

Post-viral Sepsis: Clinical Experience in Post-viral Influenza Coinfections

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Published Date: May 25, 2016

ABSTRACT

Background: Severe sepsis is traditionally associated with bacterial diseases. Influenza viruses or post-influenza bacterial coinfections are becoming a growing cause of severe sepsis in the critically ill patients worldwide. About 30% of fatal or severe 2009 pandemic influenza A (H1N1) infections had concurrent bacterial pneumonia. Influenza viruses, especially pandemic viruses, can cause diffuse alveolar damage with pulmonary edema and hemorrhage, thus promoting bacterial adhesion to the respiratory epithelial cells and can result in development of pneumonia with acute respiratory distress.

Etiology: *Streptococcus pneumoniae*, *Staphylococcus aureus* and *Haemophilus influenzae* have been widely regarded as the most common organisms co-infecting the pandemic influenza A (H1N1) infections. *Staphylococcus aureus*, including methicillin-resistant strain, was the most frequent bacterial co-infection among critically ill patients with influenza A (H1N1) infections. Other organisms were occasionally reported as copathogens of post-influenza sepsis, like *Streptococcus pyogenes*, *Mycoplasma pneumoniae*, *Legionella pneumophila*, *Pseudomonas*

aeruginosa, *Klebsiella pneumoniae* and *Mycobacterium tuberculosis*. Herpes simplex virus is a common viral nasopharyngeal isolate in the influenza patients, but its pathological significance is uncertain. Before the era of 2009 influenza A (**H1N1**) pandemic in Mexico, invasive pulmonary aspergillosis was scarcely identified in the reports of fatal influenza virus infection. Thereafter, aspergillosis has been increasingly emerging as a superinfection in critically ill patients with severe influenza.

Management: Several predictors like thrombocytopenia, C-reactive protein and procalcitonin are helpful for diagnosing bacterial infections in the patients with influenza A (**H1N1**) pneumonia or community-acquired pneumonia during the influenza seasons. Empiric antibiotic therapy should take into account the local incidence of influenza copathogens and the severity of the illness. For life-threatening post-influenza sepsis, empiric antibiotics against methicillin-resistant *Staphylococcus aureus* and prompt diagnosis for invasive pulmonary aspergillosis should be included in the current management strategies.

Conclusion: Early diagnosis of pneumonia pathogens and prompt initiation of appropriate antimicrobial therapy for post-influenza sepsis is important for clinical outcomes.

Keywords: Aspergillosis; Coinfection; Influenza; Influenza A (**H1N1**); Pandemic

INTRODUCTION

Viruses were detected in 48.7 % of influenza-like illnesses in China, in which influenza virus (20.0 %) was the most commonly detected, followed by rhinovirus (7.5 %), human corona viruses (3.6 %), human metapneumovirus (3.1 %), parainfluenza virus (3.1 %), respiratory syncytial virus (2.4 %), adenovirus (2.3 %), and human bocavirus (1.4 %). Co-infections occurred in 11.0 % of 509 infected patients [1]. Rhinoviruses (12.7%), influenza A virus (10.9%), and parainfluenza viruses (7.3%) were the most common viruses involved in the 55 cases of lower respiratory tract infections in Taiwan [2].

Severe sepsis is traditionally associated with bacterial diseases. However, viruses are becoming a growing cause of severe sepsis worldwide. Among these viruses, influenza is the most common cause of critically ill patients with severe sepsis either directly by influenza viruses, or indirectly by influenza-induced secondary bacterial infections [3]. Simultaneous or sequential infection with influenza viruses and respiratory bacteria manifests in complex processes that need aggressive antimicrobial therapy and cause substantially high mortality, particularly during influenza epidemic seasons.

The majority of deaths in the 1918-1919 influenza pandemic likely resulted directly from secondary bacterial pneumonia caused by common upper respiratory tract bacteria [4]. Secondary bacterial pneumonia following influenza was nearly all cause of influenza death and not viral pneumonitis or acute lung injury during the 1918 influenza pandemic [5]. Among the first 47 fatal cases of 2009 H1N1 influenza in New York City, 13 (28%) had evidence of invasive

bacterial coinfection [6]. In similar, 22 (29%) of the autopsy specimens from 77 fatal patients were found to have concurrent bacterial pneumonia during 2009 pandemic influenza A (**H1N1**) in United States [7]. Bacterial coinfection also complicated up to 34% of 2009 pandemic influenza A (**H1N1**) infections managed in intensive care units (ICUs) worldwide [8].

PATHOGENESIS

Influenza A and B viruses induce a general mechanism of cell death by apoptosis in hosts infected with influenza viruses [9]. Influenza A virus infections in humans can result in severe disease, secondary bacterial pneumonias, and death. Bacterial superinfection in the lungs of people suffering from influenza is a key element that promotes severe disease and mortality. The processes in pathogenicity of influenza-bacterial coinfections are multifactorial, which is characterized by complex interactions between co-infecting pathogens and the host, leading to the disruption of physical barriers, dysfunctional innate immune defenses and delays in a return to immune response [10,11].

