RESEARCH PAPER

Community-acquired pneumonia distinguished from influenza infection based on clinical signs and symptoms during a novel (swine) influenza A/H1N1 pandemic

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Abstract

Aims: The numbers of patients with influenza-like illnesses increase during influenza outbreaks. A study was undertaken to distinguish community-acquired pneumonia (CAP) from influenza based on clinical signs and symptoms.

Methods: This retrospective study investigated patients with positive results in the rapid influenza antigen test and those diagnosed with CAP during an influenza A/H1N1 pandemic. Significant factors for predicting risk for CAP within 48 hrs from onset and at diagnosis were selected by multiple regression analysis.

Results: Within 48 hrs of onset and at diagnosis, age, sputum and coarse crackles significantly increased the risk of CAP whereas sick contact, sore throat, and rhinorrhoea significantly decreased the risk of CAP. Duration of illness, sputum, dyspnoea, chest pain, and coarse crackles also significantly increased the risk of CAP at diagnosis.

Conclusions: CAP differed somewhat from influenza even within 48 hrs of onset and the differences became even more evident thereafter.

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Introduction

The numbers of patients who become ill with viral influenza increase during influenza epidemics. However, many other diseases also present as influenza-like illnesses (ILI), including community-acquired pneumonia (CAP). To distinguish influenza from ILI is important, yet the sensitivity of the rapid influenza antigen test (RIAT) is low^{1,2} and diagnosing influenza based on clinical signs and symptoms is difficult.³⁻⁵ Nevertheless, primary care physicians in this setting without a gold standard for diagnosing influenza infection must reach a decision as to whether to treat the source of the infection with

antiviral agents or antibiotics, or to treat only the symptoms.

Many patients present with CAP caused by other pathogens or influenza or with co-infection during influenza epidemics.⁶⁻⁸ Misdiagnosed or overlooked conditions such as pneumonia that actually require antibiotic treatment could negatively impact the prognosis.^{9,10} In addition, although most influenza is self-limiting and the incidence of pneumonia presenting with influenza is low – even in the general population infected with novel influenza A/H1N1¹¹⁻¹⁴ – antibiotics are recommended for treating patients with influenza-associated pneumonia because the mortality rate is higher for influenza-associated pneumonia with bacterial infection.^{7,8} Patients with CAP should therefore be differentiated from those with ILI.

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However, to diagnose CAP based on clinical signs and symptoms is also difficult.¹⁵ Patients with ILI during epidemics who have cough and fever are likely to have influenza,³⁻⁵ yet these symptoms are also the main symptoms of CAP^{15,16} and abnormal chest findings have a high specificity but a low sensitivity for diagnosing pneumonia.^{17,18} In addition, although an early diagnosis of influenza is necessary because neuraminidase inhibitors should be prescribed within 48 hrs,¹⁹ to differentiate influenza from CAP early is quite difficult.

A novel influenza A/H1N1 strain emerged in 2009 and was declared a pandemic by the World Health Organization. A retrospective study was undertaken of the diagnostic yield of signs and symptoms in distinguishing CAP from influenza infection during this pandemic. In addition, we investigated whether CAP could be distinguished from influenza within 48 hrs of onset in the primary care setting.

Methods

Setting

This study was undertaken at a single institution in Imizu City (Toyama Prefecture, Japan) with a population of 100,000. Of the approximately 200 persons per day presenting at our internal medicine department or at the emergency department of the outpatient clinic, about 10–20 are new patients with acute respiratory symptoms. However, during the influenza A/H1N1 pandemic, about 30–60 new patients per day presented at these two departments with acute respiratory symptoms. Most of these patients presented directly at our institution without attending other GPs or being visited by home doctors. These patients were therefore considered to be in a primary care setting.

Patients

During the novel influenza A/H1N1 pandemic, 3,464 patients with ILI were tested at our institution between September 2009 and February 2010 with the RIAT. However, not all patients with high pretest probabilities were tested – for example, those from clusters such as households, offices, or schools – because the sensitivity of the RIAT is low.

