 ± 88	182 ± 95	182 ± 92
% on Dialysis			
Day 3	11	9	10
Day 7	13	12	12
Day 14	15	17	16
% on Vasopressors			
Baseline	21	10	13
Day 3	27	17	20
Day 7	15	20	18
Day 14	15	24	21
Creatinine (s.d.) (mg / dL)			
Baseline	1.7 ± 1.7	1.6 ± 1.9	1.6 ± 1.8

	Clinical Bacterial Co-Infection (72hrs) (n=207)	No Bacterial Co-Infection (N=476)	All (n=683)
Day 3	1.7 ± 1.5	1.7 ± 2.1	1.7 ± 1.9
Day 7	1.6 ± 1.9	1.7 ± 1.5	1.6 ± 1.7
Day 14	1.6 ± 1.7	1.8 ± 1.7	1.8 ± 1.7
Total Bilirubin (s.d.) (mg / dL)			
Baseline	1.1 ± 1.9	0.8 ± 1.1	0.9 ± 1.4
Day 3	1.3 ± 1.8	1.0 ± 1.6	1.1 ± 1.7
Day 7	1.8 ± 3.7	1.4 ± 2.4	1.6 ± 3.0
Day 14	2.8 ± 6.1	1.9 ± 3.9	2.2 ± 4.8
Platelets (s.d.) ($\times 10^3$ / mm ^{3})			
Baseline	193 ± 102	203 ± 149	200 ± 136
Day 3	173 ± 97	185 ± 88	181 ± 91
Day 7	248 ± 136	235 ± 133	239 ± 134
Day 14	297 ± 198	295 ± 188	296 ± 190
Total SOFA Score (s.d.)			
Baseline	6.9 ± 3.7	5.4 ± 3.2	5.9 ± 3.4
Day 3	7.7 ± 4.2	6.5 ± 3.8	6.9 ± 4.0
Day 7	7.1 ± 3.2	7.2 ± 3.9	7.2 ± 3.6
Day 14	7.4 ± 3.7	7.9 ± 4.0	7.7 ± 3.9

PEEP = Positive End-Expiratory Pressure; P/F = PaO^2 / FiO^2; S/F = SpO^2 / FiO^2; SOFA = Sequential Organ Failure Assessment

Table 4

Clinical Outcomes

	Clinical Bacterial Co-Infection (72hrs) (n=207)	No Bacterial Co-Infection (N=476)	All (n=683)
28-Day Mortality (%)	28.5	18.9	21.8
60-Day Hospital Mortality (%)	30.9	21.0	23.4
Ventilator Days (to day 28) (s.d.)	13.0 ± 12.0	9.5 ± 11.1	10.5 ± 11.5
ICU Days (to day 28) (s.d.)	10.4 ± 9.1	8.8 ± 8.3	9.3 ± 8.6
Ever Ventilated (%)	74	63	66
Any Rescue Ventilation (%)	23	15	17
Nitric Oxide or Inhaled Epoprostenol (%)	14	9	10
ECMO (%)	5	3	4
High Frequency Ventilation (%)	11	7	8
Prone Ventilation (%)	10	3	5
Ever on Vasopressors (%)	39	24	29
Ever on Dialysis (%)	20	17	18
Development of PE/VTE (%)	10	8	9
Tracheostomy (%)	17	11	13

ECMO = Extracorporeal Membrane Oxygenation; PE = Pulmonary Embolism; VTE = Venous Thromboembolic disease