

## ***Streptococcus pneumoniae* Bacteraemia in a Young Man with Pandemic Influenza A (H1N1) 2009**

### **Dear Editor,**

The contributory role of bacterial infection to severe influenza illness during a pandemic is not entirely clear. The post-mortem samples of those who died between 1918 and 1919, the pre-antibiotic era, exhibited severe changes indicative of bacterial pneumonia; these are less well substantiated in the subsequent 2 pandemics in the 1950s and 1960s. Although primary viral pneumonia seems predominant in the current influenza pandemic, it is important not to overlook secondary bacterial infection. We report a confirmed case of 2009 pandemic influenza A (H1N1) infection in a young male, who had secondary *Streptococcus pneumoniae* bacteraemia and probable bacterial pneumonia.

In April 2009, 2 alarming reports were published by the US Centers for Disease Control and Prevention (CDC). One report described 2 cases of swine influenza in children living in neighbouring countries in California, who had no direct contact with pigs; the other described an outbreak in a school in New York City. Following that, the World Health Organization (WHO) sent out its first alert to the world on the emergence of a novel influenza virus. The virus was subsequently named as 2009 pandemic influenza A (H1N1). In Singapore, the virus was first detected on 26 May 2009, in a returning student from New York City. Local transmission of cases soon emerged, despite strict containment measures.<sup>1</sup> The initial local cases described by Liang et al<sup>2</sup> included mainly young returning travellers with no pre-existing medical illness. Secondary bacterial infection was not detected in the first 10 local cases. We report the first local case of bacteraemia involving a young foreign worker and discuss the role of bacterial infection in influenza pandemics.

### **Case Report**

The patient was a 29-year-old-male, an Indian national, who had no significant past medical illness and had not had any recent travel history. He was admitted for fever of 2 days' duration, which was associated with a productive cough and whitish sputum. Other pertinent symptoms included myalgia, lethargy and right pleuritic chest pain. He was not dyspnoeic and his oxygen saturation was 98% to 99% on room air, via pulse oxymetry. Significant physical examination findings included coarse crepitations over right middle and lower lobe lung areas. Laboratory investigations showed a leukocyte count of  $9.4 \times 10^9/L$ , with neutrophilic predominance; C-reactive protein was elevated beyond 380 mg/L and elevated procalcitonin at 5.07 ug/L. Nasal and throat swabs were positive for 2009 pandemic

influenza A (H1N1), via polymerase chain reaction (PCR) test. Chest X-ray showed consolidations in the right middle and lower zones (Fig. 1). A 5-day course of oseltamivir (tamiflu) (75 mg BD) together with empirical coverage for community-acquired pneumonia consisting intravenous amoxicillin-clavulanic acid (augmentin) (1.2 gm 8 hourly) and clarithromycin (500 mg BD) was started on the second day of hospitalisation.

Resolution of fever was noted on the 4<sup>th</sup> hospital day with concomitant improvement of cough and right-sided pleuritic chest pain (Table 1). Repeat nasal and throat swab for 2009 pandemic influenza A (H1N1) PCR test became negative on the 3<sup>rd</sup> hospital day or 5<sup>th</sup> day of illness. Two sets of blood culture grew *S. pneumoniae*, which was sensitive to penicillin. Sputum culture was not done. Antibiotics were de-escalated to intravenous penicillin 4 million units every 6 hours guided by sensitivity testing results. Patient was discharged after a week of parenteral antibiotic, following significant resolution of clinical symptoms. Penicillin was subsequently switched to oral amoxicillin (1 gm TDS) for another week, upon discharge.