Patients with positive RIAT results were regarded as having an influenza infection because the specificity of the test – even for influenza A/H1N1 – is high,²⁰⁻²² and modalities such as real-time reverse transcription polymerase chain reaction testing (rRT-PCR) were not available in our primary care setting. The diagnosis of CAP was based on new infiltrates on chest x-rays and a clinical course that was cured by antibiotics. Two expert respiratory specialists who were independently blinded to the clinical information and diagnosis interpreted the chest x-rays. Disagreements were resolved by consensus. Patients with positive RIAT results were retrospectively compared with those who had CAP.

The following types of patients were excluded: those diagnosed with other pulmonary infectious diseases during the clinical course; those aged <15 or >75 years; those with dementia

or cerebral vascular diseases; and those with other confirmed types of acute infectious diseases, chronic respiratory or malignant diseases, or immunodeficiency. Patients referred to our institution by any other physician were also excluded. All the data and patients described here are novel and were not part of our previous study.¹⁸ Our institutional review board approved the study. Written informed consent from each patient was not required as this study was retrospective and involved only patient records and images.

Aetiology

Sputum obtained from patients with CAP by either spontaneous expectoration or with the help of nebulised saline was cultured to determine bacteria and acid-fast bacilli. Venous blood samples were tested for *Mycoplasma pneumoniae* during the acute phase and 1–2 weeks after the first hospital visit. A more than fourfold increase in antibodies was deemed positive. Urinary *Streptococcus pneumoniae* antigen was tested in urine samples. The aetiologies of other conditions including *Coxiella burnetii*, *Legionella pneumophila*, and *Chlamydia pneumoniae* were examined in patients who were suspected of having these diseases. Blood was cultured only when sepsis was suspected. Serological samples were not tested for viruses.

Analysis of data

Data were extracted from the clinical records for each patient. Clinical signs and symptoms included age, temperature, cough, sputum, sore throat, rhinorrhoea, headache, myalgia, malaise, arthralgia, appetite loss, dyspnoea, chest pain, duration of illness, lymphadenopathy, swollen pharynxes, coarse crackles, wheezing, heart rate, and systolic blood pressure at diagnosis. Extensive sick contact in clusters such as households, schools, or offices was also recorded. Significant factors for predicting the risk of CAP at diagnosis were selected by multiple regression analysis.

Patients who were tested by RIAT at our institution within 48 hrs of disease onset were selected from among those described above to evaluate the diagnostic yields of signs and symptoms within this time frame. Clinical signs and symptoms at the first hospital visit within 48 hrs of disease onset were also extracted from the clinical records of the patients and significant factors for predicting the risk for CAP were selected by multiple regression analysis.

Statistical analysis

Data were analysed using SPSS Version 11.0 for Windows. Clinical factors including signs and symptoms significantly associated with the risk of CAP were selected by multiple logistic regression analysis. The 95% confidence intervals (95% CI) were calculated for each comparison. All tests of significance were two-tailed and a p value of <0.05 was considered significant.

Results

Figures 1 and 2 show the numbers of patients in each category. Of 3,464 patients who were tested by RIAT during the study period, 718 were positive and 68 had CAP (Figure 1).

Figure 1. Numbers of patients in each category among 3,464 tested by rapid influenza antigen test (RIAT)

Chest x-rays in 72 of the 718 patients with positive RIAT findings confirmed that none of them had pneumonia. Therefore, our cohort did not contain any patients with CAP who were also RIAT-positive. None of the patients with influenza were admitted to our hospital. Fifteen of the 68 patients with CAP were admitted to our hospital and all those with CAP improved with antibiotic therapy. Table 1 summarises the aetiologies of CAP. Among 3,464 patients who were tested by RIAT, 685 were from clusters such as households, offices, or schools. Of these 685 patients, 373 (54%) were RIAT-positive and six (0.9%) had CAP.

Of the 3,464 patients who were tested by RIAT, 2,617 attended our institution within 48 hrs of onset. Of these 2,617 patients, 586 were RIAT-positive and 31 had CAP (Figure 2). None of these patients had both CAP and RIAT positivity. Of the 586 RIAT-positive patients, 528 were positive at the first testing and 58 were positive at a second or third testing. Among the 31 patients with CAP, only 16 were diagnosed at the first visit within 48 hrs of onset, whereas 11, three and one patients were diagnosed at the second, third and fourth tests, respectively. Among the 2,617 patients who presented at our institution within 48 hrs of onset and who were tested by RIAT, 641 were from clusters, of whom 316 (49%) were RIAT-positive and five (0.8%) had CAP.

