Post-influenza Pneumonia: Everything Old Is New Again

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The 1918-1919 Influenza pandemic spread worldwide with remarkable speed. Approximately 500 million people were infected, and the death toll was between 50 and 100 million worldwide. It is hypothesized that a major cause of morbidity and mortality may not have been the viral pneumonitis, but the bacterial superinfection of the susceptible post-influenza lung. Here, we will review the role of bacterial coinfection in past influenza pandemics, and how it relates to the current H1N1 strain of 2009-2010.

MORBIDITY AND MORTALITY: LESSONS FROM HISTORY

A number of scientific accounts elaborated on the role of bacterial superinfection in the 1918-1919 influenza pandemic. In 1921, Opie et al. published an investigation of causes of respiratory diseases in military personnel, investigating an epidemic of influenza affecting 22.7% of more than 50,000 personnel at Camp Pike, Arkansas, with an incidence of pneumonia of 2.9% which was observed to follow one week after the influenza outbreak. The excess mortality, 466 deaths, was attributed to pneumonia: “In a civil hospital there is often great difficulty in deciding, even in the presence of an epidemic, if death from pneumonia is the result of influenza, but at Camp Pike the relation of the heightened death rate to the epidemic has excluded all save a trivial error in determining the relation of fatal pneumonia to influenza.”

The group’s collection of microbiological and pathological data emphasizes the pervasive presence of Bacillus influenzae (Haemophilus influenzae) as well as pneumococci, but makes mention of other Streptococcus species, Micrococcus catarrhalis (Monteolla catarrhalis) and even Bacillus coli (E. coli) as some of the most frequently found pathogens. The isolation of H influenzae was so frequent, in almost 80% of cases, that it was thought to be “constantly present.” Patterns of bronchitis, bronchopneumonia, and lobar pneumonia were identified in autopsy investigation, and microscopic examination of the lung described destruction of the epithelium as “changes in the bronchial walls [that] destroy the defences against invasion by microorganisms.” The authors observed that these findings were similar to previous epidemics, most notably a pandemic of 1889-1890.

These themes recurred in a study published by Vaughan in the same year. Comparing the 1918-19 pandemic with previous outbreaks of influenza, he stated: “The secondary invaders of pathogenic importance are the various forms of the streptococcus and pneumococcus, the meningococcus, the staphylococcus, and probably the tubercle bacillus and the influenza bacillus. In the last epidemic as in that of thirty years previously, the chief complications were bronchitis and pneumonia..”

Also in 1921, McCallum described the pathology of post-influenza pneumonia, making similar pathological and bacteriological observations from cases seen in two military camps as well as at Johns Hopkins hospital. In contrast with other scientists that regarded Bacillus influenzae as a primary pathogen in the pandemic, he states that “[n]o direct information has been gained as to the nature of the infective agent which...causes the epidemic disease influenza.”

The actual causes of influenza-related deaths have been under discussion among the scientific community. One important aspect of the 1918-19 pandemic, not always seen in other pandemics, was the “W-shaped” death curve, in which influenza mainly targeted infants, young adults (ages 20-40) and the elderly.

A modern rationale for the high numbers of young and otherwise healthy people among the casualties is the “cytokine storm,” which leads to respiratory distress syndrome through a hemorrhagic alveolitis. The pathogenic potential of the inflammatory response may have been more severe in pandemic compared to non-pandemic strains, which may explain the difference in mortality. Support for this theory has been found in animal models of infection with a reconstructed 1918 virus, which demonstrated more severe lung pathology, higher mortality, and greater activation of pro-inflammatory and cell-death pathways. An alternative hypothesis is simply that older patients had immunological memory to a related strain which had circulated in 1889, whereas the younger segment of the population lacked these protective antibodies.

Other reports, however, describe the mortality from primary pandemic influenza pneumonia as relatively uncommon. Brundage and Shanks discuss the accounts of fatalities in the US, UK and New Zealand. In all three regions the time of death was highly variable, and that those with longer duration of illness were considered to have secondary bacterial infections. H. influenzae, pneumococci, hemolytic streptococci and on occasion, staphylococci were considered the main culprits. In 2008, they went on to suggest that the actual infections with influenza were self-limited, but paving the way for lethal bacterial pneumonias, proposing the “sequential infection” hypothesis.

Mores and coworkers reviewed a vast amount of data from the 1918-19 pandemic which support the role of bacterial superinfections in the morbidity and mortality of pandemic influenza. They evaluated pathological, epidemiological, and microbiological reports published during the pandemic, encompassing a total of 8398 postmortem examinations. They then went on to directly evaluate samples obtained during autopsy from 58 influenza victims during the 1918-19 pandemic.

