

RESEARCH ARTICLE**COVID-19 related secondary bacterial pneumonia****~Comparisons with influenza~****Author**Masafumi Seki^{1*}**Affiliation**

¹Division of Infectious Diseases and Infection Control, Tohoku Medical and Pharmaceutical University Hospital, Sendai City, Miyagi, Japan

***Corresponding author:** Masafumi Seki, MD, PhD

Division of Infectious Diseases and Infection Control, Tohoku Medical and Pharmaceutical University Hospital, 1-12-1 Fukumuro, Miyagino-ku, Sendai City, Miyagi, 983-8612, Japan

Telephone: +81-22-983-1221; Fax: +81-22-983-1232

E-mail: m-seki@tohoku-mpu.ac.jp, seki@hosp.tohoku-mpu.ac.jp

ABSTRACT

The presence of secondary bacterial infection is important in viral infectious disease. Influenza is known to become more severe with secondary bacterial pneumonia in particular when the *Streptococcus pneumoniae* and *Haemophilus influenzae* are co-infected, but with COVID-19, there are thought to be few concomitant bacterial infections. However, mortality in COVID-19 patients also increases with secondary bacterial infections, mainly *Staphylococcus aureus* such as MRSA and Gram-negative bacilli, and vigilance is needed. Consequently, there is a rising trend in prescriptions for antibiotics, but more appropriate diagnosis and antimicrobial stewardship are needed to suppress antimicrobial resistance, and vaccination will be the key strategy to prevent the severe viral infections related with secondary bacterial infection.

Key words: Antibiotics, Antimicrobial Stewardship Antimicrobial Resistance, Co-infection, SARS-CoV-2, Secondary infection,

Introduction

Novel coronavirus (SARS-CoV-2) infections and the resulting disease (COVID-19) have become a historic pandemic, and dealing with it is in the forefront of everyone's minds in the treatment of infectious disease today.¹⁻³

SARS-CoV-2 has been demonstrated to show a characteristic and powerful infectivity (transmissibility) and lethality (virulence).^{1,4,5} Moreover, similar to influenza, the mechanism for increased severity in COVID-19 is known to be alveolar flood and subsequent strong vascular damage, in addition to acute respiratory distress syndrome (ARDS) from a cytokine storm.^{6,7} Antiviral drugs such as remdesivir and steroids are actively used, reflecting the knowledge that has been accumulated in the treatment of influenza.^{7,8} However, the mechanisms to become severe from mild status in COVID-19 remain still unclear although the secondary bacterial infections have been well known as one of the representative mechanisms to be severe in influenza.

In this article, we focus on secondary infections, particularly secondary bacterial pneumonia in COVID-19, which is known to be a mechanism involved in the increased severity of influenza, and considers important points in increased severity and the treatment of COVID-19 in comparison to that of influenza from the perspective of co-infection of bacteria and use of antibiotics.

Pathology And Classification Of Influenza-Related Pneumonia

Influenza virus-related pneumonia is known to be associated with old age, as well as underlying diseases of the lungs, diabetes mellitus, obesity, and pregnancy.⁹ It is included as a risk factor in various guidelines.^{10,11}

Influenza virus-related pneumonia is often a secondary pneumonia that occurs with the involvement of a bacterial co-infection.^{12,13} Frequently, it is more common than primary influenza virus pneumonia caused by the virus alone, and in this regard it is more important.^{14,15} Of the pathogenic bacteria, like the bacteria causing community-acquired pneumonia, *Streptococcus pneumoniae* and *Haemophilus influenzae* are the most important.^{9,16} We also confirmed in an experiment using mice and human cases that severity was increased in strains with co-infection of *Streptococcus pneumoniae* and *Haemophilus influenzae*.¹⁶⁻¹⁸ *Streptococcus pneumoniae* was also the most commonly detected bacteria from patients with severe influenza in a national survey, suggesting the importance of secondary infection with pneumonia pathogens centered on influenza virus—*Streptococcus pneumoniae*.^{12,13}

