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□ ORIGINAL ARTICLE □

Disease Severity in Patients with Simultaneous Influenza and Bacterial Pneumonia

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Abstract

Objective To determine the differences in the clinical features of bacterial pneumonia patients between patients co-infected with influenza virus or not co-infected.

Methods Fifteen adult patients with bacterial pneumonia (7 men and 8 women) who also tested positive for influenza virus antigen were compared with those with bacterial pneumonia alone (n=28).

Results Complications with chronic lung diseases were more frequently found in bacterial pneumonia patients with influenza virus infection, compared with those who had bacteria pneumonia alone. Statistical differences were also found in body temperature, and heart rates between the two groups. CRP levels, chest X-ray infiltrates and the severity of pneumonia, as determined using the criteria of the Japan Respiratory Society (JRS) and/or the Infectious Diseases Society of America (IDSA), were also significantly worse in patients of bacterial pneumonia infected with influenza virus, than in those who had bacterial pneumonia alone.

Conclusions The severity of pneumonia in patients co-infected with influenza virus and bacteria was significantly higher than in those infected with bacteria alone. These data suggested that the influenza virus infection enhanced the bacterial pneumonia. Further study of the pathogenesis of the synergic interaction between influenza virus and bacteria is warranted.

Key words: influenza virus, bacterial pneumonia, co-infection

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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 pneumonia can become lethal in the elderly when complications involve bacterial infections (2-5). Synergistic effects between influenza virus and bacteria have been suggested (6-9) and receptor-mediated pathways and other mechanisms are implicated in lethal synergism (10, 11).

We previously described fulminant pathological changes in the lungs of mice inoculated with *Streptococcus pneumoniae* (*S. pneumoniae*) 2 days after influenza virus infection (12). The kinetics of viral titers, bacterial numbers and immune responses such as the release of cytokines and chemokines have shown that some critical immune mediators, such as Toll-like receptor (TLR) /mitogen-activated protein kinase (MAPK) signaling, cyclooxygenase (COX) expression and prostaglandin E2 (PGE2) production are increased (12).

Furthermore, chronic *Pseudomonas aeruginosa* (*P. aeruginosa*) infection in mice is exacerbated by the influenza virus, and decreased neutrophil function due to viral infection might be one inducer of lethal pneumococcal pneumonia in such mice (13-15). These results suggest that the synergistic effects of co-infection with influenza virus and bacteria are mediated through immune reactions. Here, we examined the clinical features of bacterial pneumonia affected by influenza virus co-infection.

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Table 1. Clinical Characteristics of 15 Patients with Bacterial Pneumonia Co-Infected with Influenza Virus

Pt. #	Age	Gender	Complications	Bacteria	Xp	Temp.	HR	RR	WBC	CRP	PaO_2
1	75	M	Asthma	*S. pneumoniae*	1/3<	38.9	94	26	11950	2.5	70.2
2	77	F	Tumor, old Tbc	*S. pneumoniae*	2/3>	41.0	100	30	13600	25.4	58.5
3	75	M	Brain, tumor	*S. pneumoniae*	1/3<	37.5	100	20	6160	0.7	69.0
4	68	M	Old Tbc	*S. pneumoniae*	2/3>	37.7	95	24	22910	14.6	85.0
5	58	M	IPF	*S. pneumoniae*	1/3<	40.0	112	28	3670	8.5	60.5
6	77	F	Liver, old Tbc	*S. pneumoniae*	2/3>	37.4	90	48	13210	20.8	37.0
7	81	F	CHF, COPD	*S. pneumoniae*	2/3>	34.1	125	10	13700	32.7	85.3
8	74	M	Tumor,COPD.	*S. pneumoniae*	middle	38.1	105	24	6920	6.9	69.5
9	21	F	None	*S. pneumoniae*	1/3<	39.1	96	14	12530	8.7	90.0
10	84	F	CHF, COPD.	*S. pneumoniae*	2/3>	38.1	105	24	13000	15.0	94.0
11	19	M	None	*H. influenzae*	1/3<	39.0	62	20	8740	7.0	92.0
12	19	M	None	*S. aureus*	1/3<	38.6	90	20	5450	3.5	86.5
13	88	F	old Tbc	*S. milleri*	middle	38.6	96	24	7870	14.2	78.5
14	77	F	CHF, asthma	*S. aureus*	1/3<	39.1	72	18	4610	5.3	89.3
15	57	F	Asthma	*M. catarrhalis*	1/3<	37.5	66	18	7320	0.7	88.5

