

## The duration of cough in patients with H1N1 influenza

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### Abstract

**Background:** Cough is one of common symptoms of influenza, the cough duration and prevalence of postinfectious cough (PIC) after viral upper respiratory tract infection has not been well described.

**Objectives:** We aim to investigate the duration of cough and prevalence of PIC and its relation with acute symptoms, airway inflammation and cough sensitivity in patients with H1N1 influenza.

**Methods:** Patients with acute symptoms of H1N1 influenza were enrolled and followed up until cough relived. Spirometry, induced sputum test, capsaicin challenge test were conducted in patients with PIC. Cough sensitivity was presented as logarithm of provocative concentration inducing five or more coughs (logC5).

**Results:** A total of 141 cases with H1N1 influenza were enrolled. In patients with H1N1 influenza, 97.2% of them complained cough. The duration of cough was as following: <1 week (73.0%); 1–2 weeks (7.8%); 2–3 weeks (7.8%); ≥3 weeks (8.5%). Twelve (8.5%) patients had cough lasting more than 3 weeks (PIC), 4 (2.8%) patients developed chronic cough (>8 weeks). Acute symptoms, spirometry, bronchial responsiveness and sputum differential cell count were similar between patients with PIC and those without PIC, however, there was a higher prevalence of previous PIC (58.3% vs 14.7%,  $P < 0.05$ ) and elevated cough sensitivity (lgC5:  $1.18 \pm 0.58$  vs  $2.73 \pm 0.33$ ,  $P < 0.01$ ) in patients with PIC as compared with the patients without PIC.

**Conclusions:** Acute cough is common in patients with H1N1 PIC, only a few of patients develop chronic cough. Acute symptoms cannot predict PIC which is related with previous PIC and increased cough sensitivity.

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### Abbreviations

BHR bronchial hyperresponsiveness  
FEV1 forced, expiratory volume in 1 s  
FVC forced vital capacity  
PIC postinfectious cough

RT-PCR reverse transcription polymerase chain reaction

### Key words

cough – cough sensitivity – influenza – postinfectious cough

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### Authorship and contributorship

Ke-Fang Lai designed the study, participated in the experiments, wrote and revised the manuscript. Zi-Feng Yang participated in the experiments and was responsible for virus detection. Ling Lin, Yang-Qin Zhan and Wei Luo enrolled subjects and patients, assisted in data analysis and drafting the manuscript. Ru-Chong Chen participated in the presentation of data and interpretation. Bao-Juan Liu, Jia-Yu Pan and Fang Yi participated in the presentation of data and assisted in English writing of the manuscript. All authors read and approved the final manuscript.

### Ethics

This study was approved by The Ethics Committee of the Guangdong Provincial Hospital of Traditional Chinese Medicine. The IRB approval number is 2008GL-15.

### Conflict of interest

The authors have stated explicitly that there are no conflicts of interest in connection with this article.

## Background

Acute upper respiratory tract infections, such as influenza, are one of the most common illnesses. Cough and fever are typical symptoms of influenza, and often self-limited. Postinfectious cough (PIC) is considered if a cough persists more than 3 weeks after acute symptoms disappear. PIC is the most common cause of subacute cough (1, 2), and occurs in approximately 11%–25% patients with upper respiratory tract infections, but no evidence of pathogen were shown in these studies (3, 4). During outbreaks of *Mycoplasma pneumoniae* and *Bordetella pertussis* infection, the prevalence of PIC in children ranged from 25% to 50% (5), and pertussis infection is not uncommon in adults with persistent cough (6). Based on our clinical experience, some patients might develop chronic cough. The pathogenesis of PIC is unknown. It might be because of epithelial damage, airway inflammation with or without transient bronchial hyperresponsiveness (BHR). Cough reflex sensitivity increased in acute phase, and down to baseline during recovery phase (7, 8). It is uncertain whether the patients with PIC had more severe acute symptoms, airway inflammation and higher cough reflex sensitivity. Although influenza virus is the most common pathogen of upper respiratory tract infections, the duration of cough as well as the prevalence of PIC has been rarely investigated. In 2009, an influenza pandemic caused by a novel strain of H1N1 influenza occurred in China, the epidemiology and clinical characteristics of H1N1 have been widely reported (9–13). However, duration of cough has not been well described. We hypothesized that the prevalence of PIC might be low in patients with H1N1 influenza, while acute symptoms in greater severity, airway inflammation and higher cough sensitivity might be observed in those patients. This study aimed to investigate the duration of cough, prevalence of PIC and associated risk factors in patients with H1N1 influenza.