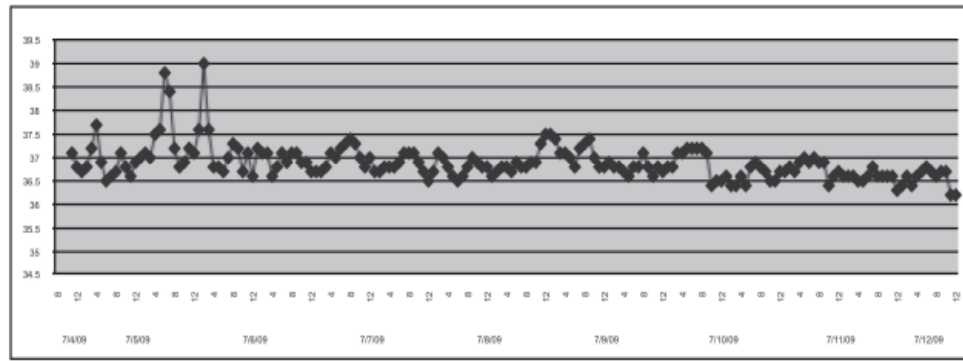
### **Discussion**

The early Mexican experience of the pandemic influenza A (H1N1) during March and April 2009 showed a disproportionately higher clinical case load among younger people<sup>3</sup> and that younger people were hospitalised for acute respiratory illness.<sup>4</sup> Of note, 44% of the hospitalised pneumonia cases had no pre-existing medical illness.<sup>4</sup> They identified that elevation of lactate dehydrogenase, creatine kinase and reduction of lymphocyte were common findings among ill cases.<sup>4</sup> Our patient was a young man with no prior medical illness. He had concurrent diagnoses of 2009 pandemic influenza A (H1N1) and *S. pneumoniae* bacteraemia, at presentation to our hospital.

Internationally, extensive studies have been conducted in an attempt to address



Fig.1. Chest X-ray.



fever	1	1	1	0	0	0	0	0	0
cough	1	1	1	1	1	0	0	0	0
pleuritic pain	1	1	1	1	1	1	1	1	0
chills	1	1	0	0	0	0	0	0	0
myalgia	1	1	0	0	0	0	0	0	0
H1N1 PCR	1	ND	0	0	ND	ND	ND	ND	ND
Blood culture	ND	1	ND	ND	ND	ND	ND	ND	ND
Oseltamivir	0	1	1	1	1	1	0	0	0
Amoxicillin-clavulanic acid	1	0	0	0	0	0	0	0	0
Penicillin	0	1	1	1	1	1	1	1	1

Table 1. Hourly Trend of Temperature, Clinical Symptoms, Influenza A (H1N1) 2009 PCR, Blood Culture, and Treatment. “1” denotes positive symptoms, influenza A (H1N1) 2009 PCR and blood culture positive, and treatment served. “0” denotes absence of symptoms and treatment not served. “ND” denotes not done.

the pertinent question of whether the pathogenesis of severe influenza illness with associated pneumonia during pandemics was primarily of viral aetiology, or a combination of viral and bacterial factors. When the tissue specimens obtained from influenza victims between 1918 and 1919 were re-examined, the epidemiologic, pathologic, and microbiologic data led to the conclusion that influenza A infection in conjunction with bacterial infection led to most of the deaths in the 1918 to 1919 pandemic.<sup>4</sup> *S. pneumoniae* was the single most common causative bacterium. In the subsequent 1957 to 1958 Asian pandemic, most deaths were attributable to secondary bacterial pneumonia; *Staphylococcus aureus* was predominant in the culture result.<sup>5-7</sup> The severity of illness and case fatality rate from pneumonia when influenza was a co-pathogen simultaneously with a bacterial pathogen was higher than in cases where the 2 infections were separated by some distinct period of recovery.<sup>6</sup> The 1968 Hong Kong influenza pandemic was mild and autopsy studies were uncommon.<sup>8</sup> In the USA, during the 1968 Hong Kong influenza pandemic, much of the excess mortality was attributed to the increased incidence of bacterial pneumonia. There was a strong correlation between staphylococcal pneumonia risk and prior influenza infection.<sup>9</sup>

As of 11 October 2009, the WHO reported more than 399,232 laboratory-confirmed cases of 2009 pandemic influenza A (H1N1) and more than 4753 deaths worldwide. The general consensus was that primary viral pneumonia was the most common finding in severe cases and a frequent cause of death.<sup>10</sup> The role of bacterial co-infection in the current

pandemic was examined on post-mortem lung specimens from fatal cases of 2009 pandemic influenza A (H1N1).<sup>11</sup> Of the 77 deaths examined, 22 (28.5%) had evidence of concurrent bacterial infection. The common bacterial pathogens included *S. pneumoniae*, *Streptococcus pyogenes*, *Staphylococcus aureus* and *Haemophilus influenzae*. This study underscores the important role of bacterial infection for early diagnosis and medical intervention as illustrated in this case report.

