Review Article

Pathogen analysis of bacterial pneumonia secondary to influenza

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ABSTRACT

In human history, there have been several times of influenza raging, which have caused tens of millions of deaths and brought serious social and economic burdens. Although with the development of science, the emergence of vaccines has significantly reduced the incidence and mortality of influenza, due to the high variability of viruses, there is still a lack of effective treatment. More and more studies have found that bacterial pneumonia secondary to influenza was an important cause of the progression to critical illness or even death. Hence, diagnosis and treatment timely of secondary bacterial pneumonia are valuable. Therefore, we discuss the pathogens of bacterial pneumonia secondary to influenza, associated morbidity, mortality, and risk factors. Hopefully, it can provide some valuable references for clinical practice. Since some clinical studies have not separated pneumonia from lower respiratory tract infections, we will discuss these two situations together.

Key words: Bacterial pneumonia, influenza, pathogen

MORBIDITY AND MORTALITY OF BACTERIAL PNEUMONIA SECONDARY TO INFLUENZA

Primary influenza virus pneumonia is relatively rare, with a mortality rate of 10%–20%. It is characterized by rapid progress and easy progression to severe pneumonia, respiratory failure, or shock within 24 h. The incidence of pneumonia caused by the mixed infection of viruses and bacteria is at least three times that of viral pneumonia, and the mortality rate is about 10%. The mortality rate of secondary bacterial pneumonia is about 7%.[1]

People's understanding of bacterial pneumonia secondary to influenza has lasted for nearly a century. The incidence of postinfluenza bacterial pneumonia varies greatly between different studies and in different regions. A research report on the autopsy of influenza deaths showed that bacteria growth could be seen on 90%–100% in >3000 lung tissue, which were all considered the presence of pneumonia.[2] An investigation of influenza during the period 1918–1919 found that the major cause of deaths was secondary bacterial pneumonia.[3] A study of hospitalized or dead patients during the influenza epidemic of 1957–1958 found that about 70%–80% of cases had bacterial pneumonia.[4-6] However, the autopsy lung tissue test results of 77 American deaths during the H1N1 epidemic in 2009 suggested that only 22% had bacterial pneumonia,[7] and another large

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clinical trial from California, USA, involving 1088 influenza hospitalized or dead patients, suggested that only 4% have bacterial pneumonia.[8] None of the patients (ten patients) admitted to the Michigan Hospital intensive care unit (ICU) due to H1N1 infection had a bacterial infection;[9] only 20% of 700 patients admitted to ICU in Australia and New Zealand during 2009 H1N1 epidemic was considered to have secondary bacterial pneumonia.[10] A prospective study in China during the H1N1 epidemic in 2009 showed that 55 patients with severe influenza A had pneumonia, and 22 (40%) of them had secondary bacterial infections.[11] Observed in chronological order, the proportion of bacterial pneumonia secondary to influenza had a gradual downward trend which may be due to the increase in the development and application of influenza vaccines and pneumonia vaccines in recent years with the advancement of science and technology, so the number of patients with secondary bacterial pneumonia had decreased; in addition, antibiotics available for clinical use had gradually increased, therefore some secondary bacterial infections could be controlled in time before progressing to severe illness.

RISK FACTORS FOR INFLUENZA COMBINED WITH BACTERIAL PNEUMONIA

Studies have shown that from the perspective of age distribution, infants and the elderly are more likely to have bacterial pneumonia after being infected with influenza.[12,13] The underlying diseases of the heart and lungs are independent risk factors for the incidence of bacterial pneumonia secondary to influenza. A retrospective study showed that the rate of pregnant women hospitalized with flu or pneumonia not only increased significantly during the influenza epidemic season compared to the noninfluenza season but also the incidence was 3–4 times that of nonpregnant women.[14]

MICROBIOLOGY OF BACTERIAL PNEUMONIA SECONDARY TO INFLUENZA

The earliest report of research on pathogens related to bacterial pneumonia secondary to influenza was in 1890, which found that secondary *Streptococcal* pneumonia caused seven patients (15.6%) to die. In the investigation of the Spanish influenza pandemic of 1918, a study involving 96 lung tissue culture from influenza death cases, suggested that bacterial infections were combined. The most common pathogens were *Streptococcus pneumonia*, *Streptococcus pyogenes*, and *Staphylococcus aureus*, in addition, there was a high proportion of cases with two or more bacterial infections. Investigations of influenza in London[15] and Boston[16] in the second half of the last century found that *S. pneumonia* was the main pathogen of secondary bacterial pneumonia, but the overall mortality rate of *S. aureus* infection secondary influenza was relatively higher, which was about 32%. A case study ($n = 91$) of an influenza that occurred in Asia between 1957 and 1958 showed that the main pathogen of secondary pneumonia was also *S. pneumonia*, followed by *Haemophilus influenzae* and *S. aureus*.[17] However, the autopsy analysis of 33 cases in Cleveland, USA, during the same time found that *S. aureus* was the main pathogenic bacteria, followed by *S. pneumonia* and *H. influenza*.[6] During the influenza pandemic in Hong Kong from 1968 to 1969, the main pathogenic bacteria associated with bacterial pneumonia were also *S. pneumonia*, *S. pyogenes*, and *S. aureus*.[18]

During the period 2003–2004, the investigation on the epidemic of influenza (H3N2) in the United States performed by the Centers for Disease Control and Prevention, which included laboratory-confirmed influenza patients (7550 children and 6010 adults), showed 151 children and 97 adults developed a secondary bacterial infection. About half (48%) of the adult patients required mechanical ventilation, and 17 (18%) died. The main pathogen was *S. aureus*; however, the *S. pneumonia* was the main pathogenic bacteria in children. Whether in adult or pediatric patients, the majority of *S. aureus* were methicillin-resistant *S. aureus* (MRSA).