Lung tissue blocks obtained from autopsies performed during the pandemic, and preserved by the US military showed that, in virtually all cases, there was compelling histological evidence of severe acute bacterial pneumonia, either as predominant pathology or in conjunction with features now known to be associated with influenza virus infection: desquamation of respiratory epithelium of tracheobronchial and bronchiolar tree; dilation of alveolar ducts, hyaline membranes, evidence of bronchial and/ or bronchiolar epithelial repair. There were also changes consistent with either pneumococcal or streptococcal
pneumonia, and some had evidence of staphylococcal pneumonia, in the form of multiple small abscesses. In virtually all cases bacteria were seen in massive numbers.

Published articles from the pandemic period discuss postmortem examination findings as well as epidemiological data. Most agree that without secondary bacterial pneumonia most patients with influenza may have indeed recovered. There is a prevalent description of desquamative tracheobronchitis and bronchiolitis as the primary lesion of early severe influenza-associated pneumonia. This was associated with a sloughing of broncholar epithelial cells to the basal layer, hyaline membrane formation in alveolar ducts and alveoli, and ductal dilatation, as described by Opie et al.1 in 1921. A primary “panbronchitis” gave way to an aggressive invasion of bacteria throughout the denuded bronchial epithelium. In the most severe cases, zones of vasculitis, capillary thrombosis and necrosis surrounding the bronchial damage were noted. Despite this, there was also noted a “histopathological asynchrony,”1 with early epithelial regeneration, capillary repair and occasional fibrosis even in the most fulminating cases. This may be a reason why, despite the severe damage to the tracheobronchial tree that is generally ascribed to influenza-associated pneumonias, there are few reports of chronic respiratory damage noted in survivors.

Blood cultures were positive in 70.3% of cases, mostly growing known pneumopathogens such as Streptococcus pneumoniae and other streptococci. These were also the primary pathogens reported on cultures of pleural fluid and lung tissue. During the 1918-19 pandemic the incidence of Staphylococcus aureus was low, and a significant percentage of identified bacteria were nonpneumopathogens such as viridans group streptococci, E. coli, Klebsiella and H. influenzae, which were seen in coinfection with known pneumopathogens. Bacillus (later Haemophilus) influenzae was the primary coinfecting pathogen in early symptomatic influenza and was associated with diffuse bronchitis and bronchiolitis. Outbreaks of meningococcal pneumonia were also documented.

An interesting alternative hypothesis for the distribution of influenza-related deaths is provided by Starko.9 She notes that the doses in which aspirin was prescribed at the time are now known to be toxic, and may have resulted in pulmonary toxicity. Salicylate overdose may have resulted in pulmonary edema, impairment of mucociliary clearance and increase in protein levels may have predisposed these patients to secondary pulmonary infections.

**Prominent pathogens:**

**Pneumococcus and S. aureus**

Two pathogens that deserve special attention for their role in post-influenza pneumonia are Streptococcus pneumoniae and Staphylococcus aureus. These are particularly noteworthy because they occur frequently in the role of superinfecting pathogen, and their virulence often results in significant morbidity and mortality.

In their review of historical culture data of specimens from the 1918-1919 pandemic, Morens et al.8 S. pneumoniae was generally the single most commonly isolated organism, appearing in 1235/5266 positive lung tissue cultures (23.5%), 509/1887 positive blood cultures (27.0%), and 263/1245 pleural fluid cultures (21.1%). Brundage and Shanks10 cited much of the same data, and argued that the median time to death of 7-11 days in military populations correlated with pneumococcal bacterial superinfection. Klugman et al.10 generated a startling graph showing that the distribution of days of illness before death from influenza-related pneumonia during the 1918-1919 pandemic precisely reproduced that of untreated pneumococcal pneumonia in the 1920s and 1930s, leading to their conclusion that “similar times to death provide additional evidence that the influenza-related pneumonia deaths during the 1918 influenza pandemic were largely due to the pneumococcus.”

In 1949, after the influenza virus had already been identified as the etiologic agent of the disease, Maxwell et al.11 also noted the particular role of pneumococcus in coinfection. They studied cases of known bacterial pneumonia from 1946-7, spanning a time when influenza A was prevalent in the community, as well as during a time described as an “interepidemic period.” They found that “there was a simultaneous infection with pneumococci and influenza virus in about one-half of the human cases of lobar pneumonia studied during an influenza epidemic,” suggesting that “bacterial pneumonia is in some way related to recent or concurrent infection with influenza virus.”