COPD, chronic obstructive lung disease; Tbc, tuberculosis, IPF, idiopathic pulmonary fibrosis; CHF, chronic heart failure; tumor, malignant neoplasm; *S. pneumoniae*, *Streptococcus pneumoniae*; *H. influenzae*, *Haemophilus influenzae*; *S. aureus*, *Staphylococcus aureus*; *S. milleri*, *Streptococcus milleri* group; *M. catarrhalis*, *Moraxella catarrhalis*, Xp; Chest X ray

Materials and Methods

Patients and diagnostic criteria

Fifteen consecutive patients who attended our hospital between December 2003 and April 2004 were diagnosed with concurrent influenza virus infection and bacterial pneumonia on admission. Influenza virus infection was confirmed using a rapid antigen detection kit (Espline Influenza A&B-N; Fujirebio, Tokyo, Japan) by nasopharyngeal swab samples. In addition, they had fever, cough, and yellow sputum when they attended the hospital, and we found infiltrated shadows on chest X-rays. Specific bacteria, including *S. pneumonaie, Haemophilus influenzae* (*H. influenzae*), *Streptococcus milleri* (*S. milleri*), *Staphylococcus aureus* (*S. aureus*), and *Moraxella catarrhalis* (*M. catarrhalis*) were cultured from the sputum samples, and diagnosed as bacterial pneumonia co-infected with influenza virus.

Patients were diagnosed with bacterial pneumonia alone (n=28) when nasopharyngeal swabs were negative for influenza virus antigen, but cough and sputum were accompanied by an infiltration shadow on chest X-rays.

Pneumonia was defined as the presence of symptoms of lower respiratory tract infection along with a new infiltrate on chest radiography and no emerging alternative diagnosis. The diagnosis of bacterial pneumonia was considered probable in patients with sputum culture positive for the bacteria. It was classified as definite if one of the following criteria was met: a culture yielding the bacteria exclusively, or the presence of the organism in: 1) blood culture; 2) pleural fluid; 3) a transthoracic needle aspirate; 4) a tracheobronchial aspirate with $\geq 10^5$ cfu/ml; 5) a protected specimen brush (PSB) sample with $\geq 10^3$ cfu/ml; 6) a bronchoalveolar lavage fluid (BALF) specimen with $\geq 10^4$ cfu/ml; or 7) sputum with $\geq 10^7$ cfu/ml (16).

All patients and volunteers 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 Nagasaki University and Kitakyushu Yahata Hospital.

Assessment of severity

Pneumonia severity was assessed using the clinical severity scale published by the Japan Respiratory Society (JRS: Japan) (17, 18) and/or Infectious Diseases Society of America (IDSA: USA) on admission (2). In brief, pneumonia severity was classified by the JRS as mild, moderate or severe, depending on the results of a physical examination (body temperature, pulse rates, respiratory rates and dehydration) and laboratory data (WBC, CRP and PaO_2). The Pneumonia Severity Index (PSI) of the IDSA was also calculated from data regarding age, complications, a physical examination and laboratory data on admission.

Chest X-ray findings were reviewed and assessed by three physicians blindly, and then the levels of infiltrates were determined.

Data collection and statistical analysis

Demographic data were normally distributed and analyzed with analysis of variances with Fisher's test for multiple comparisons. Clinical data of the patients were not normally distributed and were statistically analyzed with nonparametric statistics: Mann-Whitney U-rank test. Where 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 are expressed as means ± S.D and analyzed by using Stat View software (Abacus Concepts, Cary, NC, USA). A p -value below 0.05 denoted a statistically significant difference.

Results

Patients

Table 1 shows the demographics and baseline characteristics of the 15 patients with both bacterial pneumonia and influenza. Respiratory tract cultures were positive in all of the patients and *S. pneumoniae* was isolated from 10 of these patients. *S. aureus* was isolated from two patients, and *H. influenzae, S. milleri* and *M. catarrhalis* was isolated from one co-infected patient each. On the other hand, bacterial

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Table 2. **Subject Demographics**

	Flu.(-) (n=28)	Flu. (+) (n=15)
Age	68.3± 15.4	69.1 ± 18.3
Gender (Male/Female)	17/11	7/8
Complicatins	25 (89.3%)	12 (80.0%)
Chronic Lung Diseaes	12/28(42.9%)	11/15 (73.3%)‡
Chronic Heart failure	4/28(14.3%)	3/15 (20.0%)
Neoplastic Diseasess	4/28(14.3%)	3/15 (20.0%)
Old Cerebral Infarction	3/28(10.7%)	1/15 (6.7%)
Liver Diseaes	2/28 (7.1%)	1/15 (6.7%)
Collagen Diseaes	1/28 (3.6%)	0/15 (0.0%)

Age are expressed as means ± SD.
‡ p<0.05 between groups, Fisher's PLSD test.

pneumonia alone patients consisted of pneumonia due to *S. pneumoniae* infection (n=21), *H. influenzae* (n=5), and *M. catarrhalis* (n=2) (data not shown).

