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Clinical Differences in Hospitalized Adult Influenza Patients between the A (H1N1) pdm09 and the A (H3N2) Seasons in Japan

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Abstract

To determine the differences in the clinical features of hospitalized elderly patients with influenza between the A (H1N1) pdm09 and the A (H3N2)-dominant seasons, 12 adult patients (mean age, 76.5 years) with influenza who were hospitalized during the 2015-2016 A (H1N1) pdm09-dominant season were compared with 26 adult patients (mean age, 82.5 years) with influenza who were hospitalized during the 2016-2017 A (H3N2)-dominant season. Compared with the A (H3N2)-dominant 2016-2017 season, the A (H1N1) pdm09-dominant 2015-2016 season had fewer non-survivors, but had significantly fewer patients who required oxygenation/respirator support and intravenous anti-influenza agents, such as peramivir. Among the severe patients who received oxygenation/respirator support, the outcomes were better in the A (H3N2)-dominant 2016-2017 season than in the A (H1N1) pdm09-dominant 2015-2016 season. The pneumonia types and detected bacteria did not differ between the two seasons, but the use of sulbactam/ampicillin was more frequent in the A (H1N1) pdm09-dominant 2015-2016 season than in the A (H3N2)-dominant 2016-2017 season. These data suggest that peramivir treatment and oxygenation/respirator support, but not sulbactam/ampicillin administration, may improve the outcome of severe elderly patients hospitalized for influenza, especially the A (H3N2) type.

Keywords: Influenza; Pneumonia; Peramivir; Oxygenation; Respirator; Sulbactam/ampicillin

Introduction

Influenza virus infection is a major respiratory infectious disease that generally induces bronchitis and pneumonia [1]. The virus causes an acute febrile illness with malaise, and complication with bacterial pneumonia can become fatal in the elderly [2,3]. The potentially fatal synergistic effect between the influenza virus and bacteria has been suggested to result from receptor-mediated pathways and other mechanisms [4-6].

In 2009, a novel influenza A (H1N1) pdm09 virus caused outbreaks of respiratory illness in the southern United States of America and reached nearly every country in the world within several weeks [7]. Data published early in the pandemic showed that infection and serious illnesses occurred mostly in children and young adults; this situation differed significantly from that of seasonal influenza [8,9]. In contrast, seasonal influenza A (H3N2) is known to affect the elderly and was shown by Esposito et al. to have similar symptom severity and risk of serious outcomes (i.e., admission to the ICU or death) to those of the pandemic H1N1 [10]. Nevertheless, it remains unclear whether there are some differences between the A (H1N1) pdm09 and the pre-existing influenza A (H3N2), especially in adult patients with severe disease that necessitates hospital admission. In this study, we examined and compared the clinical features of adult influenza patients hospitalized during the A (H1N1) pdm09-dominant season with those hospitalized during the A (H3N2)-dominant season.

Materials and Methods

Patients and diagnostic criteria

This study enrolled a total of 38 adult patients (aged 20 years or older) with severe influenza who were admitted to the Tohoku Medical and Pharmaceutical University Hospital because of pneumonia and/or other severe conditions, such as severe dehydration, between November 2015 and April 2017, which is the influenza season in the post-pandemic period. Influenza virus infection was confirmed by examination of nasopharyngeal swab samples using a rapid antigen detection kit (Espline Influenza A&B-N; Fujirebio, Tokyo, Japan). The patients presented with fever, cough, and yellowish sputum, as well as infiltrates on chest X-ray. A diagnosis of bacterial pneumonia co-infection with influenza was confirmed by the presence of the following bacteria on culture of sputum samples: Streptococcus pneumoniae; Haemophilus influenza, including the beta-lactamase-negative, ampicillin-resistant (BLNAR) type; *Staphylococcus aureus*, including the methicillin-resistant type (MRSA); and *Escherichia coli*, including the extended beta-lactamase-producing type. Patients were diagnosed with pneumonia alone when the nasopharyngeal swabs were negative for influenza virus antigen, but there was cough and sputum production accompanied by infiltration shadows on chest X-rays.