Studies of later epidemics highlight the pneumococcus as well: patients confirmed to have epidemic influenza in Stockholm12 (1969-70, 1971-72) showed bacteriologic and/or serologic evidence of pneumococcal infection in 12/116 patients (10%) in 1969-1970, and 37/176 patients (21%) in 1971-72.
However, since the seasonality of pneumococcal infection mirrors that of seasonal influenza, it has been unclear whether the correlation between influenza circulation and invasive pneumococcal disease has been causal. The most recent study of this association, using data in the United States from 1995-2006, found that in influenza circulation was associated with 11%-14% of pneumococcal pneumonia during periods of elevated influenza circulation, with rates of 5%-6% overall. 13

Vaccination of children with a heptavalent protein-polysaccharide conjugate and adults with a 23-valent polysaccharide vaccine has led to a decline in invasive disease. Pediatric vaccination seems to be associated with a decreased incidence in viral pneumonia due to influenza A, as well as other viral etiologies such as RSV, parainfluenza, and adenovirus, presumably through a “synergism between viral and pneumococcal infection.” 14

The role of S. aureus had not historically been as significant. Morons et al. 8 also identified S. aureus in autopsy cultures from 1918-1919, in 427/5266 (8.1%) of positive cultures of lung tissue, and 68/1887 (3.6%) of positive blood cultures, and 59/1245 (4.7%) of pleural fluid cultures. During the Hong Kong influenza epidemic of 1968-1969, the bacterial etiology of pneumonia admissions to Grady Memorial Hospital shifted: 25.9% of all pneumonias included S. aureus, compared to 10.2% from the previous year 15; although the actual rate of true influenza-S. aureus coinfection was not documented.

However, beginning in 2003, S. aureus, most notably community-acquired methicillin-resistant S. aureus (CA-MRSA), had been noted to be a significant cause of influenza-associated bacterial pneumonia as reported in a small case series 9, with a case fatality rate of 4/15 (26.7%), generally in people without comorbidities. A larger series of cases from the 2006-2007 influenza season 16, 17 confirmed that S. aureus pneumonia occurred in younger patients without comorbidities, the strains involved were predominantly CA-MRSA (28 out of 31 S. aureus isolates), and documented influenza virus coinfection was associated with a worse outcome. Worse outcomes of CA-MRSA-influenza coinfection have also been seen in the pediatric population. 18

CA-MRSA pneumonia is often characterized by high fever, hypotension, rapid progression, and a requirement for ventilator support, often with multilobar infiltrates or cavitation. 19 Since it has now been firmly established as a major etiological agent of post-influenza pneumonia, it is worth considering empiric therapy for MRSA in any patient with a severe pneumonia fitting this presentation. 20 Vancomycin has long been considered the drug of choice for MRSA pneumonia; however, several recent retrospective studies and pharmacologic advantages of linezolid – greater penetration into the lung, the ability to shut down production of toxins such as the Panton-Valentine Leukocidin — support the empiric use of linezolid. 19

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The current H1N1 pandemic

The role of superinfection in the current H1N1 pandemic (2009-2010) has been extensively studied. The pathology of H1N1 influenza infection has overall been similar to that of prior pandemics, 21, 22 with findings including diffuse alveolar damage, pulmonary hemorrhage, and necrotizing bronchiolitis. These results are thought to be due to some combination of direct damage from the virus and the host inflammatory response.

Of interest is the lower fraction of cases in which bacterial superinfection have been evident on pathology: There was no clear evidence of bacterial infection in a series of 5 confirmed H1N1 fatalities from Mexico 23, and only 3 of 21 patients who had bacteria seen on histology in a series from Brazil. 24 However, antibiotics were given to many of these patients, possibly decreasing the amount of bacteria detectable on histochemistry alone compared to prior eras.

Other efforts to determine the relative contributions of viral pneumonitis and bacterial superinfection included a study of the immunomodulatory effect of H1N1 on the host 25. Unsurprisingly, pro-inflammatory cytokines were elevated in the serum of infected patients, much with other strains of influenza. However, when peripheral blood mononuclear cells from H1N1-infected patients were stimulated with S. pneumoniae, they produced decreased amounts of TNFα and IFNγ, suggesting a defective cytokine response which may predispose to superinfection.