Influenza viruses can replicate in epithelial cells throughout the respiratory tree and can cause diffuse alveolar damage with pulmonary edema and hemorrhage, and interstitial and airspace inflammation in enhanced disease, resulting in development of pneumonia and acute respiratory distress, especially prominent in pandemic viruses. The respiratory epithelium damage as well as impaired innate and adaptive antibacterial immunity can cause bacterial overgrowth and facilitate secondary infection with common bacterial pathogens and thus lead to secondary bacterial pneumonias and increased morbidity [12,13]. In an animal model of bacterial co-infection caused by influenza A virus followed by *Streptococcus pneumoniae*, the pneumococcal adhesion to the infected tracheas was significantly enhanced on Day 6 after virus inoculation into the mice [14]. Respiratory viruses promote bacterial adhesion to respiratory epithelial cells, a process that may increase bacterial colonization and contribute to disease [15].

POST-INFLUENZA PNEUMONIA

In contrast to regular influenza seasons characterized by increased rates of invasive *Streptococcus pneumoniae* infections, pandemic H1N1 influenza during 2009-2010 additionally increases invasive *Staphylococcus aureus* and *Streptococcus pyogenes* infections [16]. *Staphylococcus aureus*, *Streptococcus pneumoniae*, and *Streptococcus pyogenes* are most commonly isolated from 683 critically ill patients within the first 6 days of 2009 pandemic influenza A (**H1N1**) infection admitted to 35 ICUs in the United States [8]. In 2009, of 50 (1.1%) patients with co-infections in 4491 pandemic influenza A (**H1N1**) infections, *Streptococcus pneumoniae* (16 patients; 32%), *Staphylococcus aureus* (13 patients; 26%) and *Haemophilus influenzae* (9 patients; 18%) were the most commonly cultured organisms in Queensland [17]. In Australia, however, bacterial co-infection was identified in 20-25% of patients with severe influenza A infection in 14 ICUs. *Staphylococcus aureus* was the most frequent bacterial co-infection followed by *Streptococcus pneumoniae* and *Haemophilus influenzae* [18].

Staphylococcus aureus

Staphylococcus aureus frequently causes secondary pneumonia during influenza infection. Influenza has been found to attenuate subsequent type 17 immunity, enhancing susceptibility to secondary bacterial infections. IL-27 is known to inhibit type 17 immunity through the induction of IL-10, and thus regulates enhanced susceptibility to *Staphylococcus aureus* pneumonia following influenza infection [19].

Panton-Valentine Leukocidin (**PVL**) is a cytotoxin that causes leukocyte destruction and lung necrosis. PVL corresponded to 85 to 97% of patients with necrotizing or fatal staphylococcal pneumonia [20, 21]. Denison *et al.* reported 45 *mecA*-positive and PVL-positive cases, representing 68% of the fatal cases with an influenza virus coinfection [22]. Bacterial pneumonia with PVL-producing methicillin-sensitive *Staphylococcus aureus* or PVL-producing Methicillin-Resistant *Staphylococcus aureus* (**MRSA**) pneumonia commonly happens in patients with influenza A virus infection [23, 24], but less frequently occurs concurrently with influenza B virus infection [25].

Of 421 autopsy tissues from influenza cases in the Infectious Diseases Pathology Branch of the Centers for Disease Control and Prevention, 121 (28.7%) had a bacterial coinfection. Among them, 66 (54.5%) were identified as *Staphylococcus aureus* [22]. In Australia, on the contrary, of 4491 patients with influenza A (**H1N1**) infection, MRSA was detected in only two patients, both of whom were admitted to ICUs and survived after prolonged admissions [17].

During the 2009-2010 H1N1 pandemic, pediatric patients with influenza A and methicillin-sensitive or -resistant *Staphylococcus aureus* coinfections were sicker and more likely to develop disseminated intravascular coagulation than patients with other or no coinfections [26]. Especially in critically ill children, simultaneous infection with MRSA increased the risk for influenza-related mortality 8-fold in the United States [27].

Clinical Experience

A 61-year-old diabetic woman had intermittent fever, dry cough, myalgia and generalize weakness in recent days. She visited the emergency room with sore throat, chest pain and severe dyspnea. Intubation with mechanical ventilator support was initiated. The Chest X-Ray (**CXR**) film showed consolidation in Right Lower Lung (**RL**) field (Figure 1-1A). Results of laboratory tests revealed leukocytosis, 16,200/ uL; bandemia, 22%; lactic acidosis, 4.3 mmole/L; HbA1C, 8.4%; procalcitonin, 18.78 ng/ml; C-Reactive Protein (**CRP**), 81.1 mg/L and positive rapid influenza A antigen test in nasal swab. Hypotension was noticed. Then she was admitted to an intensive care unit on 3 March 2015 for further management. The polymerase chain reaction in nasopharyngeal swab for novel influenza A (**H1N1**) was positive. Initial anti-influenza oseltamivir and antibiotic moxifloxacin were given for influenza-related pneumonia.