The results of multiple regression analyses of the clinical signs and symptoms at the first presentation within 48 hrs of onset for predicting a risk of CAP are presented in Table 2. Age, sputum and coarse crackles significantly increased the risk of CAP. Sick contact, sore throat, and rhinorrhoea significantly decreased the risk of CAP.

The results of multiple regression analyses of the clinical signs and symptoms at diagnosis for predicting a risk of CAP in all patients with positive RIAT results and in all patients with CAP are presented in Table 3. Age, duration of illness, sputum, dyspnoea, chest pain, and coarse crackles significantly increased the risk of CAP, whereas sick contact, sore throat, and rhinorrhoea significantly decreased the risk of CAP.

Figure 2. Numbers of patients in each category among 2,617 attending our institution within 48 hrs of onset and tested by rapid influenza antigen test (RIAT) **Table 1. Bacterial pathogens in patients with pneumonia**

Aetiology	n (%)
<i>Streptococcus pneumoniae</i>	17 (25)
<i>Mycoplasma pneumoniae</i>	12 (17.6)
<i>Haemophilus influenzae</i>	7 (10.3)
<i>Staphylococcus aureus</i>	3 (4.4)
<i>Klebsiella pneumoniae</i>	3 (4.4)
<i>Moraxella catarrhalis</i>	2 (2.9)
Unknown	24 (35.2)
Total	68

Discussion

The findings of this study show that CAP is a widespread disease that presented as ILI during the 2009 pandemic. Influenza and CAP are not easy to distinguish based on signs and symptoms, as only about half of patients with CAP could be diagnosed at first hospital presentation within 48 hrs of disease onset. However, CAP and influenza infection differed somewhat. More advanced age and the absence of a sore throat or rhinorrhoea significantly increased the risk of CAP, even within 48 hrs from onset. A few days after onset, sputum also significantly increased the risk of CAP, and relatively specific findings for pneumonia such as dyspnoea or chest pain or coarse crackles were likely to be evident in patients with CAP. Findings specific to CAP would become more obvious over time because pneumonia is most likely to deteriorate without antibiotic treatment.^{9,10,18}

The definition of sick contact in this study is extensive contact derived from households, offices, or schools. Almost half of our cohort from such environments had positive RIAT results, although not all of them were necessarily tested because the sensitivity of RIAT ranges from 47% to 64% during influenza A/H1N1 pandemics²⁰⁻²² and almost 70% of patients with ILI and extensive sick contact are positive in rRT-PCR tests for H1N1.¹⁴

Table 2. Findings of multiple regression analysis of clinical signs and symptoms of patients during first presentation at our institution within 48 hrs of onset for predicting risk of CA

	Positive RIAT (n=586)	CAP (n=31)	OR (95% CI)	p value
Age (yrs)	28.2±10.8	49.0±18.6	1.338 (1.166 to 1.961)	0.0001
Sex (female)	59%	47%	0.877 (0.453 to 1.877)	0.616
Sick contact*	54%	16%	0.072 (0.019 to 0.292)	0.0001
Temperature	38.3±0.7	38.3±0.8	1.236 (0.581 to 2.629)	0.582
Cough	83%	78%	0.689 (0.207 to 2.290)	0.543
Sputum	21%	41%	4.041 (1.315 to 12.419)	0.006
Sore throat	51%	21%	0.341 (0.118 to 0.988)	0.048
Rhinorrhoea	50%	20%	0.315 (0.103 to 0.962)	0.045
Dyspnoea	2%	19%	4.885 (0.718 to 33.212)	0.105
Chest pain	2%	14%	5.263 (0.804 to 34.446)	0.083
Headache	35%	27%	1.600 (0.545 to 4.701)	0.393
Fatigue	37%	46%	1.951 (0.652 to 5.838)	0.232
Myalgia	24%	22%	0.543 (0.164 to 1.800)	0.318
Arthralgia	25%	33%	0.656 (0.184 to 2.335)	0.515
Coarse crackles	1%	28%	17.306 (3.495 to 85.708)	0.0001
Wheeze or rhonchi	1%	1%	0.899 (0.112 to 97.155)	0.900
Neck lymphadenopathy	2%	2%	0.815 (0.136 to 85.775)	0.887
Tonsillitis	6%	2%	0.654 (0.209 to 56.355)	0.696

Data are presented as numbers (%) or means ± standard deviation.