The use of molecular methods as an adjunct to traditional culture techniques adds another dimension to the estimation of the epidemiology of superinfection. On one hand, it can be argued that it enhances the sensitivity of culture techniques, which is especially important when the routine use of broad-spectrum antibiotics may cause false-negative results, both in culture and in lung pathology. On the other hand, the high sensitivity may result in colonizing organisms in low colony counts (e.g. as in chronic bronchitis) being counted as true pathogens.

With this caveat in mind, the most publicized study of bacterial coinfection in H1N1 found that, by a combination of PCR and immunohistochemistry, a coinfecting organism could be identified in 22/74 fatal cases 26. The distribution of organisms was comparable to that observed in prior influenza superinfections: S. pneumoniae (45%), S. pyogenes (27%), S. aureus (32%), Streptococcus mitis (9%), H. influenza (5%), and multiple organisms (18%). (So far, the literature contains only one published report of a definitive coinfection with H1N1 and CA-MRSA.) The editorial note in the study concludes that “[t]he findings in this report indicate that, as during previous influenza pandemics, bacterial pneumonia is contributing to deaths associated with pandemic H1N1” but cautions that “the results cannot be used to assess the prevalence of bacterial pneumonia among patients who have died from pandemic H1N1.” A series of 36 pediatric deaths also showed significant coinfections with S. aureus, S. pneumoniae, and other Streptococcus species 27.

A molecular study of 199 cases of H1N1 in Argentina allowed for the identification of coinfecting bacteria and viruses by PCR of nasopharyngeal swabs 28. This study provided the best estimate of superinfection so far, detecting at least one additional potential pathogen in 152/199 (76%) of cases. Clinical outcomes seen in this molecular survey suggested that
coincident with *S. pneumoniae* (62 cases) was associated with a worse prognosis. Additional bacteria identified included *H. influenzae* (104 cases), methicillin-sensitive *S. aureus* (35), and MRSA (6), as well as a smaller number of cases of *Klebsiella pneumoniae*, *Acinetobacter baumannii*, and *Serratia marcescens*. These methods also allowed for the identification of coinfecting respiratory syncytial viruses (12 cases), rhinoviruses (5), and coronaviruses (3), adding an entire additional dimension to the possible causes of superinfection.

Given the prominent role of bacterial superinfection in morbidity and mortality, the fraction of critically ill H1N1 patients with evidence of bacterial pneumonia is lower than might be expected. Surveys of critically ill patients with H1N1 in Canada, Mexico, and Spain documented a relatively low rates of detection of bacterial pneumonia after ICU admission, respectively 24.4%, 8%, and 3%. Bacterial pneumonia was not noted to be associated with a poorer outcome, but overall the use of empiric antibiotics was very high. Nosocomial pneumonia has also been noted in these studies, and should be considered for any hospitalized patient not improving on appropriate therapy.

**IMPLICATIONS FOR MANAGEMENT**

The practical application of these data to the current H1N1 pandemic ultimately comes down to a few clinical questions: which H1N1 patients have post-influenza pneumonia, how should they be managed, and how do we prevent or prepare for it?

A textbook description of post-influenza bacterial pneumonia is as follows: “The patients (most often older adults or those with chronic pulmonary, cardiac, and metabolic or other disease) have a classic influenza illness followed by a period of improvement that lasts usually 4 to 14 days. Recrudescence of fever is associated with symptoms and signs of bacterial pneumonia such as cough, sputum production, and an area of consolidation detected on physical examination and chest radiograph.”

Specifically pertaining to H1N1, Wright et al. also suggest that secondary bacterial pneumonia is more likely to be characterized by a secondary fever after a period of defervescence, a positive sputum Gram stain and/or culture, increased white blood cell count, and a later onset of respiratory compromise.

There are, however, difficulties with applying these generalizations, especially in the setting of the current H1N1 pandemic:

- **Cases of infection and death appear to be concentrated in younger patients.** Older age may reduce the likelihood of H1N1 infection, possibly due to exposure to related viruses earlier in life.
- **No data are available to confirm the timing of bacterial infection described above,** and bacteria are often cultured on first presentation with H1N1.
- **Chest radiography findings in H1N1 influenza may be unilateral or bilateral,** may include consolidations or ground glass opacities, and this cannot reliably exclude bacterial pneumonia.

Cunha raises issues as to whether antibiotics should be withheld in H1N1 patients unlikely to be superinfected, since it may be rarer than previously thought. He then goes on to propose that patients without lobar or segmental infiltrates on chest radiography may not need antibiotics.