All patients provided informed consent to participate in all procedures associated with the study, and the protocol of this study was approved by the ethics committee of Tohoku Medical and Pharmaceutical University Hospital.

Data collection and statistical analysis

The clinical and demographic data that were normally distributed were subjected to analysis of variance, with Fisher's exact test for multiple comparisons; those that were non-normally distributed were analyzed by non-parametric statistics, such as the Mann–Whitney U-rank test. When necessary, the results were further corrected using the Bonferroni method. Spearman's rank correlation was used to examine the relationships between various parameters. All data were expressed as mean ± SD. A p-value below 0.05 denoted a statistically significant difference. All analyses were carried out using Stat View software (Abacus Concepts, Cary, NC, USA).

Results

Patients

Table 1 shows the demographics and baseline characteristics of the adult influenza patients hospitalized during the A (H1N1) pdm09-dominant 2015-2016 season (n=12) and during the A (H3N2)-dominant 2016-2017 season (n=26).

		2015-2016 (n=12)	2016-2017 (n=26)	P value
Age(year)		76.5 ± 16.6	82.5 ± 22.1	0.1143
Male/female				
	Male	9 (75.0%)	15 (57.7%)	
	Female	4 (33.3%)	11 (42.3%)	0.485
Influenza A/B				
	A	8 (66.7%)	25 (96.2%)	P=0.035*
	B	4 (33.3%)	1 (3.8%)	
Underlying diseases				
	Heart diseases	4 (33.3%)	10 (38.5%)	0.71715
	Diabetes Mellutitis	3 (25.0%)	8 (30.8%)	0.7016
	Respiratory diseases	3 (25.0%)	5 (19.2%)	0.6686
	Malignacies	2 (16.7%)	1 (3.8%)	0.1955
	Cerebrovascular diseases	2 (16.7%)	0 (0.0%)	0.118
	Chronic renal failure	1 (8.3%)	1 (3.8%)	0.4345
	Autoimune diseases	1 (8.3%)	0	0.2756
	Others	3 (25.0%)	1 (3.8%)	P=0.008**
	None	1 (8.3%)	5 (19.2%)	0.3427
*p<0.05, **P<0.01				

Table 1: Clinical characteristics between H1N1 (2015-2016) and H3N2 (2016-2017)–dominant seasons.

In both seasons, the majority of the patients who needed admission and critical care were elderly, as shown by the high mean age. Both groups had a similar ratio of men to women and underlying diseases, but compared with the A (H1N1) pdm09-dominant 2015-2016 season, the A (H3N2)-dominant 2016-2017 season had more patients and tended to have more patients without underlying diseases.

Pneumonia as a complication and treatment-related outcomes

As shown in Table 2, the number of patients who survived pneumonia as a complication was significantly higher during the A (H3N2)-dominant 2016-2017 season than during the A (H1N1) pdm09-dominant 2015-2016 season. Although pneumonia is known to be one of the most common and important diseases for which admission is indicated in influenza patients, its incidence was similar in both seasons. However, the need for oxygenation/respirator support and intravenous anti-influenza agents, such as peramivir, was significantly higher during the A (H3N2)-dominant 2016-2017 season than during the A (H1N1) pdm09-dominant 2015-2016 season. In addition, among the severe patients who received oxygenation/respirator support, the outcome was better during the A (H3N2)-dominant 2016-2017 season than during the A (H1N1) pdm09-dominant 2015-2016 season (Table 3).

