Invasive Group A Streptococcal Infection Concurrent with 2009 H1N1 Influenza

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We describe 10 patients with 2009 H1N1 influenza and concurrent invasive group A streptococcal infection with marked associated morbidity and mortality. Seven patients required intensive care, 8 required mechanical ventilation, and 7 died. Five of the patients, including 4 of the fatalities, were previously healthy.

Since the emergence of the 2009 H1N1 influenza virus, conflicting reports have been published about the role of bacterial coinfection in the severity of disease. Although recent studies have found bacterial coinfection in 29%–43% of fatalities with 2009 H1N1 influenza, several case series of hospitalized patients have noted the infrequent detection of bacterial coinfection, ranging 2%–4% [1–4]. Infection with Streptococcus pneumoniae or Staphylococcus aureus concurrent with seasonal influenza has been associated with severe morbidity and mortality [5]. Descriptions of severe illness due to coinfection with Streptococcus pyogenes (group A Streptococcus) have been uncommon. In this report, we describe 10 patients coinfected with 2009 H1N1 influenza and invasive group A Streptococcus (GAS), with associated severe morbidity and mortality.

Methods. Confirmed and probable cases of 2009 H1N1 influenza were reported to the California Department of Public Health (CDPH) by local health departments. Testing for influenza is recommended for hospitalized patients and patients who die with influenza-like illness (defined as temperature >37.8°C plus cough and/or sore throat). Patients who have influenza-like illness and real-time polymerase chain reaction (PCR) test results that are confirmed 2009 H1N1 influenza are considered to be confirmed cases of 2009 H1N1 influenza, whereas patients with influenza-like illness and real-time PCR test results positive for influenza A but negative for human subtypes H1 and H3 are considered to be probable cases of 2009 H1N1 influenza. Through 11 August 2009, health department and hospital staff completed standardized case report forms for all hospitalized patients and fatalities. Subsequently, individual case reports were completed only for intensive care unit (ICU) patients and fatalities. Medical records were reviewed to verify bacterial infection and to determine clinical course. Infections were considered to be invasive if GAS was isolated from a sterile site. GAS emm typing and typing of the streptococcal inhibitor of complement (sic) gene were performed by the CDPH Microbial Diseases Laboratory [6, 7].

Results. During 3 April–26 December 2009, there were 8075 hospitalized patients and/or fatalities with 2009 H1N1 influenza reported in California, including 1656 ICU patients and 461 fatalities. Of these 8075 persons, 10 patients with concurrent invasive GAS infection were identified (Table 1). Two of these patients were part of a household cluster of influenza-like illness; a third household member had invasive GAS but had negative test results for influenza.

The median age of the 10 patients with 2009 H1N1 influenza and invasive GAS infection was 37 years (range, 5–66 years); 3 were <18 years old. Six patients (60%) were male; 7 (70%) were Hispanic. The most common symptoms before admission were fever (in 10 [100%]), cough (in 8 [80%]), nausea or vomiting (in 7 [70%]), shortness of breath (in 7 [70%]), sore throat (in 5 [50%]), diarrhea (in 5 [50%]), and muscle aches (in 5 [50%]). None of the patients with sore throat had exudative pharyngitis. No patients had skin or soft-tissue infection. The median time from onset to hospital admission was 6 days (range, 4–14 days). All 9 patients who had chest radiographs performed had evidence of pneumonia. Seven patients required ICU support and mechanical ventilation. There were 7 fatalities; 4 of the fatalities occurred <24 hours after presentation at the hospital, including a patient who presented in full cardiac arrest. The median length of hospitalization for the 6 patients hospitalized ≥24 hours was 15 days (range, 1–71 days).