*Sick contact in this study is defined as extensive contact derived from households, offices, or schools.

CAP=community acquired pneumonia; CI=confidence interval; OR=odds ratio; RIAT=rapid influenza antigen test.

Table 3. Findings of multiple regression analysis of clinical signs and symptoms at diagnosis for predicting risk of CAP in all RIAT-positive patients and in all those with CAP

	Positive RIAT (n=718)	CAP (n=68)	OR (95% CI)	p value
Age (yrs)	28.9±11.2	53.5±20.6	1.919 (1.891 to 1.947)	0.0001
Sex (female)	58%	48%	0.827 (0.239 to 12.255)	0.951
Sick contact*	52%	9%	0.145 (0.0297 to 0.267)	0.0001
Duration of illness (days)	2.0±1.1	5.0±3.2	1.515 (1.401 to 1.662)	0.001
Temperature	38.3±0.7	38.4±0.7	1.341 (1.170 to 1.686)	0.766
Cough	86%	94%	5.026 (0.513 to 49.249)	0.166
Sputum	29%	65%	3.102 (1.247 to 7.720)	0.025
Sore throat	54%	24%	0.245 (0.076 to 0.785)	0.028
Rhinorrhoea	53%	20%	0.357 (0.114 to 0.651)	0.048
Dyspnoea	3%	25%	4.974 (1.271 to 19.470)	0.021
Chest pain	4%	14%	5.348 (1.435 to 19.929)	0.012
Headache	29%	22%	0.981 (0.353 to 2.730)	0.971
Fatigue	41%	56%	1.019 (0.377 to 2.758)	0.970
Myalgia	21%	24%	0.473 (0.156 to 1.434)	0.186
Arthralgia	32%	28%	0.675 (0.256 to 1.781)	0.427
Coarse crackles	1%	38%	39.294 (7.176 to 215.156)	0.0001
Wheeze or rhonchi	1%	2%	1.886 (0.177 to 25.135)	0.865
Neck lymphadenopathy	2%	3%	1.599 (0.147 to 17.434)	0.700
Tonsillitis	7%	2%	5.106 (0.279 to 93.504)	0.272

Data are presented as numbers (%) or means ± standard deviation.

*Sick contact in this study is defined as extensive contact derived from households, offices, or schools.

CAP=community acquired pneumonia; CI=confidence interval; OR=odds ratio; RIAT=rapid influenza antigen test.

Most patients with a high pretest probability of influenza infection were from clusters, and typical symptoms would indicate a provisional diagnosis of influenza infection in the primary care setting. However, this did not mean that all patients from clusters would always have influenza. In fact, about 1% of such patients had CAP, which indicates a need for caution when considering the diagnosis of patients presenting with ILI. Even cluster patients should undergo the RIAT when they are at high risk or have co-morbidities such as pneumonia.

Because the transmission rate of influenza is higher, sick contact should be the most significant factor for influenza infection.^{13,14} More advanced age is a significant factor for CAP because the transmission rate in children and young adults during the H1N1 pandemic is higher^{13,14} and the incidence of pneumonia is higher among the elderly.⁶ On the other hand, cough and fever are the main symptoms of both influenza infection and CAP, which causes difficulties in distinguishing between them.^{4,5,15,16} Because sputum tends to have a positive predictive value and sore throat and rhinorrhoea tend to have a negative predictive value for CAP,¹⁵ these factors could be useful for differentiation. However, the differences between each of these factors were small within 48 hrs from onset. The notable findings of the present study were that differences between CAP and influenza became clearer, and more characteristic findings for CAP including dyspnoea, chest pain and coarse crackles became significant risk factors for CAP over time. This could be because CAP deteriorates without antibiotic therapy and symptoms specific to pneumonia start to develop, whereas influenza usually improves after several days.

