RESEARCH ARTICLE

Mechanisms and Managements of Influenza and its Related Pneumonia

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ABSTRACT

Influenza have been a huge issue mainly in elderly people, particularly on the management of patients with pneumonia.

The influenza-related pneumonia were generally divided in to two categories, such as primary influenza pneumonia and influenza-related bacterial pneumonia, respectively. The molecular mechanisms, including neutrophil extracellular traps (NETs) might be contributed to severe influenza mediated through the 'cytokine storms', similar to COVID-19. Co-infection with influenza virus and bacteria were suggested to synergic, and also exacerbate the influenza.

The importance of administration of anti- influenza, including Baloxavir, a novel anti-influenza agent, and preventive efforts centered on vaccinations combined with influenza and pneumococcal vaccines should be considered.

Key words: Anti-influenza agents, Antimicrobial stewardship, Vaccine, SARS-CoV-2, COVID-19, *Streptococcus pneumoniae*

INTRODUCTION

Although the SARS-CoV-2 infectious diseases (COVID-19) has been become huge issue in the world from 2020, influenza is one of the most important respiratory infections because outbreaks occurred each winter not only in Japan, but also all over the world, and the excess mortality rate increased greatly in the pandemic years. [1-3]

In Japan, the "Nursing and Healthcare-Associated Pneumonia (NHCAP) Guideline" published by the Japanese Respiratory Society in 2011 also listed for the first time "secondary bacterial pneumonia associated with influenza," as contributing factors and again confirmed that the elderly accounted for the majority of cases.[2] As such, there is a particular need for specific measures to treat adult patients with severe influenza and those with associated pneumonia, mainly among the elderly.

Furthermore, the neuraminidase inhibitors (NAI), oseltamivir, zanamivir, peramivir and laninamivir are approved for therapeutic or prophylactic treatment of influenza virus infection, and favipiravir, a viral RNA-dependent RNA polymerase inhibitor, is approved and stockpiled for use against novel influenza virus infections in Japan should existing antivirals be ineffective [4,5]. In addition, the novel cap-dependent endonuclease inhibitor (CEI) baloxavir marboxil was approved during 2018 to treat influenza A and B virus infections and has become available [6]

In this review, we present the pathology and management of influenza pneumonia, as well as the trends of treatment, also concerned with novel anti-influenza agents.

TYPE of INFLUENZA-RELATED PNEUMONIA

Influenza virus-associated pneumonia can be largely classified into:

1. Pneumonia caused by viral infections alone (primary influenza virus); and
2. Pneumonia caused by the involvement of bacterial infections (influenza virus-associated bacterial pneumonia).[7-9]Known risk factors for these forms of pneumonia or susceptibility to aggravation include aging, underlying pulmonary disease, diabetes, obesity, and pregnancy, which are also listed in the several guidelines (Table 1).[1-3]

Table 1. Risk Factors for Aggravation of Influenza Pneumonia

- **Age 65 years or older**
- **Chronic respiratory disease (asthma or COPD)**
- **Cardiovascular disease (excluding hypertension alone)**
- **Chronic renal, hepatic, hematologic, or metabolic (e.g., diabetes) disease**
- **Neuromuscular disease (motor paralysis, convulsion, dysphagia)**
- **Immunosuppressed condition (including HIV infection or drug-induced immunosuppression)**
- **Pregnancy**
- **Residency in a long-term care facility**
- **Marked obesity**
- **Long-term treatment with aspirin**
- **Tumor-bearing**

Source: Reference 1

Primary influenza viral pneumonia is caused by viruses alone and is commonly referred to as pure viral pneumonia. It manifests in the form of so-called severe interstitial pneumonia and is very serious, since it can be further complicated and more related with so called 'cytokine storm' by bacterial infections, leading to a high mortality rate.[4,10]

Recently, one of the molecular mechanisms, such as Neutrophil extracellular traps (NETs) were reported to contribute the pathogenesis of severe influenza. NETs were consisted of DNA and enzymes, and can be induced to catch the pathogens, but are sometimes responsible for immune tissue damage collaterally.[11,12] Zhu L et al investigated NETs production in plasma and supernatant of cultured neutrophils by measuring cell-free deoxyribonucleic acid (DNA) and myeloperoxidase (MPO)-DNA complexes, and found that patients with severe influenza showed elevated plasma NET level.[13] They also found that NETs from H7N9 and H1N1 patients increased the permeability of alveolar epithelial cells, and, consequently, NET production was positively correlated with acute physiology and chronic health evaluation (APACHE) II score and multiple organ dysfunction syndrome (MODS). These data suggested that high level of NETs contributes to lung injury and is correlated with severity of disease. Thus, NETs and neutrophils might be a key factor to predict the severe prognosis in influenza patients.