The blood and sputum cultures both yielded MRSA, which was susceptible to minocycline, teicoplanin and fusidic acid. Thus teicoplanin was added. Cardiac echo and transesophageal

echocardiogram did not find any evidence of vegetation. The patient was extubated on 11 March 2015. After she was transferred to the ward, however, followed-up CXR film showed a cavitation lesion in RLL field (Figure 1-1B). A chest computed tomography scan revealed septic emboli involving bilateral lungs (Figure 1-2). Relapse of fever and thrombocytopenia occurred. The antibiotics were adjusted to vancomycin and minocycline. The condition improved and CRP became 9.7 mg/L on 30 March. The CXR showed near resolution of the pneumonia (Figure 1-3). Then she was discharged on 3 April 2015 and she was well maintained with fusidic acid 500 mg TID and minocycline 100mg BID.

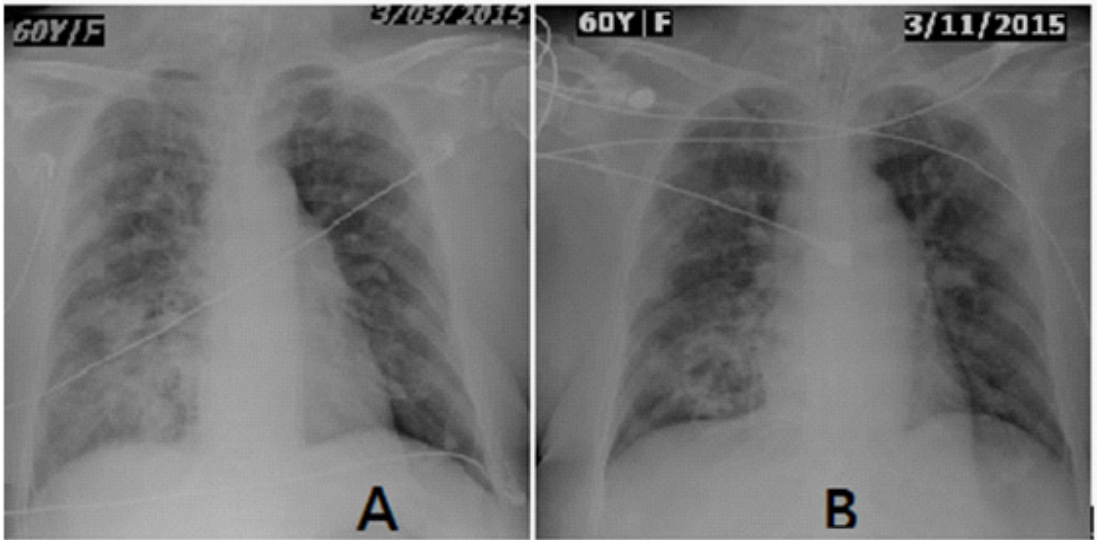


Figure 1-1: CXR series show consolidation in right lower lung field (A), and a cavitation lesion in right lower lung later (B).

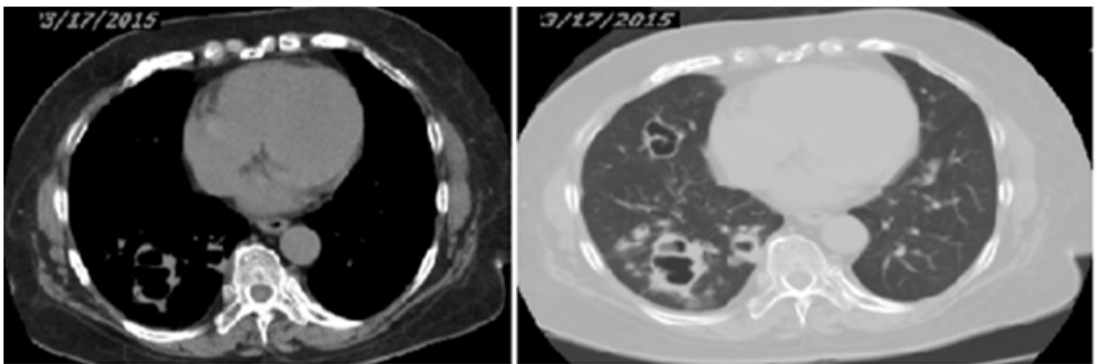


Figure 1-2: Chest CT shows septic emboli involving right lower lung.