Understanding the interaction between virus and bacteria leading to respiratory illness is vital to effectively support the treatment and prevention of influenza infections. Animal studies suggested that the influenza virus can act synergistically with any of several pneumopathic bacteria, to produce a higher disease incidence and mortality rate, as well as a shortened time to death.<sup>5,11</sup> The mechanisms involved in such interactions are highly complex. The influenza virus is highly cytopathic to bronchial and bronchiolar epithelial cells, and can extend rapidly and diffusely down the respiratory tree. It can sufficiently damage the epithelium to break down the muco-ciliary barrier, facilitating bacterial spread. Other than simple cytotoxicity, the virus can mediate effects on the lungs that benefit the bacteria, such as through the dysregulation of the immune system, obstruction of the small airways due to disruption of lung surfactant, increased in mucinous secretions, and an influx of inflammatory cells which create dead space and provision of a culture medium for bacterial growth.<sup>12-13</sup>

We postulate that our patient had 2009 pandemic influenza A (H1N1) infection that provided the conducive

and synergistic factors, which allowed the invasion of lung tissue by *S. pneumoniae*. *S. pneumoniae* bacteraemia was secondary to fulminant bacterial pneumonia. He presented to our hospital early in the course of illness (day 2), allowing early diagnosis and treatment of concurrent infections, which resulted in a favourable outcome. In clinical practice, the timeliness of initiation of antibacterial therapy during the course of an influenza illness, will undoubtedly pose a problem. An abnormal chest X-ray may not signify bacterial pneumonia. The elevated C-reactive protein and procalcitonin<sup>14</sup> may aid to differentiate between viral and bacterial pneumonia, as in the case described in this study.

This case underscores the importance of recognising bacterial co-infection during an influenza infection. It also emphasises efforts needed on the prevention, early diagnosis, prophylaxis and treatment of bacterial co-infection in influenza patients.<sup>5,9,11,15</sup> The US CDC's Advisory Committee on Immunization Practices (ACIP) recommends a single dose of pneumococcal polysaccharide vaccine (PPSV) for all people 65 years of age and older and for persons 2 through 64 years of age with certain high-risk conditions.<sup>16</sup> The Hospital Influenza Workgroup (Singapore) recommends that 23-valent pneumococcal polysaccharide vaccine should be encouraged for those at risk, which is for persons >65 years of age and for high-risk groups of all ages.<sup>15</sup> Stockpiling of antibiotics in addition to antiviral agents has also been strongly advocated as a key component in pandemic preparedness.<sup>5,15</sup>

Of interest, there was a cluster of pneumonia cases among foreign workers in Singapore in 2008.<sup>17</sup> Among those with *S. pneumoniae* co-infection included 4 cases with influenza B and 2 cases with influenza A. This highlighted probable increase in susceptibility to air-borne infections among foreign workers that might be related to their work, housing conditions, and possibly host susceptibility. Further study assessing the usefulness of pneumococcal vaccination to this population group is needed. There is also a recent renewed interest in methicillin-resistant *Staphylococcus aureus* (MRSA), particularly community-associated methicillin-resistant *Staphylococcus aureus* (CA-MRSA). In the US CDC Morbidity and Mortality Weekly Report (MMWR) on bacterial co-infection in lung tissue specimen from fatal cases of 2009 pandemic influenza A (H1N1), among the 7 cases of *Staphylococcus aureus* co-infection, 5 were MRSA.<sup>11</sup> Locally, CA-MRSA pneumonia has not been well described.<sup>18</sup> Thus far, there have been only 3 local cases of CA-MRSA pneumonia reported locally, including 2 cases of fatal bacteraemic pneumonia reported by Chua and Lee.<sup>18,19</sup> Since CA-MRSA in Singapore appears relatively limited, the empiric antibiotic combination treating community-acquired pneumonia may differ from settings where CA-MRSA is prevalent. Further evaluation on the impact of CA-MRSA on clinical management of 2009 pandemic influenza A (H1N1) cases in Singapore would be required.

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