Furthermore, influenza virus-associated bacterial pneumonia is caused by the involvement of bacterial infections and, importantly, is more prevalent than primary influenza viral pneumonia.[7,14,15] The most important causative bacteria for such pneumonias are the same as those that cause community-acquired pneumonia, namely pneumococci and *Haemophilus influenzae*. We have also confirmed the aggravation of

such infections in an experiment conducted using a mouse model of co-infection by pneumococci and *Haemophilus influenzae*.[8,16-18] Moreover, influenza virus-associated bacterial pneumonia is characterized by a high prevalence of coinfection by *Staphylococcus aureus*. [2,3] This is thought to be attributable to the bacterial protease of *Staphylococcus aureus*, which promotes the cleavage of surface protein hemagglutinin (HA) on influenza virus, leading to viral activation.[19]

These influenza-related pneumonia were mainly found in elderly, such as 70 to 90 years old ages, in recent national surveillance data in Japan, however, non-survival patients were found in younger age groups, including from 30 to 70 years old (Figure1). These data suggested that not only viral and bacterial factors, but also the activated immunological factors might be important to exacerbate of influenza.[20] In children, it is known that atelectasis after influenza were frequently found, and bronchoscopy should be considered to release the obstructive lesions (Figure 2).[21]

Figure 1

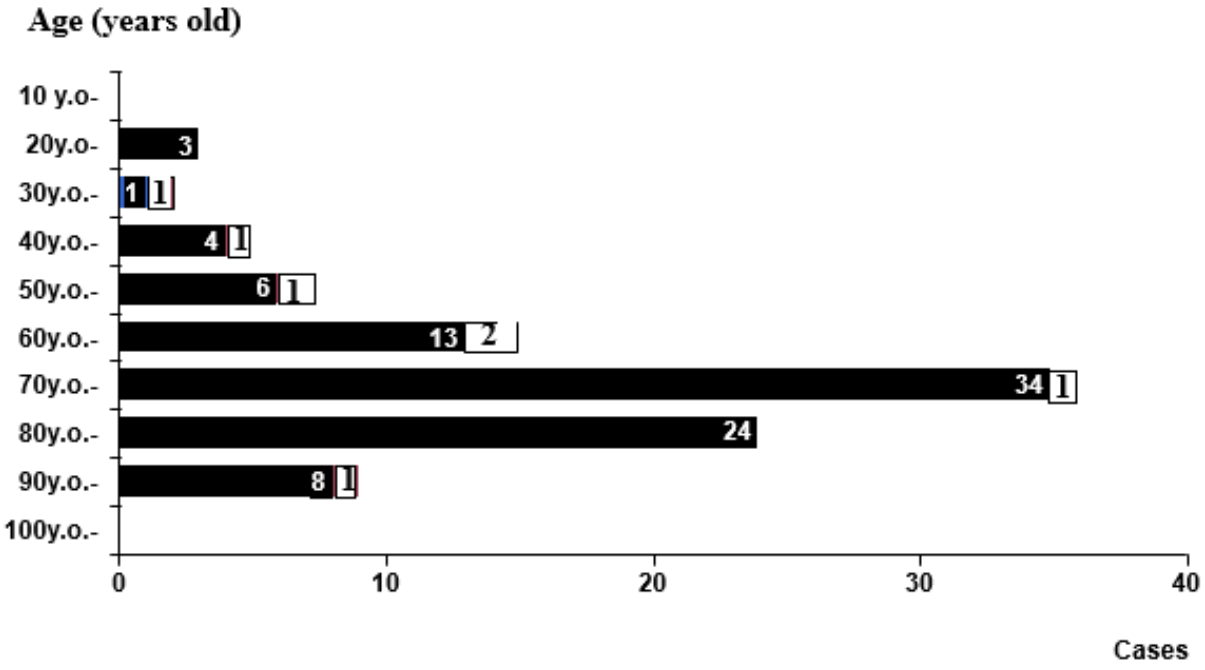

Figure 1: The number of hospitalized cases of influenza-related pneumonia from the prospective multicenter cohort study via internet surveillance in Japan (n-100). Black bars shows the number of survived and improved patients, and white bars shows the non-survived patients, respectively.