So, who is to be treated for bacterial superinfection? It is, perhaps, a tautology to state that a patient who meets criteria for diagnosis of community-acquired pneumonia or healthcare-associated pneumonia should be treated as such.

Patients who are not ill enough to be hospitalized may be considered for oral antibiotic therapy (see Cilley and Silverblatt, in this issue). Superinfection with atypical organisms such as *Mycoplasma, Chlamydia*, and *Legionella* species is rare and need not be a focus of the regimen, although tetracyclines, macrolides, or fluoroquinolones may cover them incidentally.

Patients ill enough to be hospitalized may be considered for broader-spectrum antibiotics, and risk-stratified for resistant organisms. The high prevalence of CA-MRSA in influenza cases, coupled with the high morbidity and mortality, make it essential that critically ill patients receive therapy to cover MRSA, such as linezolid or vancomycin.

Of course, the optimal method of managing post-H1N1 bacterial pneumonia is prevention. Thus, vaccination against both influenza and *S. pneumoniae* are essential components of preventive health care, as are all age-appropriate vaccinations.

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Community-Acquired Pneumonia In Children

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Community-acquired pneumonia (CAP) is one of the most common infections encountered in pediatrics, with an annual incidence of approximately 40 cases per 1000 children in North America.1 Despite its frequency, CAP in children remains difficult to diagnose, evaluate, and manage because many pathogens may be responsible, co-infections occur frequently, clinical features may vary widely, and laboratory testing to support the diagnosis is limited.

**Etiology of Community-acquired Pneumonia**

Many pathogens cause pneumonia in children, including bacteria, viruses, and fungi. Because culture of lung parenchyma or pleural fluid requires an invasive procedure, most studies in children have relied on indirect methods such as rapid viral testing or **polymerase chain reaction assay (PCR)** on upper respiratory tract secretions, serology, and/or blood culture to identify the infecting pathogen. Studies that include an intensive search for etiology in hospitalized children with pneumonia identified a likely cause in up to 85% of cases, but an etiologic diagnosis is made in a much smaller proportion of outpatient cases. Due to a reluctance to perform invasive diagnostic procedures on young children, the epidemiology of CAP in children remains poorly defined.

The most common etiologies of pneumonia vary with the age of the patient (Table 1). In neonates, group B streptococcus and gram-negative enteric bacteria are the most common bacterial pathogens and are generally acquired through vertical transmission.2 Viral pneumonia with cytomegalovirus and herpes simplex virus should be considered even without a suspicious maternal history. *Chlamydia trachomatis* infection, once a common cause of infection in infants, has become much less common through prenatal screening and treatment of maternal infection.

The most common cause of bacterial pneumonia in children older than 3 weeks is *Streptococcus pneumoniae*. Before the pneumococcal vaccine was introduced in 2000, *Streptococcus pneumoniae* accounted for 13% to 28% of pediatric CAP.3 Postlicensure epidemiologic studies show that all-cause pneumonia hospitalizations in children under age 2 in the United States have decreased by 39%, providing further evidence of the role of pneumococcus as a major cause of childhood CAP.4,5

Group A streptococcus, *Staphylococcus aureus*, *Haemophilus influenzae* type b, and *Moraxella catarrhalis* are less common bacterial causes of pneumonia. The organisms *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* (formally *Chlamydia pneumoniae*) commonly cause CAP in school-age children and adolescents, although they may infect preschool-age children more commonly than generally recognized. In one study, the age of patients with atypical infection ranged from 9 months to 13 years, with 47% of infections occurring in those aged younger than 5 years.6 *Bordetella pertussis* should be considered in young or unimmunized children with paroxysmal cough, whoop, posttussive emesis, or apnea. Tuberculosis should also be considered if the patient has suggestive clinical signs, has recently been to an endemic area, or has had contact with an individual with active tuberculosis.

Most cases of CAP in preschool-age children are caused by viruses, including **respiratory syncytial virus** (RSV), adenovirus, parainfluenza 1, 2 and 3, influenza A and B, human metapneumovirus, and rhinoviruses. Preceding viral illness is thought to play a part in the pathogenesis of bacterial pneumonia. A study by Ampofo and colleagues recently showed a strong temporal association between confirmed viral respiratory illness with RSV, influenza, and human metapneumovirus and invasive pneumococcal disease over six winter seasons.7 Although their data do not prove causation, rates of invasive pneumococcal disease rose in close association with the diagnosis of respiratory viral illnesses each winter season.

Mixed infections may occur in 30% to 50% of children with CAP, including...