The bacterial infection rate of patients who died of influenza during the “Spanish flu” pandemic around 100 years ago, when penicillin drugs and other effective

antibiotics did not exist, rose to about 90%.¹⁹ Only about ten years ago, at the time of the “novel influenza,” a study of autopsy cases reported that the bacterial infection rate was greater than 30%, which strongly backs the importance of secondary bacterial infection in influenza.²⁰

Status of Covid-19 Related Secondary Infection and Antibiotic Use

The situation is different with COVID-19 today. In COVID-19 patients, there are far fewer cases of co-infection with bacteria than with influenza, and the bacterial infection rate at the time of diagnosis is reported to be only about 3.5%.²¹ In an analysis that included mild–moderate cases, as well as severe cases, the rate of secondary bacterial pneumonia after hospitalization jumped to 15.5%.^{2,3,22} Thus, the impression is that, though vigilance is still needed, the frequency of bacterial co-infection is lower than in influenza.

Unlike influenza virus infection that mainly breaks down alveolar epithelial cells, the major characteristics of SARS-CoV-2

infection are viremia from damage to vascular endothelial cells, which have a high distribution of angiotensin-converting enzyme 2 (ACE2) receptors, pulmonary edema, and septic embolization.^{6,7} This is thought to be why the typical pneumonia and pulmonary damage are not always the main pathology.

This is also strongly suggested from a report that the bacteria detected in COVID-19 patients with secondary bacterial pneumonia are mainly bacteria related to blood stream infection, which are often detected in cases of bacteremia and sepsis, such as *Staphylococcus aureus* and Gram-negative bacteria, rather than the main pathogenic bacteria in typical pneumonia, such as *Streptococcus pneumoniae* and *Haemophilus influenzae*.^{22,23} These cases with demonstrated bacterial infection in COVID-19 were all severe, and although the frequency of secondary pneumonia and secondary infectious disease, especially due to *Streptococcus pneumoniae* in COVID-19 is low, the mortality rate is thought to rise considerably with these secondary diseases as we experienced (Figure 1).