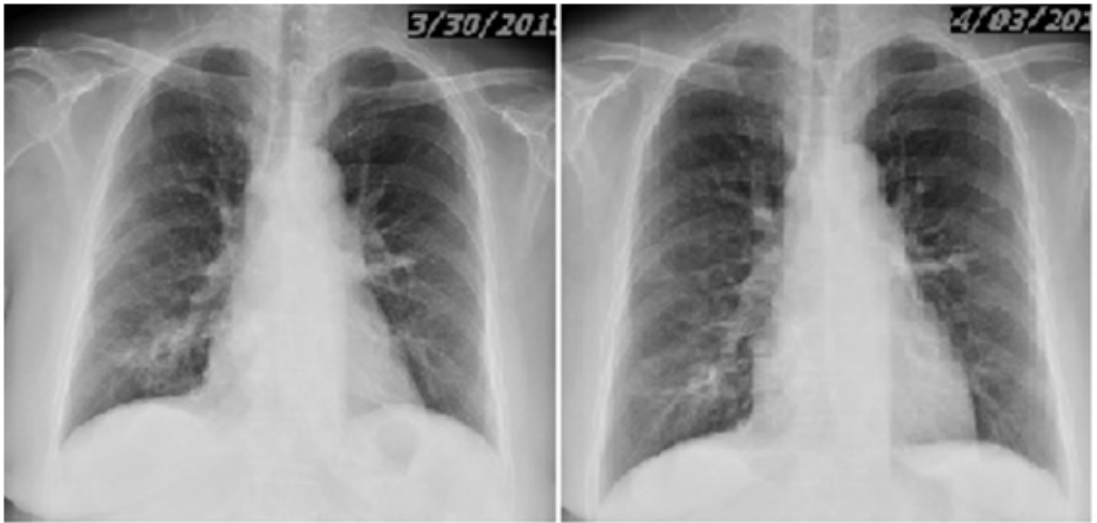


Figure 1-3: CXR shows near resolution of the pneumonia of right lower lung.

In conclusion, the diabetic woman experienced influenza A (**H1N1**) pneumonia co-existing with MRSA necrotizing pneumonia and bacteremia.

Streptococcus pyogenes

Streptococcus pyogenes was reported as a co-infecting microorganism of the 2009 influenza A (**H1N1**) and rarely of influenza B infection [28]. In an animal model of bacterial co-infection, a nonlethal dose of influenza A virus followed by *Streptococcus pyogenes* resulted in invasive *Streptococcus pyogenes* infection and a death rate of more than 90% in mice [29]. An England reported 4 cases of influenza B with *Streptococcus pyogenes* co-infection, which had the potential to cause significant morbidity and mortality [30].

Streptococcus pneumoniae

Streptococcus pneumoniae is the most frequently isolated pathogen associated with influenza [31,32]. Severe pneumococcal pneumonia occurs closely after influenza A virus infection [33]. The presence of *Streptococcus pneumoniae* was strongly correlated with severe disease of H1N1 pandemic influenza [34].

Clinical Experience

A 47-year-old man of kidney transplant recipient was admitted due to symptoms of upper respiratory infection and dyspnea for several days. Influenza type B rapid antigen test was positive. The Chest X-Ray (**CXR**) film showed consolidation over Right Lower Lung (**RLL**) field, suspicious of influenza pneumonia (Figure 2A). The anti-influenza oseltamivir was initiated. Laboratory data showed a white blood cell count of 3,800/ μ l; band form, 11%; monocyte, 10%; platelet count, 75,000/ μ l; procalcitonin, 175.93 ng/ml and C-reactive protein, 424.0 mg/L. The urine *Legionella* antigen test was negative but *Pneumococcus* rapid antigen test was positive. Empirical antibiotics with imipenem, teicoplanin, caspofungin and levofloxacin were administered.

Blood cultures yielded *Streptococcus pneumoniae* susceptible to levofloxacin and antibiotic treatment was shifted to imipenem plus levofloxacin. A sputum culture yielded *Staphylococcus aureus*. The CXR revealed partial resolution of RLL consolidation one week later (Figure 2B). The blood *Aspergillus galactomannan* antigen index revealed 0.14 (normal, < 0.5). The cytomegalovirus DNA by polymerase chain reaction in blood sample was not detected. The isolation of virus from throat swab was not found. Antibiotic therapy was maintained with intravenous levofloxacin for a total of 2 weeks and then was de-escalated to oral form levofloxacin for one week. Followed-up CXR showed complete resolution of the pneumonia (Figure 2C).

In conclusion, a post-kidney transplant recipient experienced influenza B pneumonia co-infected with *Streptococcus pneumoniae*. Probably *Staphylococcus aureus* played a minor role in the pneumonia for this case as no occurrence of necrotizing process in the lung parenchyma. Oseltamivir and appropriate antibiotic therapy achieved a good clinical outcome.