## Materials and methods

### Study design

From July to November 2009, outpatients with upper respiratory tract infections were prospectively evaluated in fever clinic of The First Affiliated Hospital of Guangzhou Medical University. Inclusion criteria were as follows: (i) patients presented with acute symptoms such as fever, headache, myalgia, rhinorrhoea, nasal congestion or cough; (ii) 2009 novel H1N1 influenza or other viral infection was confirmed with real-time fluorescent polymerase chain reaction (PCR) or viral culture; and (iii) patients were willing to participate in this study and signed written informed consent. Exclusion

criteria included: (i) patients with chronic respiratory disease such as bronchial asthma, chronic obstructive pulmonary disease (COPD), bronchiectasis, pulmonary tuberculosis or severe systemic diseases; (ii) current smoker or ex-smoker with smoking cessation for less than 6 months; and (iii) pregnant or breast-feeding female patients. The Ethics Committee of the Guangdong Provincial Hospital of Traditional Chinese Medicine approved this study. The Institution Review Board (IRB) approval number is 2008GL-15. All patients signed the consent form prior to the study.

The demographic data, clinical symptoms of eligible patients were recorded at the entry. Some patients received treatment for symptoms. All patients were followed up every week by clinic visit or telephone interview. According to the duration, cough could be divided into four subtypes: ① <1 week, ② 1~2 weeks, ③ 2~3 weeks and ④ ≥3 weeks. Clinical investigation, including chest X-ray, spirometry and induced sputum test, would be performed in patients with or without PIC at the fourth week, in order to rule out evident lung diseases or other causes of cough.

## Methods

### *Real-time fluorescent reverse transcription PCR and viral culture*

The reverse transcription polymerase chain reaction (RT-PCR) method has been described previously (14). Nasopharyngeal swab sample were collected and tested for H1N1 and other respiratory viruses by RT-PCR. The test set a synthetic internal control sequence as an amplification control.

The viral culture method has been described by Yang *et al.* (15). H1N1 were isolated from nasopharyngeal swab sample. The cytopathic effect in the virally infected cells was observed microscopically.

### *Spirometry and BHR*

Spirometry and bronchoprovocation test were performed as recommended by the American Thoracic Society (16). The forced expiratory volume in 1 s (FEV<sub>1</sub>), forced vital capacity (FVC) and FEV<sub>1</sub>/FVC were recorded. BHR was defined by a 20% decrease in the FEV<sub>1</sub> (PD<sub>20</sub>) at less than 12.8 μmol of methacholine.

### *Cough reflex sensitivity*

Cough reflex sensitivity was measured by capsaicin provocation test as described previously (17). Doubling concentrations of capsaicin (1.95–1000 μmol/L) was inhaled with a breath-activated dosimeter [automatic provocation system (APS) Jaeger] until the

**Table 1.** Clinical characteristics in patients with H1N1 influenza A or non-influenza A at entry

	Influenza A	Non-influenza A	Total
Cases	141	22	163
Age (years)	25.7 ± 10.8	35.11 ± 5.4	27.2 ± 12.6
Female/male	73/68	10/12	83/80
Mild fever (37.4–38.0°C)	26 (18.4)	5 (22.7)	31 (19.0)
Moderate fever (38.1–39.0°C)	79 (56.0)	9 (40.9)	88 (54.0)
Severe fever (>39.0°C)	36 (25.5)	7 (31.8)	43 (26.4)
Chills	28 (19.9)	3 (13.6)	31 (19.0)
Headache	100 (70.9)	14 (63.6)	114 (69.9)
Myalgia	76 (53.9)	14 (63.6)	90 (55.2)
Nasal congestion	52 (36.9)	11 (50.0)	63 (38.7)
Rhinorrhoea	70 (49.6)	12 (54.5)	82 (51.0)
Sneezing	9 (6.4)	0 (0.0)	9 (5.5)
Sore throat	88 (62.4)	17 (77.3)	105 (64.4)
Cough	128 (90.8)	17 (77.3)	145 (89.0)
Productive cough	44 (31.2)	9 (40.9)	53 (32.5)

Note: Data are presented as *N* (%) or mean ± standard deviation.

concentration inducing five or more coughs (C5). Cough sensitivity was presented as logarithm of provocative concentration inducing five or more coughs (logC5).