The male/female ratio did not differ substantially between the two groups, and the age of patients diagnosed with bacterial pneumonia alone (68.3 years) and co-infection (69.1 years) were also similar (Table 2).

Co-infected patients also had complications such as chronic lung disease (n=11: old tuberculosis, 4; bronchial asthma, 3; COPD, 3; idiopathic pulmonary fibrosis, 1) chronic heart failure (n=3), neoplastic diseases (n=3), old cerebral infarction (n=1) and liver disease (n=1). Among complications, chronic lung diseases were significantly found in co-infected patients, compared with bacterial pneumonia alone patients.

Physical examinations and laboratory data

Fever was the most common frequent physical finding and the temperature was higher in co-infected patients, compared with those infected with bacteria alone (Table 3). Heart rates, but not respiratory rates were higher in the co-infected patients. Co-infected patients were not significantly dehydrated, in comparison to patients with bacterial pneumonia alone. The laboratory data revealed a significantly higher C-reactive protein (CRP; mean 11.1 mg/dl; range 0.7 to 32.7 mg/dl) in co-infected patients than in those with bacterial infection alone. However, white blood cell count (WBC) was not significantly different between co-infected patients and bacterial pneumonia alone patients, and PaO_2 did not significantly differ between the 2 groups of patients.

Chest infiltrates comprised the most common radiographic abnormality in co-infected patients. Those with mild levels (8 of 15, 53.4%) had less than one-third of the lateral lung field occupied by infiltrates; those with severe levels had infiltrates occupying over two-thirds of the lateral lung field (severe level: n=5, 33.3%) and those with moderate levels lay between (n=2, 13.3%). On the other hand, X-rays showed that all patients infected with bacteria alone had infiltrates covering over one-third of the lateral lung: moderate (n=6) and severe (n=2) infiltrates accounted for 21.4% and 7.1%, respectively, of those infected with bacteria alone (Table 3). Levels of chest X-rays findings were significantly more severe in co-infected patients than bacterial pneumonia alone.

Severity of pneumonia

The severity of bacterial pneumonia in the presence of influenza virus was assessed by the criteria of both the JRS and the PSI of IDSA. The co-infected patients were evaluated by the JRS criteria as having severe (3/15, 20.0%), moderate (9/15, 60.0%) and mild (3/15, 20.0%) pneumonia. Severe (1/28, 3.6%), moderate (7/28, 21.4%), and mild (20/28, 71.4%) pneumonia was found in patients with only bacterial infection alone (Table 3).

The PSI of IDSA criteria identified 86.1±29.5 in co-infected patients, 67.3±21.3 in bacteria infected alone patients (Table 3). The PSI of the co-infected patients was significantly higher than those of patients infected with bacteria pneumonia alone.

Discussion

The "Spanish flu" pandemic of 1918 was responsible for >20 million deaths worldwide (19, 20), a new strain of influenza (H5N1) caused many deaths in Hong Kong during 1997 and recently an avian type influenza (21) has become an epidemic. Pathological analyses of patients who succumbed to these infections have suggested that death was characteristically due to multi-system organ failure, including fulminant pneumonia: an acute respiratory distress syndrome-like process in the lung. However, the pathogenesis of the lung damage remains controversial. Our previous investigation and other studies have identified acute lung haemorrhage with massive pneumonia in the lungs of mice co-infected with influenza virus and bacteria, whereas infection with either influenza virus or *S. pneumoniae* alone in-

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Table 3. Clinical Data and Severity of Pneumonia

	Flu.(-) (n=28)	Flu. (+) (n=15)
Body Temperature(℃)	37.2± 0.9	38.2 ± 8.2‡
Heart Rates(/min.)	87.3± 17.9	102.2± 10.3‡
Respiratory Rates (min.)	23.7± 6.1	24.8± 10.2
Dehydration	23/28 (82.1%)	14/15 (93.3%)
WBC(/mm3)	11045.6± 4603.7	10109± 5000.1
CRP (mg/dl)	5.9± 6.5	11.1± 9.4 ‡
PaO_2 (Torr)	70. 5± 3.1	76.2±16.0
Chest Infiltrates(#):		
>2/3	2 (7.1%)	5 (33.3%)‡
Middle	6 (21.4%) ‡	2 (13.3%)
<1/3	20 (71.4%) ‡	8 (53.4%)
Pneumonia Severity (JRS, #):		
Severe	1 (3.6%)	3 (20.0%)‡
Moderate	7 (25.0%)	9 (60.0%)‡
Mild	20 (71.4%) ‡	3 (20.0%)
Pneumonia Severity Index (IDSA)	67.3± 21.3	86.1± 29.5‡