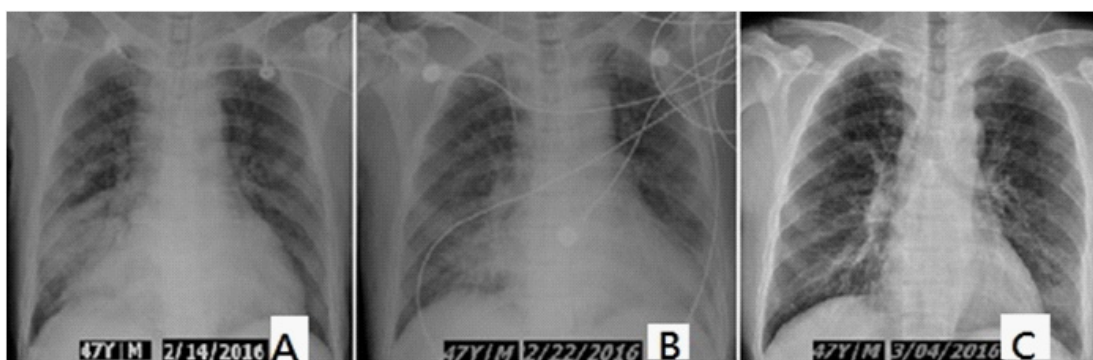


Figure 2: Chest X-ray film series show consolidation over right lower lung field (A), partial resolution one week later (B) and complete resolution at last (C).

Haemophilus influenzae

During the 1918-19 global influenza pandemic, *Haemophilus influenzae* was one of the bacteria most often recovered from the sputum, lungs and blood of pneumonia patients [35]. The severe damage to the airway epithelium and confluent pneumonia observed in victims of the 1918 pandemic could be evidenced by a mouse model of dual infection with sublethal doses of influenza virus and *Haemophilus influenzae*, resulting in lethal synergism [36]. *Haemophilus influenzae* was ever the primary identifiable isolate from 9 of 19 (47.4%) patients with pneumonia during two outbreaks of influenza A (**H₃N₂**) and influenza B among military recruits in Taiwan [37]. Routine use of the *Haemophilus influenzae* type b (**Hib**) conjugate vaccines has resulted in a remarkable decline in Hib disease in developed and developing countries [38].

Mycoplasma pneumoniae

In a study from Malaysia, *Mycoplasma pneumoniae* was the commonest bacteria of coinfection among the hospitalized patients with influenza A (**H1N1**) infection [39].

Legionella pneumophila

In a report from Italy, of the 33 influenza A (**H1N1**) pneumonia cases with bacterial coinfection, 6 (18%) were caused by *Legionella pneumophila* serogroup 1, indicating that *Legionella* and influenza A (**H1N1**) coinfections occur more often than previously expected [40].

Pseudomonas aeruginosa

Pseudomonas aeruginosa was ever reported to be responsible for 14% of bacterial co-infection in influenza A H1N1 infection during the pandemic period in Spain [41].

Klebsiella pneumoniae

Concurrent bacteremic pneumonia due to *Klebsiella pneumoniae* and pandemic (**H1N1**) 2009 influenza in a patient with nasopharyngeal cancer was ever reported in Taiwan [42].

Herpes Simplex Virus (HSV)

Igusa *et al* reported an immunocompetent patient with MRSA and HSV-1 pneumonia secondary to influenza A (**H1N1**) pdm 2009 viral infection with Acute Respiratory Distress Syndrome (**ARDS**), which was not responsive to anti-influenza treatment. Administration of acyclovir, linezolid, and methylprednisolone successfully improved the pneumonia and ARDS [43]. Multiple viruses co-infecting epithelial cells of the respiratory tract may be beneficial to influenza A virus replication and subsequent severe illness. HSV is frequently isolated in the respiratory tract of mechanically ventilated patients and can sometimes be responsible for HSV pneumonitis. Although not evaluated for this indication, acyclovir can be a therapeutic option for patients with HSV pneumonitis and ARDS [44].

Clinical Experience

A 79-year-old woman with coronary artery disease and congestive heart failure was admitted due to symptoms of leg edema and dyspnea for several days. Right pleural effusion was noted and pig-tail drainage was inserted with improvement (Figure 3A). Initial influenza type A and type B rapid antigen tests in nasal swabs were negative. Empirical antibiotics with piperacillin-tazobactam and levofloxacin were administered. However, extensive infiltration over right lung field occurred during hospitalization (Figure 3B). Laboratory data showed a white blood cell count of 8,400/ μl and platelet count, 64,000/ μl . The Polymerase Chain Reaction (**PCR**) in nasopharyngeal swab was positive for influenza A, but was different to novel influenza A (**H₁N₁**) and H₃N₂. The blood Aspergillus galactomannan antigen index revealed 0.38 (normal, < 0.5). The anti-influenza oseltamivir was initiated. The urine rapid antigen tests for *Legionella* antigen and *Pneumococcus* were negative. Antibiotic treatment was shifted to levofloxacin as a sputum culture yielded *Stenotrophomonas maltophilia*, which was susceptible to levofloxacin and minocycline. The isolation of virus from throat swab yielded Herpes Simplex Virus-1 (**HSV-1**). The anti-herpes acyclovir was not prescribed as pneumonia was improving. Antibiotic therapy was maintained

with intravenous levofloxacin for one week and was followed by oral form levofloxacin for one week. The right lung consolidation was near complete resolution later (Figure 3C). Followed-up viral isolation from throat swab still yielded HSV-1, but PCR for influenza A became negative.