As mentioned previously, during the H1N1 epidemic in 2009–2010, the incidence of bacterial pneumonia was relatively lower than in the past.[19,20] Bacterial pneumonia was found in 13%–55% of the death cases.[8,19,21] An analysis of lung biopsies from 77 patients diagnosed with H1N1 infection showed that the most common pathogens were *S. pneumonia* (10 cases), *S. aureus* (7 cases, MRSA in 5 cases), and *S. pyogenes* (6 cases), *Streptococcus mitis* (2 cases), *H. influenzae* (1 case), and mixed infection (4 cases).[7]

In summary, *S. pneumonia*, *S. aureus*, *S. pyogenes*, and *H. influenzae* are more common pathogens in bacterial infection secondary to influenza. At the same time, the possibility of secondary MRSA pneumonia secondary to H1N1 should also be paid attention to in areas with high MRSA isolation.

PATHOGENESIS OF BACTERIAL INFECTION SECONDARY TO INFLUENZA

More and more epidemiological evidence suggested that there was synergism between influenza virus and bacteria. *S. pneumonia*, *S. aureus*, *S. pyogenes*, and *H. influenzae*, and *Moraxella catarrhalis* are normal parasites of the nasopharynx. In the immunocompetent host without virus infection, the above bacteria are not pathogenic.[22,23] However, when viral infection breaks this balance, bacteria have chances to invade the downward respiratory tract. Potential mechanisms for synergism could include: viruses destruct the respiratory epithelial barrier, increase bacterial adhesion and facilitate bacteria into the blood; experimental studies demonstrate that viral neuraminidase exposes pneumococcal receptors on host cells by removing terminal sialic acids, thereby increasing bacterial adhesion and

colonization; viruses can induce immunosuppression leading to bacterial susceptibility.[24]

Animal experiments have found that influenza viruses could cause neutrophils and macrophages dysfunction, excessive production of some neutrophil-independent cytokines, and activation of the immune medium, resulting in a marked increase in susceptibility to *S. pneumonia* and furthermore leading to more serious lung tissue damage than simple virus infection.[25] In addition, influenza virus infection could also damage bronchial ciliary power and reduce the removal of pathogenic bacteria. It is particularly worth mentioning that some studies suggested that influenza virus infection initiated a complex series of inflammatory waterfalls which involved innate-immune and acquired-immune mechanisms, and this inflammatory waterfall reaction would not disappear or stop in a short time, on the 12th day after influenza infection, the patient was still susceptible to secondary bacterial sepsis.[26,27]

DIAGNOSIS AND TREATMENT

Definite microbiological diagnosis is a prerequisite for targeted therapy. However, microbiological diagnosis is usually hard to make because of the limitation of test methods and materials. Obtaining sputum, respiratory aspirates, or bronchoalveolar lavage fluid depends on patients' conditions such as the severity of the disease and whether the patient can cooperate. For children, nasopharyngeal aspirates are more accurate than nasopharyngeal swabs, and the consistency of the culture of upper and lower respiratory tract specimens in children is better than in adults.[28]

With the advancement of scientific and technological methods, utilization of molecular-based pathogen panels is increasing in clinics. This method can detect multiple viruses and pathogens that are difficult to cultivate, and the detection rate is higher, and the results are obtained more quickly. However, a positive result does not necessarily indicate an active infection. Clinically, the manifestations such as cough and purulent sputum, peripheral blood white blood cell >10,000/dl, accompanied by increased neutrophil ratio, or signs of bacterial pleurisy, or even empyema, suggest that the patient has a bacterial infection.

In addition, the use of biomarkers has also significantly improved the diagnosis rate of bacterial infections. C-reactive protein and procalcitonin (PCT) are widely used clinical indicators. One study found that the sensitivity and specificity of PCT in the diagnosis of bacterial infection secondary to H1N1 were 84% and 43%, respectively, and the negative predictive value was 94% (the cutoff value is 0.29 ng/ml).[29] Accordingly, lower PCT levels seem to be a good tool for excluding secondary bacterial infection.

Based on the results of previous studies, the common pathogens of bacterial pneumonia secondary to influenza are similar to community-acquired pneumonia (CAP). Therefore, for patients with influenza suspected of secondary bacterial infection, antibiotics should be used as soon as possible. The selection of empirical antibacterial drugs can refer to the treatment guidelines of CAP and sometimes should cover MRSA.

In summary, bacterial pneumonia or lower respiratory tract infection secondary to influenza is an important cause of disease progression and increased mortality. The most common pathogens are *S. pneumonia*, *S. pyogenes*, *S. aureus*, and *H. influenza*. The mortality rate among patients with MRSA was high. In the flu season, influenza patients, especially severe patients, should be performed bacterial pathogens detection as soon as possible and give targeted treatment, which may reduce mortality and improve patient prognosis.

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