#### Induced sputum test and differential cell count

Sputum was induced and processed as described by our previous report (18). Briefly, sputum was induced with 3%, 4% and 5% saline inhaled in sequence for 5 min via an ultrasonic nebulizer, and cells were dispersed with dithiothreitol, filtered through nylon gauze. The cell smear was stained with haematoxylin and eosin for differential cell count. Sputum eosinophils count being or >2.5% was considered sputum eosinophilia.

#### Statistical analysis

Continuous variables were expressed as median (range) and mean ± standard deviation; Categorical variables were expressed as percentages. Data analysis was conducted using SPSS 16.0 software. Independent-samples *t*-test was applied under an equal condition of variance and chi-square test was used to compare the difference of prevalence of symptoms. *P* value of less than 0.05 was considered statistically significant.

## Results

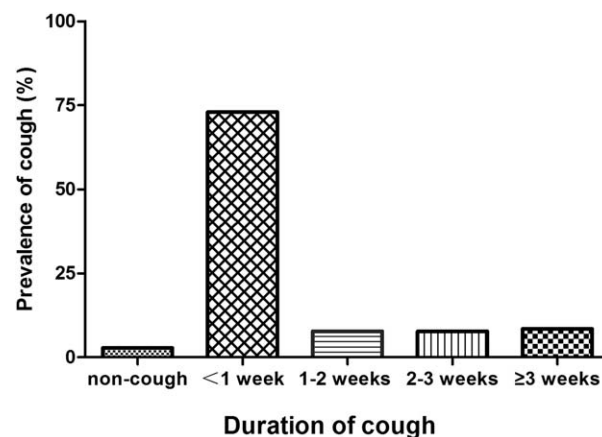
### Clinical features

From July to November 2009, upper respiratory tract viral infections were identified in 206 patients in the fever clinic of our hospital. Of whom, 43 were excluded because of active respiratory diseases, severe systemic

diseases or previous history of chronic cough and poor compliance, 22 (13.5%) had positive results of other viruses, including influenza-B, respiratory syncytial virus, adenovirus and coronavirus. 141 patients had positive results of 2009 influenza A H1N1. The median duration of acute symptoms at entry was 3 days (range, 1–7 days). The demographic characteristic and prevalence of acute symptoms were summarized in Table 1. The most common symptoms were fever (100%), cough (90.8%) and headache (70.9%) at entry.

### Duration of cough

In 141 patients with H1N1 influenza A, 97.2% of them reported cough during follow-up; 67.2% of them had non-productive cough. The distribution of duration of cough was as follows (Fig. 1): no cough, 2.9% (4/141); <1 week, 73.0% (103/141); 1–2 weeks, 7.8% (11/141);



**Figure 1.** The distribution of duration of cough.

**Table 2.** Clinical features on entry in H1N1 patients with PIC and patients without PIC

	Patients without PIC (Cough < 3 weeks)	Patients with PIC (Cough ≥ 3 weeks)
N	129	12
Sex (female, %)	66 (51.2)	7 (58.3)
Age (years)	25.5 ± 11.6	31.9 ± 12.3
Temperature (°C)	38.7 ± 0.6	38.5 ± 0.5
Nasal congestion (%)	49 (38.0)	3 (25.0)
Pharyngalgia (%)	79 (61.2)	9 (75.0)
Cough (%)	116 (89.9)	12 (100)
Productive cough (%)	38 (29.5)	6 (50.0)
History of previous post infectious cough (%)	19 (14.7)	7 (58.3)*
Duration of acute symptom (days)	4.5 ± 3.0	4.6 ± 3.8

Note: Data are presented as N (%) or mean ± standard deviation, compared with patients without PIC.

\* $P < 0.01$ .

PIC, postinfectious cough.

2–3 weeks, 7.8% (11/141); ≥3 weeks, 8.5% (12/141) (Fig. 1). Of these 12 patients with cough ≥3 weeks, 4 (2.8%) had cough lasting for more than 8 weeks which was improved during follow-up. Compared with patients with cough lasting for <3 weeks, the prevalence of previous history of PIC was significantly higher in patients with cough ≥3 weeks (58.3% vs 14.7%,  $P < 0.01$ ) (Table 2). No remarkable differences were found in body temperature, type of cough and