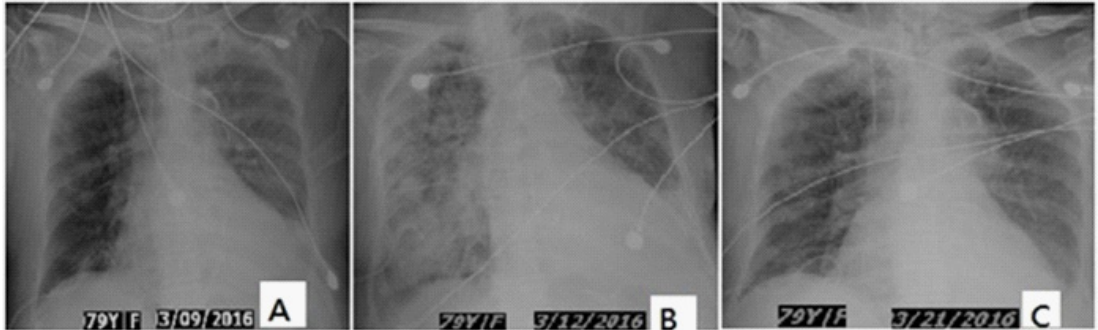


Figure 3: Chest X-ray film series show pig-tail drainage in right pleural space (A), subsequent extensive infiltrates over right lung field (B) and near complete resolution at last (C).

In conclusion, a congestive heart failure patient experienced seasonal influenza A pneumonia co-infected with *Stenotrophomonas maltophilia*. Despite of persistent presence of HSV-1 in the nasopharyngeal epithelium, it seemed not necessary to initiate routine antiviral therapy for the case. Oseltamivir and appropriate antibiotic therapy achieved a good clinical outcome.

Mycobacterium tuberculosis

The concurrence of active pulmonary Tuberculosis (**TB**) in patients with influenza was reported in Japan [45], South Africa [46], Taiwan [47], Thailand [48], and Korea [49]. Physicians should not forget a concurrent pulmonary TB diagnosis for influenza patients with radiologic abnormalities consistent with TB or with prolonged respiratory symptoms, especially in TB-endemic areas.

Nocardia

Pulmonary nocardiosis with co-infection with influenza A is extremely rare. *Nocardia farcinica* was ever recovered from the expectorated sputum in a nonresponsive influenza A-associated pneumonia [50].

Invasive Pulmonary Aspergillosis (IPA)

Before the era of the H1N1 influenza pandemic, IPA was scarcely identified in a report of fatal influenza virus infection [51]. Since the influenza A (**H1N1**) pandemic flu in Mexico in April 2009, IPA has been increasingly reported as a superinfection in patients with a severe influenza virus infection. Several cases of IPA accompanying influenza infections were reported during the influenza A (**H1N1**) pdm 2009 pandemic [52-54]. Moreover, a systematic literature review identified 68 patients with IPA following influenza infection. The majority of patients had underlying comorbid illnesses and overall mortality rate was 47% [55].

Clinical Experience

This 51-year-old woman of chronic kidney disease presented with progressive shortness of breath, productive cough and low urine output with limb edema for one week. As exacerbated symptoms, she visited the emergency room. There were no fever, chest pain, abdominal pain and skin rashes. On physical examination, fever, pale conjunctiva, bilateral rhonchi and wheezing in chest auscultation and limb edema were found. Laboratory tests revealed leukopenia (1,500/ μL), severe anemia with a low hemoglobin count (5.7 g/dL), high procalcitonin (54.47 ng/ml), elevated C-reactive protein (157.4mg/L), metabolic acidosis and impaired renal function (blood urea nitrogen, 153 mg/dL; creatinine, 21.14 mg/dL). The nasopharyngeal swab rapid influenza A antigen test was positive. The Chest X-Ray film (**CXR**) showed patches over left upper and right lower lung fields (Figure 4A). Electrocardiogram showed sinus tachycardia. The patient was intubated due to impending respiratory failure. The anti-influenza oseltamivir was initiated. Under the impression of bilateral pneumonia with severe sepsis, respiratory failure, acute kidney injury and acidosis, she was admitted to the intensive care unit for further management.

Adequate sedation, pain control and muscle relaxant were given for lung protection under ventilator support with a high fraction of inspired oxygen of 100%. The initial sputum culture yielded *Klebsiella pneumoniae* and *Staphylococcus aureus* followed by *Pseudomonas aeruginosa* two days later. The blood culture yielded *Klebsiella pneumoniae*, which was susceptible to cefazolin, cefuroxime and ceftazidime, but was only resistant to ampicillin. As severe hypotension, hypoxemia, leukopenia (1,900/ μL with an absolute neutrophil count of 1309/ μL), thrombocytopenia (with the lowest value of 9,000/ μL) and increased fibrin degradation product (18.1 $\mu\text{g}/\text{mL}$), broad-spectrum antibiotics were given, including meropenem and tigecycline. The polymerase chain reaction in nasopharyngeal swab was positive for novel influenza A (**H1N1**). Meanwhile, post-influenza aspergillosis was also considered and empirical caspofungin was given. However, metabolic acidosis persisted due to acute deterioration of renal function and septic shock with lactic acidosis (lactate, 7.7 mmole/L). Continuous venovenous hemofiltration was initiated, but it could not correct the acidosis. Severe acute respiratory distress syndrome with hypoxemia persisted. The CXR showed worsening consolidation over bilateral lung fields (Figure 4B). The family did not agree the salvage management by extracorporeal membrane oxygenation. The patient expired on day 4 of hospitalization. The blood *Aspergillus galactomannan* antigen index revealed 0.56 (normal, < 0.5).