		2015-2016 (n=12)	2016-2017 (n=26)	P value
Pneumonia				
	Yes	8 (66.7%)	22 (84.6%)	
	No	4 (33.3%)	4 (15.4%)	0.207
Oxygenation/Respirator				
	Yes	6 (50.0%)	22 (84.6%)	
	No	6 (50.0%)	4 (15.4%)	P=0.04755*
Anti-influenza agents				
	Peramivir (div)	8 (66.7%)	20 (76.9%)	P=0.031*
	Osertamivir (po)	3 (25.0%)	5 (19.2%)	0.6697
	Laninamivir (Inhaled)	1 (8.3%)	1 (3.8%)	0.4345
Antibiotics use				
	Yes	10 (83.3%)	25 (96.2%)	
	No	2 (16.7%)	1 (3.8%)	0.195594
Outcome				
	Survived	9 (75.0%)	26 (100%)	
	Not Survived	3 (25.0%)	0	P-0.009642**
*p<0.05, **p<0.01				

Table 2: Complicated pneumonia, treatments and outcome between H1N1 (2015-2016) and H3N2 (2016-2017)–dominant seasons.

	2015-2016 (n=6)	2016-2017 (n=22)	P value
Survive	3 (50.0%)	22 (100%)	
Not survive	3 (50.0%)	0	P=0.0029**
**p<0.01			

Table 3: Outcome of the severe patients who received oxygenation/respirator between H1N1 (2015-2016) and H3N2 (2016-2017)–dominant season.

Type of pneumonia, pathogens, and antibiotics

Pneumonia types were similar between the 2 groups, but the incidence of community-acquired pneumonia and bacterial pneumonia, including mixed and secondary co-infection types, tended to be higher during the A (H3N2)-dominant 2016-2017 season than during the A (H1N1) pdm09-dominant 2015-2016 season (Table 4). The bacterial species detected were similar between the 2 groups, except for MRSA, which was more frequent during the A (H3N2)-dominant 2016–2017 season than during the A (H1N1) pdm09-dominant 2015-2016 season.

		2015-2016 (n=8)	**2016-2017 (n=22)**	**P value**
Location				
	CAP	4 (50.0%)	14 (63.6%)	
	HAPNHCAP	4 (50.0%)	8 (36.4%)	0.504
Viral-Bacteria interaction				
	Mix	5 (62.5%)	18 (81.8%)	0.6498

	Secondary bacterial	1 (12.5%)	4 (18.2%)	0.5796
	Mostly pure viral	1 (12.5%)	0	0.2501
	Not classified	1 (12.5%)	0	0.2501
Pathogens				
	Escherichia coli	0	1 (4.5%)	0.2575
	Escherichia coli ESBL	0	1 (4.5%)	0.2575
	Haemophilus influenza	1 (12.5%)	0	0.2501
	Haemophilus influenzae BLNAR	1 (12.5%)	0	0.2501
	Staphylococcus aureus	1 (12.5%)	2 (9.1%)	0.4913
	Staphylococcus aureus MRSA	0	6 (27.3%)	P=0.08#
	Streptococcus pnuemoniae	0	1 (4.5%)	0.2575
	Not detected	5 (62.5%)	13 (59.1%)	0.6734
#p<0.1				

Table 4: Pneumonia types and pathogens between H1N1 (2015-2016) and H3N2 (2016-2017)–dominant seasons.

Furthermore, among the antibiotics administered for influenza-related pneumonia, sulbactam/ampicillin was used less frequently during the A (H3N2)-dominant 2016-2017 season than during the A (H1N1) pdm09-dominant 2015-2016 season (Table 5), although the antibiotics administered during both seasons had the same course, dose, and duration.

	2015-2016 (n=10)	**2016-2017 (n=25)**	**P value**
PIPC	0	3 (12.0%)	0.5
CTX	0	1 (4.0%)	0.2575
CTRX	2 (20.0%)	13 (52.0%)	0.1311
SBT/ABPC	4 (40.0%)	2 (8.0%)	P=0.00405**
TAZ/PIPC	1 (10.0%)	3 (12.0%)	0.55
LVFX	1 (10.0%)	3 (12.0%)	0.55
STFX	1 (10.0%)	0	0.2575
GRNX	1 (10.0%)	0	0.2575
AZM	0	1 (4.0%)	0.2575
VCM	0	1 (4.0%)	0.2575
**p<0.01			

Table 5: Comparison of antibiotics use between H1N1 (2015-2016) and H3N2 (2016-2017)–dominant seasons.