Differences in the signs and symptoms of influenza and CAP have not been investigated in detail, although some studies have examined predictors for CAP during periods other than influenza outbreaks.¹⁵⁻¹⁸ This could be due to difficulties associated with ruling out influenza infection in patients with CAP in primary care because rRT-PCR testing is not available in many clinical settings. However, the significance of treating patients with ILI, most of which was self-limiting, was to decrease the likelihood of missing patients who require optimal therapy for non-self-limiting diseases such as CAP. This study was conducted to determine clinical symptoms and signs that can distinguish CAP from influenza.

The major limitations of this study are that it was retrospective and included a single institution without an adequate reference standard for diagnosing influenza infection. Many patients with influenza should have false-negative RIAT results, and the RIAT was applied based on corresponding physicians' decisions for patients from clusters because the number of patients with false-negative results in diagnostic tests with low sensitivity increases in such populations. Therefore, this study did not include all patients with influenza at our institution during the pandemic. However, because the test is highly specific even for influenza A/H1N1,²⁰⁻²² nearly all patients with positive results were regarded as having influenza infection. Even

patients from clusters should be examined by the RIAT when clinical signs or symptoms are atypical or when a definite diagnosis is necessary due to high risk.

None of our patients with positive RIAT results had CAP. This might be due to false-negative RIAT results, to missing those with mild influenza-associated pneumonia, or to patients with severe influenza attending other institutions. However, the incidence of pneumonia with influenza A/H1N1 infection is low in the general population.¹¹⁻¹⁴ In addition, these patients with CAP were representative because the rate of pathogen detection and the bacterial aetiologies were similar to those in previous studies.^{23,24} Therefore, most of the CAP in this study was probably caused by bacterial infection in the absence of influenza. This study could identify significant factors that distinguish CAP from influenza during the A/H1N1 pandemic, and to differentiate CAP with or without influenza is significant because pneumonia requires optimal treatment. A study using an optimal reference standard for influenza A/H1N1 and chest radiography for diagnosing pneumonia in all patients with ILI might generate clearer results.

On the other hand, many patients with influenza A/H1N1 infection who are hospitalised or admitted to emergency departments have pneumonia.^{25,26} Primary care physicians should be aware of such conditions because influenza-associated pneumonia can rapidly progress to respiratory distress and extensive pulmonary involvement.²⁷ This study could not identify differences between CAP with and without influenza or between influenza infection with and without CAP.

The transmission rate in children and young adults during the H1N1 pandemic was higher,^{13,14} which is a different course from the usual seasonal influenza. However, because the clinical features of A/H1N1 and seasonal influenza are almost identical,^{3,5,11-14} the results of this study could also be useful during seasonal influenza epidemics. This study excluded older patients, those with dementia, cerebral vascular diseases, immunodeficiency, or malignant and chronic respiratory diseases because the signs, symptoms, and clinical course of influenza infection in such patients and in normally healthy adults might differ. Most of our study population included otherwise healthy adults who comprise the majority of patients with ILI seen in general practice. In addition, many other infectious diseases of the airway presented as ILI including the common cold, acute sinusitis, streptococcus pharyngitis and infectious mononucleosis. This study did not compare the features of influenza infection with these conditions, although to differentiate such diseases from influenza is also important. However, overlooking CAP could negatively impact the prognosis among the various types of ILI.

Many patients with ILI including CAP attend GPs or emergency departments during influenza epidemics. To distinguish CAP from influenza infection based on clinical signs and symptoms soon after onset is difficult. The findings of this study during the influenza A/H1N1 pandemic uncovered a few

differences between CAP and influenza infection even within 48 hrs of onset, and even more differences became evident thereafter. More advanced age, absence of sick contact, duration of illness, sputum, absence of sore throat or rhinorrhoea, chest pain, dyspnoea, and coarse crackles were significant factors with which to predict CAP during the influenza A/H1N1 pandemic. Evaluating these factors is useful to select patients with suspected or probable CAP and to decrease the likelihood of missing CAP even during seasonal influenza epidemics.

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Conflicts of interest

The authors declare that they have no conflicts of interest in relation to this article.

Contributorship

All authors clinically treated corresponding patients in this study. Nakanishi and Yoshimasa Yoshida reviewed all chest X-rays and clinical records.

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