JRS, Japan Respiratory Society; IDSA, Infectious Diseases Society of America.
Data are expressed as means ± SD.
‡ p<0.05 between groups 2 and 3, Mann-Whitney U rank test.
NS= not significant

duces only moderate pneumonia (6, 12). Superinfected mice died significantly earlier than mice infected with one type of organism, due to severe fulminant lung damage rather than septic changes. These data suggest that extant influenza virus infection plays a key role in the pathogenesis of lethal lung diseases.

Here, we analyzed patients with bacterial pneumonia and influenza, and compared them with patients with bacterial pneumonia alone. The physical condition and laboratory data were significantly worse in co-infected patients compared with those infected with bacteria alone. X-ray infiltrates and the severity of pneumonia were also significantly increased in co-infected patients.

In demographics of patients, age and rates of complications were almost the same between co-infected and bacterial pneumonia alone patients, however, the rates of underlying chronic lung diseases were significantly higher in co-infected patients compared with those with bacterial pneumonia alone. Furthermore, three severe pneumonia cases were found in co-infected patients (patients #2, 7, 10 in Table 1), and all these patients had chronic lung disease, including COPD and old tuberculosis. Three patients without underlying diseases showed mild or moderate pneumonia (patients #9, 11, 12 in Table 1). These data suggested that underlying chronic lung diseases may be one of the most important factors that affect the pneumonia severity. It has been suggested that the incidence of secondary bacterial pneumonia is most common in elderly and in those with underlying diseases, and vaccinations against influenza virus and *S. pneumoniae* infection are recommended for those patients (1-5). Here, 8 of 15 co-infected patients and 14 of 28 bacterial pneumonia alone patients were vaccinated against influenza virus (53.3% vs 50%, not significant differences: data not shown), and none of the patients had been vaccinated for *S. pneumoniae*. An increase of vaccinated patients in Japan, especially against *S. pneumoniae* is necessary as soon as possible.

The present data suggest that a synergistic effect of viral and bacterial co-infection is related to the pathogenesis of severe pneumonia; that is, the influenza virus enhances the severity of bacterial pneumonia. The synergy between bacteria and virus were also found in other pathogens (22, 23). In influenza virus infection, severe pneumonia due to bacterial infection was reported in the pandemics of 1957-1958 (24) and 1995-1996 season (25). Influenza virus infection causes phagocytic cell dysfunction, damage to ciliated epithelium, tissue edema and other obscure disturbances of normal host defense mechanisms (26-29). These changes might be associated with increased adherence of bacteria and the prevalence of secondary bacterial diseases principally due to *S. pneumoniae, H. influenzae* and *S. aureus*. (30, 31).

Severe pneumonia develops after co-infection with bacte-

ria and influenza virus, it rapidly progresses, and is mediated by host immune mechanisms. Impaired neutrophil function with decreased lysozyme secretion and bactericidal activity might foster bacterial colonization in the respiratory tract after influenza infection, and IL-6, IL-8 and RANTES are induced in human NCI-H292 bronchial epithelial cells by influenza virus infection (13, 29, 32). We and Abramson et al analyzed co-infected mice and found an increase of immune molecules and a decrease in neutrophil function (13-15). These studies suggested that host immune reactions contribute to the pathogenesis of severe bacterial pneumonia due to co-infection of influenza virus infection. We therefore measured the concentrations of cytokines, including IL-6, RANTES, and soluble ICAM-1 in the sera of the patients in this study, but unfortunately, there was no difference between the two groups (data not shown). All patients in this study recovered, in contrast, all mice died in our previous mice study, in which IL-6 and RANTES were significantly increased in those mice lungs (12).

In conclusion, pneumonia was more severe in patients co-infected with influenza virus and bacteria, than in those with bacteria alone. Underlying chronic lung diseases may be the important factor in the frequent increase in secondary bacterial infection and subsequent development of severe pneumonia. Such severe pneumonia might be initiated by the influenza virus and mediated by the host immune response. Further studies are necessary to more precisely elucidate the pathogenesis of lung pathology and to identify effective treatment and prevention.

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