In conclusion, the woman experienced influenza A (**H1N1**) pneumonia with septic shock, disseminated intravascular coagulation and severe acute respiratory distress syndrome due to *Klebsiella pneumoniae* septicemia and *Staphylococcus aureus* pneumonia. Probably invasive pulmonary aspergillosis was co-existing, which requires a high index of suspicion for the timely identification and treatment of the diseases.

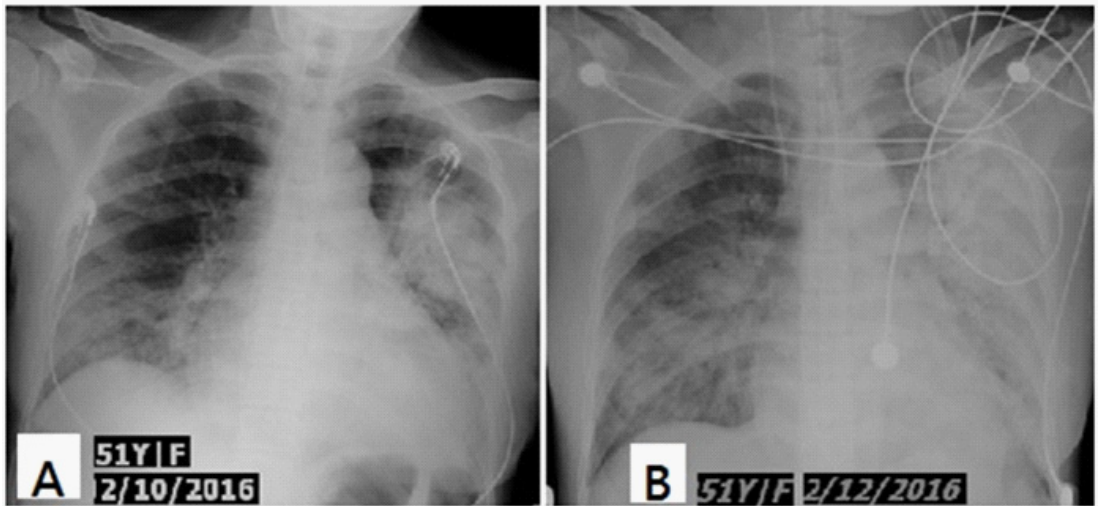


Figure 4: CXR series revealed initial consolidation over left upper lung field and right lower lung field (A), which rapidly deteriorated 3 days later (B).

DIAGNOSIS

Bacteremia in adults with influenza is associated with increased complications and mortality; thrombocytopenia and elevated C-reactive protein levels could identify those at risk [56].

Procalcitonin (**PCT**) is helpful for diagnosing bacterial infections. In critically ill patients with H1N1 pneumonia or community-acquired pneumonia during the influenza season, PCT is a reasonably accurate marker for detection of bacterial pneumonia [57]. Of 972 ICU patients with confirmed influenza A (**H1N1**) pdm09 infection, 196 (20.3%) had bacterial coinfection. PCT (<0.29 ng/mL) has a high negative predictive value (94%) and lower PCT levels seems to be a good tool for excluding coinfection, particularly for patients without shock [58].

In a systemic review for six studies, PCT tests have a high sensitivity, particularly for ICU patients, but a low specificity for identifying secondary bacterial infections among patients with influenza. Because of its suboptimal positive likelihood ratio and good negative likelihood ratio, it can be used as a suitable rule-out test but cannot be used as a standalone rule-in test [59].

The performance of *Aspergillus galactomannan* and polymerase chain reaction in serum and/or bronchoalveolar lavage fluid of the critically ill patients with severe influenza might be helpful in the diagnostic workup of patients with IPA [60].

THERAPY

Advisory Committee for Immunization Practices guidelines recommend oseltamivir or zanamivir to treat 1) hospitalized patients with suspected or confirmed influenza, 2) outpatients who are at greater risk for influenza complications, and 3) persons with suspected or confirmed influenza who have evidence of severe illness, even >48 hours after illness onset [61]. Empiric

influenza antiviral treatment should be provided to such patients even if test results are not available immediately or if patients are not tested.

Influenza virus infection increases susceptibility to bacterial infection and mortality in humans. Early initiation of appropriate antimicrobial therapy for post-influenza bacterial pneumonia might be more important than previously thought. Inappropriate empiric antimicrobial therapy could lead to poor clinical outcomes.