Figure 2

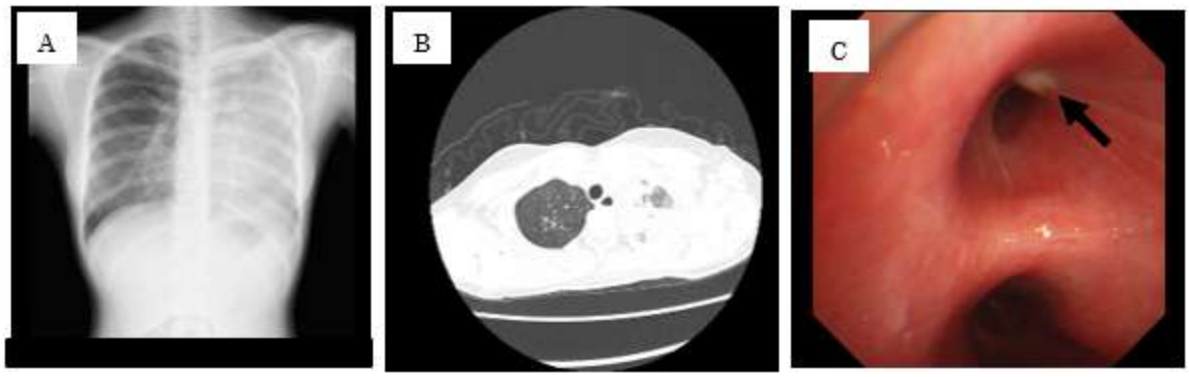

Figure 2: Chest X-ray (A), computed tomography (B), and bronchoscopy (C) findings of the 16 years old girl influenza pneumonia patient. Massive atelectasis were found in upper left lung of the patient (A and B), and pus in the left main bronchus (C, arrow) suggest occlusion of the left lung.

TREATMENTS by ANTI-INFLUENZA AGENTS

The treatment of influenza per se has seen remarkable advances with the availability of oseltamivir (Tamiflu®), zanamivir (Relenza®), and other anti-influenza agents; it is far different from the past when conventional symptomatic treatments were become available and standardized.[1,4]

Subsequently, with a pandemic of a new strain of influenza in 2009, new anti-influenza agents were approved for use one after another, ushering in a new phase in the field of influenza treatment. The biggest feature of these new drugs is that a single intravenous dose or inhalation is sufficient to achieve efficacy; thus, the challenge is how best to prescribe antibiotics and other agents to complement the use of these drugs.[4,22,23]

In addition, recent recommendation for the Management of Influenza also provide the clinical indications for favipiravir (trade name: Avigan).[24,25] Favipiravir exhibits an extremely powerful antiviral effect owing to its inhibition of viral replication. It has further attracted attention because of reports of its indication for the treatment of Ebola hemorrhagic fever and COVID-19, which is caused by an RNA virus as well. However, with some unresolved issues in terms of adverse drug reactions such as hyperuricemia, the Ministry of Health, Labour and Welfare has required particularly strict adherence to its clinical indication when prescribing the drug.

The availability in 2018 of baloxavir marboxil (trade name: Xofluza), an anti-influenza agent with a novel mechanism, is also an important topic (Table 2).[6] While the emergence of low-sensitive viruses has been a concern, its overwhelming antiviral activity has been demonstrated. The key is

how to use the drug in severe cases of influenza, particularly those with pneumonia, and there are additional challenges in the treatment of severe cases of influenza, including switch therapy (Figure 3).[26] We have two different types of ant-influenza agents, such as NAI and CEI, and appropriate and combination use of these drugs could also improve the severe influenza and its related pneumonia patients.

Table 2. Development and Characteristics of Recent Anti-influenza Agents

Generic Name	Laninamivir (Laninamivir)	Peramivir Hydrate (Peramivir hydrate)	Favipiravir (Favipiravir)	Baloxavir Marboxil (Baloxavir Marboxil)
Development code	CS-8958	S-021812	T-705	S-033188
Compound originator	Daiichi Sankyo	BioCryst	Toyama Chemical	Shionogi (Japan)
Development /marketing	Daiichi Sankyo	Shionogi (Japan) BioCryst (U.S.)	Toyama Chemical	Shionogi (Japan)
Route of administration	Inhalation	Injection	Oral	Oral
Number of doses	1	1	Twice daily ×5 days	1
Mechanism of action	Neuraminidase inhibition (LANI)*	Neuraminidase inhibition (LANI)*	RNA polymerase inhibition	CAP-dependent endonuclease (CEN) inhibition
Marketing authorization (trade name)	Oct. 2010 (Inavir)	Jan. 2010 (Rapiacta)	Mar. 2014 conditional approval (Avigan)	Mar. 2018 (Xofluza)

*LANI: Long Acting Neuraminidase Inhibitors (Long-acting neuraminidase inhibitors