Five of the 10 patients were previously healthy, including 4 of the fatalities. Underlying medical conditions for the re-
<table>
<thead>
<tr>
<th>Identifier</th>
<th>Age in years, sex</th>
<th>Race or ethnicity</th>
<th>Comorbidities</th>
<th>Prodrome</th>
<th>Days from onset to admission</th>
<th>CXR findings</th>
<th>Hospitalized ≥24 hr</th>
<th>LOS</th>
<th>ICU</th>
<th>Intubated</th>
<th>Complications</th>
<th>Death</th>
<th>Rapid test result</th>
<th>Antiviral treatment</th>
<th>Antibiotic treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5, F</td>
<td>Hispanic</td>
<td>None</td>
<td>Fever, sore throat diagnosed as thrush, weakness, abdominal pain, and vomiting</td>
<td>5</td>
<td>RLL consolidation, diffuse infiltrates</td>
<td>No</td>
<td>&lt;24 hr</td>
<td>No</td>
<td>Yes</td>
<td>Pneumonia, sepsis, respiratory failure</td>
<td>Yes</td>
<td>Negative</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>2</td>
<td>9, F</td>
<td>Hispanic</td>
<td>None</td>
<td>Fever, vomiting, diffuse joint and muscle pain</td>
<td>5</td>
<td>NA</td>
<td>No</td>
<td>NA</td>
<td>No</td>
<td>Yes</td>
<td>Patient presented in full cardiac arrest</td>
<td>Yes</td>
<td>Positive</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>3</td>
<td>12, M</td>
<td>API</td>
<td>Exercise-induced asthma</td>
<td>Cough, SOB, chest pain</td>
<td>4</td>
<td>Large right-sided pneumonia with pleural effusion</td>
<td>Yes</td>
<td>9 days</td>
<td>No</td>
<td>Yes</td>
<td>Pneumonia, empyema</td>
<td>No</td>
<td>NA</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>4</td>
<td>35, M</td>
<td>Hispanic</td>
<td>HTN</td>
<td>Coughing with blood</td>
<td>7</td>
<td>Significant RUL infiltrate</td>
<td>Yes</td>
<td>12 days</td>
<td>No</td>
<td>No</td>
<td>Pneumonia, sepsis</td>
<td>No</td>
<td>NA</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>5</td>
<td>35, M</td>
<td>API</td>
<td>None</td>
<td>Fever, cough, progressive SOB, chest pain, vomiting of blood</td>
<td>7</td>
<td>Bilateral dense pulmonary consolidation</td>
<td>No</td>
<td>&lt;24 hr</td>
<td>Yes</td>
<td>Yes</td>
<td>Pneumonia</td>
<td>Yes</td>
<td>NA</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>6</td>
<td>39, M</td>
<td>Hispanic</td>
<td>None</td>
<td>Fever, progressive SOB, nausea, vomiting</td>
<td>14</td>
<td>Bilateral infiltrates</td>
<td>Yes</td>
<td>35 days</td>
<td>Yes</td>
<td>Yes</td>
<td>Pneumonia, empyema</td>
<td>No</td>
<td>Negative</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>7</td>
<td>39, F</td>
<td>Hispanic</td>
<td>None</td>
<td>Fever, cough, nausea, vomiting, shortness of breath, abdominal pain, and vomiting</td>
<td>7</td>
<td>Pneumomediastinum and bilateral LL pneumonia with infiltrates</td>
<td>Yes</td>
<td>1 day</td>
<td>Yes</td>
<td>Yes</td>
<td>Pneumonia, pneumomediastinum, ARDS</td>
<td>Yes</td>
<td>Negative</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>8</td>
<td>43, M</td>
<td>Unknown</td>
<td>Obesity, HTN, DM-II, renal disease</td>
<td>Fever, cough, sore throat</td>
<td>5</td>
<td>RML and RLL pneumonia</td>
<td>No</td>
<td>&lt;24 hr</td>
<td>Yes</td>
<td>Yes</td>
<td>Pneumonia, sepsis</td>
<td>Yes</td>
<td>NA</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>9</td>
<td>60, F</td>
<td>Hispanic</td>
<td>Cardiac disease, asthma, seizure disorder</td>
<td>Fever, cough, SOB, nausea, vomiting, diarrhea</td>
<td>0</td>
<td>RLL infiltrate, LLL consolidation</td>
<td>Yes</td>
<td>17 days</td>
<td>Yes</td>
<td>Yes</td>
<td>Pneumonia, sepsis, secondary bacterial pneumonia</td>
<td>Yes</td>
<td>Positive</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td>10</td>
<td>66, M</td>
<td>Hispanic</td>
<td>Obesity, DM-II, HTN</td>
<td>Fever, nausea, vomiting</td>
<td>7</td>
<td>Bilateral pulmonary infiltrates consistent with pneumonia</td>
<td>Yes</td>
<td>71 days</td>
<td>Yes</td>
<td>Yes</td>
<td>Pneumonia, possible septic shock</td>
<td>Yes</td>
<td>Negative</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

**NOTE.** API, Asian or Pacific Islander; ARDS, acute respiratory distress syndrome; CXR, chest x-ray; DM-II, type 2 diabetes mellitus; HTN, hypertension; ICU, intensive care unit; LL, lower lobe; LLL, left lower lobe; LOS, length of stay; NA, not applicable; RLL, right lower lobe; RML, right middle lobe; RUL, right upper lobe; SOB, shortness of breath.

a Initial test by polymerase chain reaction was negative for influenza.

b Patient received treatment and died on the same day.

c Part of a household cluster; a third family member described in the report had invasive group A streptococcal infection but had negative test results for influenza.

d Defined as body mass index ≥30.

e Patient died in a rehabilitation center, 82 days after initial hospital admission.
maintaining 5 patients included hypertension (3), obesity (2), type 2 diabetes mellitus (2), asthma (2), cardiac disease (1), renal disease (1), and seizure disorder (1). Six patients received antivirals and antibiotics within 48 hours of admission; 3 survived, 2 died <48 hours after admission, and 1 died 82 days after admission. None of the patients was vaccinated for either seasonal or 2009 H1N1 influenza during the 2008–2009 or 2009–2010 seasons.