In the murine models of bacterial co-infection caused by initial influenza A virus followed by *Streptococcus pneumoniae*, some fluoroquinolones demonstrated high levels of bacterial eradication in the lung, low mortality, and potent histopathological improvements [62]. In addition, linezolid has some modulatory effects and decreased susceptibility to secondary bacterial pneumonia following influenza infection [63]. However, effective anti-influenza therapy alone could inhibit viral replication, consequently leading to bacterial clearance and prevention of mortality during severe murine bacterial co-infections [64,65].

Emergence of novel influenza A (**H1N1**) pdm09 and the concomitant global spread of Community-Associated MRSA (**CA-MRSA**) have led to increasing prevalence of CA-MRSA pneumonia following influenza infection. During influenza season, empiric antibiotics with staphylococcal activity for patients with influenza A infection should take into account the local incidence of MRSA and the severity of the illness [66]. For example, when high clinical suspicion for serious *Staphylococcus aureus* coinfection exists, empiric coverage with antibiotics, including those with activity against MRSA, should be instituted [67, 68]. Gram-negative bacilli and *Staphylococcus aureus* infections are frequently seen in immunosuppressed patients with pandemic influenza [69].

Analysis of antimicrobial susceptibility data from England, Wales and Northern Ireland revealed that susceptibilities of *Streptococcus pneumoniae*, *Staphylococcus aureus* and *Haemophilus influenzae* to tetracyclines or co-amoxiclav were high, which supports the use of doxycycline or co-amoxiclav as appropriate empiric treatment for influenza-associated pneumonia in primary care [70].

Compared to ARDS by non-H1N1 influenza, H1N1-ARDS patients have more severe gas exchange impairment and more need for Extracorporeal Membrane Oxygenation (**ECMO**) [71]. The treatment of ARDS in patients with influenza A (**H1N1**) includes a protective lung strategy (tidal volume 6-8 ml/kg and plateau pressure <30 mmHg), prone position, muscle relaxation, recruitment maneuvers and positive end-expiratory pressure set to prevent atelectasis [72]. ECMO is a rescue technique in refractory ARDS due to influenza A (**H1N1**) infection and will be advisable if all other options have failed to improve oxygenation.

Nowadays, ECMO has been effective in the treatment of H1N1-induced ARDS across the globe. Papadopoulos *et al* reported a 44% survival rate of ECMO support for 18 patients with severe H1N1-related ARDS during 2009-2011 periods in Germany [73]. A study of ECMO

therapy for 17 patients with H1N1-induced ARDS reported a mortality of 35% in Croatia [74]. From Italian experience in patients with H1N1-related ARDS, survival to hospital discharge in patients receiving ECMO was 68% [75]. From England experience in patients with H1N1-related ARDS, ECMO-referred patients has lower hospital mortality rate of 24% than 53% in non-ECMO-referred patients ($p = 0.006$) [76]. In similar, a 21% mortality rate was achieved for ECMO-treated influenza A (H1N1)-associated ARDS patients during 2009 in Australia and New Zealand [77]. However, from a report in France, influenza A (H1N1)-related ARDS patients treated with ECMO had the hospital mortality rate (56%, 5/9), similar to those without ECMO support [78].

While venovenous ECMO remains the method of choice for ARDS patients with stable hemodynamic conditions, venoarterial ECMO may be considered if the ARDS status requires high dose vasopressor support [73]. For example, early induction of venoarterial ECMO followed by venovenous ECMO therapy was reported to successfully survive a 27-year-old woman with severe ARDS due to PVL-expressing *Staphylococcus aureus*-associated pneumonia co-infected with influenza, which seemed poor responsive to aggressive antibiotic management, including meropenem and vancomycin [79]. Patients may be converted from venovenous to venoarterial ECMO because of right heart failure or life-threatening cardiac arrhythmias [80].

CONCLUSION

Severe sepsis is traditionally associated with bacterial diseases. *Streptococcus pneumoniae*, *Staphylococcus aureus* and *Haemophilus influenzae* have been widely regarded as the most common organisms of post-influenza sepsis. Invasive pulmonary aspergillosis has been increasingly emerging as a superinfection in critically ill patients with severe influenza. Anti-influenza treatment with oseltamivir or zanamivir should be provided to treat patients with severe influenza illness. For post-influenza severe sepsis, early empiric antibiotics with coverage of methicillin-resistant *Staphylococcus aureus* and prompt diagnosis for invasive pulmonary aspergillosis should be included in the current management strategies. ECMO may be an effective salvage treatment for patients with influenza A (**H1N1**)-related ARDS presenting with rapid refractory respiratory failure, and initial venoarterial ECMO may be required in unstable hemodynamic status due to septic coinfections.

ACKNOWLEDGEMENT

The Institutional Review Board (**IRB**) of the Chi Mei Medical Center, Tainan city, Taiwan, had approved the work (IRB Serial No.10503-003). We declared no financial funding for this work. No potential conflicts of interest were disclosed.

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