Figure 3

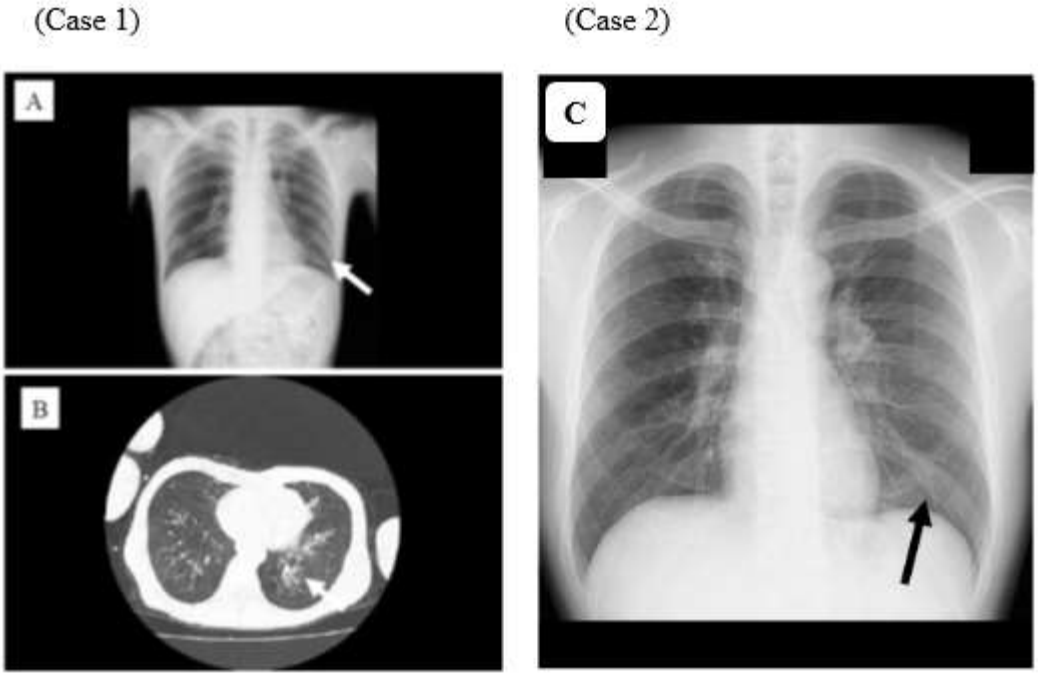

Figure 3: The chest findings those improved influenza patients by switching the anti-influenza agents. (Case 1 A and B): 34 years old male patient who had infantile paralysis were improved by the switching from peramivir (neuraminidase inhibitors: NAI) to baloxavir/marboxil (cap-dependent endonuclease inhibitor: CEI). Isolated influenza virus were A/H3N2 type and found no mutation in PA region of the virus. (Case 2 C); 40 years old male patient who had the IgG related immunological disease were worsed by the baloxavir/marboxil, however, after switching to peramivir, his condition were improved. Isolated influenza virus were A/H3N2 type and found I38T mutation in PA region of the virus.

PREVENTIONS: VACCINEs

A pillar of prevention against influenza viral infections and associated pneumonia would be vaccination. Vaccination should be considered essential for high-risk patients, such as the elderly, especially those with a chronic lung disease, from the perspective of controlling aggravation and reducing mortality, rather than preventing onset.[2,3]

In recent years, the pneumococcal vaccine has become common in Japan as well, and revaccination for those aged 65 years or older has been approved. Reports indicating that there are synergistic effects with influenza vaccines have greatly increased the opportunities for their use.[27]

In Japan, the 23-valent vaccine was first approved for periodic vaccination in 2014, and the 13-valent vaccine that has been used for the pediatric population has received approval for adult use as well. Although the 13-valent vaccine covers a slightly narrower range of pneumococcal

serotypes, the conjugates it contains make stronger immunostimulation possible.[28-30] Therefore, assessments are ongoing on a regimen consisting of an initial 13-valent vaccination followed by a booster 23-valent vaccination.[31]

CONCLUSIONS

The influenza epidemic each winter has resulted in a large number of victims, who are mostly elderly, and has become a major social problem. Pneumonia is particularly important as a key complication in influenza. It is clear that co-infection by influenza virus and bacteria leads to a synergistic worsening, and measures to control both are urgently needed.

Recently, SARS-CoV-2 have been spread and become pandemic in the world, however, we will be able to manage this tremendous viral infection by the lessons from influenza managements, including the appropriate use of the anti-viral agents and vaccines to prevent mutant and resistant strains.

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