Discussion

This study showed that patients with A (H1N1) pdm09 influenza had similar clinical characteristics, but had slightly higher disease severity and worse outcomes compared with patients with seasonal influenza A (H3N2). Usually, season influenza A (H3N2) is known to affect and lead to worse outcomes in the elderly; however, our data showed otherwise and were similar to those previously reported in China by Yang SQ et al. who showed that patients with A (H1N1) pdm09 pneumonia had similar clinical characteristics, but slightly higher disease severity and stronger systemic inflammatory response than those who had A (H3N2) pneumonia during the first post-pandemic influenza season [11]. Moreover, compared with the A (H3N2) cohort, the A (H1N1) pdm09 cohort presented with higher serum levels of aspartate aminotransferase, lactase dehydrogenase, interleukin (IL)-10, and IL-12 (p70), and longer duration of fever.

These data suggest that the A (H1N1) pdm09 influenza virus may be more toxic and have greater immunogenicity than the seasonal A (H3N2) influenza virus. In the study by Yang SQ et al. [11] although the treatment was similar between A (H1N1) pdm09 and A (H3N2) influenza pneumonia, immediate and early administration of intensive care and anti-influenza agents may be very critical to improve the prognosis of severe influenza, especially in elderly patients.

Peramivir is an intravenous neuraminidase inhibitor. Treatment with either peramivir or oral oseltamivir for acute seasonal influenza in hospitalized adults resulted in generally similar clinical outcomes and safety, but peramivir is suggested to have better tolerability [12]. An open-label, randomized study that was initiated during the 2009 H1N1 pandemic showed that peramivir at two different dosing regimens of 300 mg twice daily or 600 mg once daily for 5–10 days of treatment was associated with further decrease in viral shedding and clinical improvement, especially in patients with severe influenza and who could not tolerate oral feeding [13].

Oxygenation/respirator support is required for cases with severe respiratory failure. One study showed that 48 of 68 patients (71%) who received ECMO for very severe influenza-associated ARDS survived until intensive care unit discharge [14]. Among the patients with severe influenza who received oxygenation/respirator support in our study, the outcome was better during the A (H3N2)-dominant 2016-2017 season than during the A (H1N1) pdm09-dominant 2015–2016 season. These data strongly suggest the importance of early administration of intensive care.

In the A (H1N1) pdm09-dominant 2015-2016 season, *H. influenzae* and BLNAR, which are known to not respond to sulbactam/ampicillin, were included as pathogens of influenza pneumonia [15,16]. Usually, fluoroquinolones and third-generation cephalosporins are effective against *H. influenzae*, which is known to be one of the representative pathogens of community-acquired pneumonia [17-20]. Therefore, ceftriaxone might have been the better antibiotic of choice for influenza-related pneumonia during the A (H3N2)-dominant 2016-2017 season.

In this study, MRSA tended to be isolated more frequently during the A (H3N2)-dominant 2016–2017 season. MRSA pneumonia is usually known as a mimicker because intensive treatment with anti-MRSA drugs, such as vancomycin, has been shown to worsen, rather than improve, the severity of pneumonia [21]. In Japan, compared with the United States of America, vancomycin might not be needed for cases of influenza-related pneumonia because the toxin-producing type of community-acquired MRSA is very rare [15,22]

In conclusion, the outcome of influenza was better during the A (H3N2)-dominant 2016-2017 season than during the A (H1N1) pdm09-dominant 2015-2016 season. Although the incidence of pneumonia co-infection and the clinical backgrounds of the patients were similar in both seasons, immediate peramivir administration and oxygenation/respirator support, along with antibiotic administration for bacterial pathogens, including *H. influenzae*, may be important factors that contribute to the survival of patients who are hospitalized for severe influenza.

Conflict of Interest

Authors declare no conflicts of interest.

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