All 10 patients had PCR results indicative of 2009 H1N1 influenza infection. Of the 6 patients who had rapid influenza testing performed, 4 initially had false-negative results. GAS was isolated from blood in all 10 patients; 9 had samples for culture obtained <24 hours after admission, and the remaining 1 had a sample for culture obtained during the autopsy performed 3 days postmortem. Five patients had isolates typed as emm 1.0 at CDPH Microbial Diseases Laboratory. Molecular typing of the sic gene, present in all strain M1 GAS isolates, revealed 3 sic alleles: sicl.02(3), sicl.13, and sicl.178.

Two of the 10 patients were part of a household cluster. In July 2009, a 39-year-old male developed influenza-like illness. During the next week, all other household members, including his diabetic 66-year-old father and his 35-year-old brother, developed similar symptoms. Household members shared a β-2 agonist inhaler that had been borrowed from a friend. The index patient, his brother, and his father developed increasing shortness of breath and simultaneously presented to the hospital with severe respiratory insufficiency that required ICU admission and mechanical ventilation. The index patient and his father tested positive for influenza by PCR; the younger brother tested negative. All had GAS bacteremia and presumed GAS pneumonia; the brothers also had GAS empyemas that required drainage. GAS isolates from all 3 patients were typed as emm 1.0 and sicl.02, suggestive of household transmission. The father never fully recovered; he died of respiratory failure and pneumonia 82 days later in a rehabilitation center.

Discussion. Although severe GAS infection concurrent with seasonal or 2009 H1N1 influenza has been previously described, to our knowledge this report describes the largest series to date. Other reports describing bacterial coinfection with seasonal influenza have focused on S. aureus [5, 8]. Similarly, reports of fatal 2009 H1N1 influenza cases have described S. pneumoniae and S. aureus as the most frequently identified causes of bacterial coinfections [2–4].

In contrast, GAS infection concurrent with either seasonal or 2009 H1N1 influenza has been less frequently reported. In 153 pediatric deaths that were associated with seasonal influenza in 2003–2004, 3 cases of concurrent GAS infection were identified by autopsy [9]. In 2 studies of 2009 H1N1 influenza fatalities, immunohistochemistry tests and PCR assays for bacteria identified GAS in 1 of 23 pediatric patients who had culture and/or pathology results and in the lungs of 6 of 77 patients overall [1, 2]. Although our numbers are also small, it is remarkable that 70% of the patients described in this series died, compared with an overall 6% mortality rate for hospitalized 2009 H1N1 influenza patients in California.

The mechanisms by which influenza increases the risk of contracting severe bacterial infection are still being determined. Some researchers have suggested that influenza may cause viral immunosuppression. An altered cytokine response may strip sialic acid from the lung, thus exposing receptors for bacterial adherence. Interestingly, early treatment with neuraminidase inhibitors, which interrupts the cleavage of sialic acids, may inhibit this mechanism [10]. Of the 9 patients in our series who required intensive care or died, 5 were previously healthy, reminding us that concurrent GAS infection and 2009 H1N1 influenza can lead to severe disease or death among persons who typically are not considered to be at risk for severe illness from either of these pathogens.

Notably, rapid tests for influenza gave false-negative results in 4 (67%) of 6 cases tested, which is consistent with observations of the suboptimal sensitivity of these tests for 2009 H1N1 influenza [11]. Three of the 6 patients who received treatment with antiviral drugs (all started <48 hours after admission) survived. Two fatalities who were treated had been ill 1 week before being hospitalized; both died <48 hours after admission. A third fatality died several months after treatment. Recent evidence suggests that early initiation of antiviral treatment (<48 hours after symptom onset) can reduce influenza mortality [12]. Although 2009 H1N1 influenza vaccine was not available at the time of infection in these cases, 1 study has found that seasonal influenza immunization may reduce the number of GAS infections [13].

In the household cluster described, all three patients required intensive care and mechanical ventilation. Although household transmission of GAS has been documented, the risk of invasive disease among household contacts remains rare. For this reason, the Centers for Disease Control and Prevention guidelines do not recommend routine testing or chemoprophylaxis of asymptomatic household contacts of persons with invasive GAS infection [14]. More study is needed to determine whether there should be routine testing and chemoprophylaxis of household contacts of persons with confirmed GAS infection during the current pandemic.

Our data are subject to several limitations, including limited case numbers and review of nonstandardized medical records. Case ascertainment was based on passive reporting by clinicians; underreporting may have occurred because of the nonspecificity of influenza-like illness and of the symptoms of GAS infection. In addition, not all influenza cases were tested for secondary bacterial infection, and the diagnostic sensitivity of performed tests may have been reduced by prior antibiotic treatment. Also, it is possible that not all invasive GAS infection
cases were tested for influenza and that, if they were tested, inaccurate rapid tests or samples obtained too late in the course of illness may have led to negative results.

In conclusion, our findings suggest that GAS infection concurrent with 2009 H1N1 influenza is often severe. Clinicians should remain vigilant for the possibility of severe illness caused by bacterial coinfection, including GAS infection. The performance of routine cultures of blood samples obtained early in the hospital course and before administration of antibiotics cannot be overemphasized. Although judicious use of antimicrobials is recommended, physicians should strongly consider early coverage for both 2009 H1N1 influenza and bacterial coinfection in critically ill patients suspected to have influenza.

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References