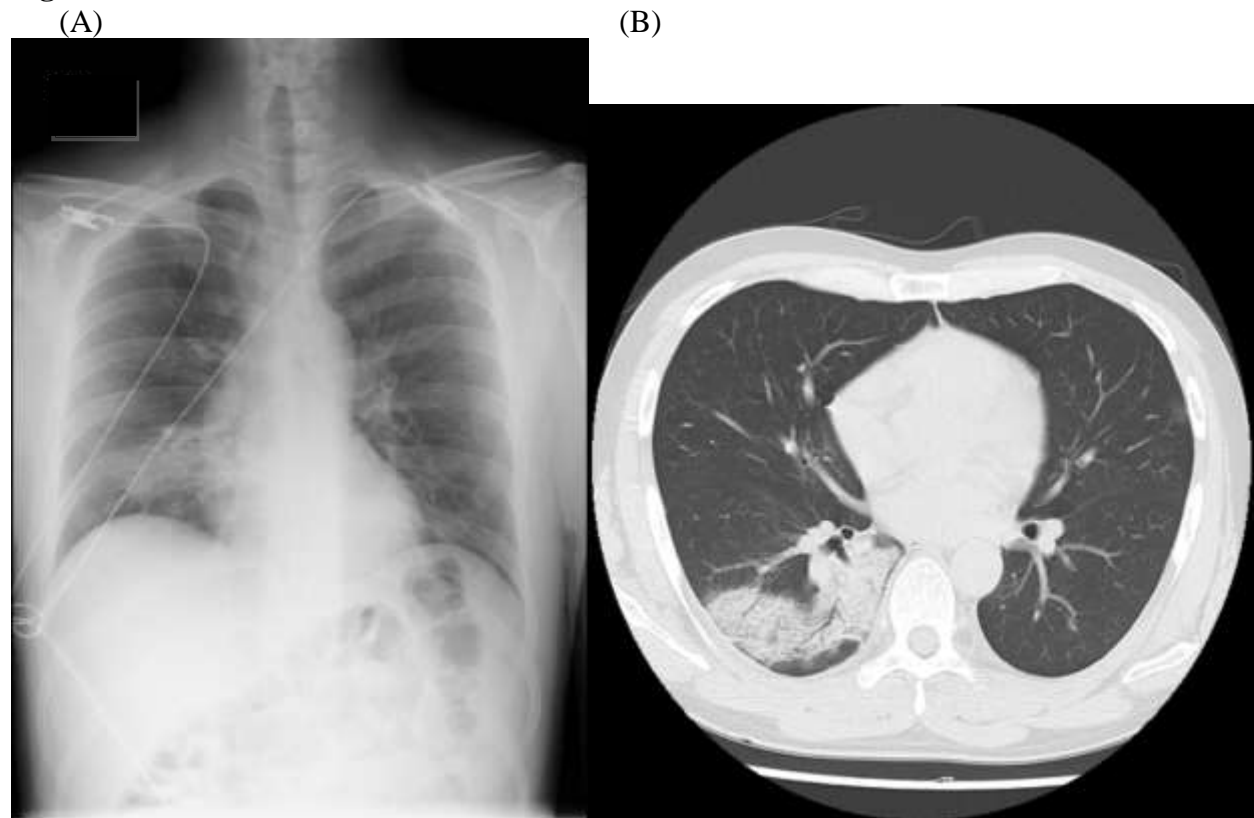
Figure 1

Figure 1: Chest X-ray (A), and computed tomography (B) findings of the 38 years old male COVID-19-related pneumococcal pneumonia patient. Massive infiltration shadow was found in lower left lung of the patient. This patient finally died although he received the appropriate treatments by remdesivir and ampicillin/sulbactam.

For *Staphylococcus aureus* in particular, the detection rate is second to *Streptococcus pneumoniae* even in influenza, and many influenza cases presenting with septic embolization are reported to become serious to the point of death.¹² With COVID-19, further caution is needed with respect to *Staphylococcus aureus*, including MRSA.^{22,23} Therefore, with *Staphylococcus aureus* in mind, it may become necessary to use antibiotics, including vancomycin. However,

whereas the use of diverse antibiotics, such as carbapenem drugs, is also reported with Gram-negative bacteria in mind, the possibility of somewhat excessive and preventive use cannot be ruled out.²² As mentioned above, although the involvement of bacterial infection in COVID-19 is relatively small, prescriptions for antibiotics rose 71.3%.²¹ In influenza, not only antiviral agents, also antibiotics use might be improve the mortality and hospitalization rates,²⁴

however, the use of unnecessary antibiotics is linked to an increase in antimicrobial resistance, and so antimicrobial stewardship, the basis of infectious disease treatment that has been recommended for some time, and, above all, performing basic tests, such as blood cultures, urine cultures, and radiographs, in all cases to accurately diagnose bacterial co-infection and bacterial strains may be considered crucial.^{25,26}

Conclusions

Importance of prevention, including vaccines

Vaccination may be considered the pillar in preventing influenza virus infections and bacterial infections and pneumonia related to viral infections such as COVID-19.^{7,27,28} The appearance of COVID-19 vaccines that are promising not only in inhibiting severity and

decreasing mortality, but also in preventing onset, has been a breakthrough.^{28,29} Vaccination of the elderly, as well as high-risk patients, particularly those with chronic lung disease, is important in COVID-19 similar to influenza and pneumococcal pneumonia.^{30,31}

In recent years, pneumococcal vaccines have become generally available in Japan and elsewhere, and following public subsidies for 23-valent capsular polysaccharide vaccines for those ≥ 65 years old, 13-valent conjugate vaccines for those aged 6–64 years old have been approved.³² In a fair number of reports, *Streptococcus pneumoniae* has been among the bacteria detected in secondary bacterial pneumonia of COVID-19,²² and the skillful combination of pneumococcal vaccines with influenza vaccines and COVID-19 vaccines will be a major issue.

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