**Table 3.** Pathophysiological characteristics in H1N1 patients with PIC and patients without PIC

	Patients without PIC (Cough < 3 weeks)	Patients with PIC (Cough ≥ 3 weeks)
N (female)	10 (6)	10 (6)
Age (years)	27.3 ± 11.3	32.6 ± 12.0
FEV1.0pred (%)	104 ± 10	102 ± 11
FVCpred (%)	105 ± 12	102 ± 14
FEV1.0/FVC (%)	90 ± 12	92 ± 13
IgC5	2.73 ± 0.33	1.18 ± 0.58*
Differential cell in induced sputum		
Neutrophil (%)	45.1 (15.0, 80.6)	63.5 (20.3, 93.5)
Eosinophil (%)	0.5 (0, 2.5)	0.5 (0, 4.5)
Macrophage (%)	63.5 (12.1, 90.4)	32.3 (1.0, 54.7)
Lymphocyte (%)	2.2 (0.5, 10.4)	2.0 (0, 9.3)

Note: Data are presented as N (%), mean ± standard deviation or median (range). Compared with patients without PIC.

\* $P < 0.01$ .

PIC, post infectious cough.

duration of acute symptoms between PIC and non-PIC group. Notably, patients with older age were more likely to have PIC.

### Pathophysiological characteristics

Of 12 patients with PIC, 10 went through all clinical tests at the fourth week. Ten patients without PIC were enrolled as control group. All patients had normal lung function. Only 1 patient with PIC showed transient BHR, which was back to normal 12 weeks later. The cough sensitivity in patients with PIC was significantly higher than that in patients without PIC (IgC5:  $1.18 \pm 0.58$  vs  $2.73 \pm 0.33$ ,  $P < 0.01$ ) (Table 3). Sputum eosinophilia was observed in one patient (sputum eosinophils count 4.5%) with normal bronchial responsiveness, whose cough resolved after treatment with antihistamine plus decongestant.

### Discussion

The present study was conducted during the outbreak of 2009 H1N1 influenza. All patients with fever should attend fever clinic in hospital, according to the policy of China Health Ministry. Therefore, all patients with H1N1 influenza in this study had fever. Apart from fever, cough was also the most common symptom (97.2%), which was higher than that in other report (9, 19). Cao *et al.* revealed that cough occurred in 67.4% patients infected with the 2009 H1N1 influenza-A (9). Acute upper respiratory tract infectious disease is often self-limited, cough could relieve spontaneously within 3 weeks (20). By monitoring the time-course of pathogens via fluorescent PCR, Cao reported that the time window for virus clearance was <1 week in most patients; however, in a few patients virus still could be detected on day 17 after the onset of infection (9). In the present study, we found that acute symptoms other than cough lasted for no more than 1 week. This result was in line with the time window for virus clearance reported by Cao *et al.* (9).

To the best of our knowledge, this is the first study concerning cough duration following H1N1 virus infection. We found that cough lasted for no more than 1 week in most patients, only a few patients developed subacute cough, even chronic cough. When patients with subacute cough, normal chest X-ray and lung function and lack of obvious chronic airway diseases had subacute cough, PIC should be considered. The prevalence of PIC was not increased in present study. We exclusively observed the prevalence of PIC in patients with H1N1 influenza, which may be different from other virus infections. Some retrospective studies revealed that the incidence of post respiratory tract



infectious cough ranged from 11% to 25% (3, 4), but pathogens were not specified in these studies. The incidence of prolonged cough following *B. pertussis* infection was as high as 25%–50% (5). The subjects included infants, young children and preschool children, the definition of prolonged cough varied from 1 to 8 weeks in these studies. Children was more susceptible to atypical pathogen infection than adults, this may explain the higher incidence of PIC in these studies than our study. In addition, low pathogenicity of H1N1 virus could partly explain the lower incidence of PIC in our study. However, Ryan reported that the incidence of PIC was as high as 43% in patients with H1N1 in Australia (21). We postulated that difference in prevalence of PIC between our study and study by Ryan *et al.* might result from the inconsistency of the study design. In Ryan's study, the subjects with confirmed H1N1 influenza at least 8 weeks before were asked to complete a symptoms questionnaire, which may result in higher proportion of subjects with cough being enrolled. While in our study, almost all patients with H1N1 influenza stick to follow-ups from acute phase to recovery phase and went through the clinical tests if cough lasted for more than 3 weeks. Since only one patient had medication history of antiviral drugs in our study, it is unclear whether antiviral therapy could reduce the occurrence of PIC. For the first time, we investigated the relationship between acute symptoms and the onset of PIC. We noticed that the degree of fever and incidence of acute symptoms were similar between patients with and without PIC, which indicated acute symptoms could not predict the occurrence of PIC. We found that many patients with prolonged cough reported a previous history of PIC, as well as heightened cough sensitivity, which suggested the occurrence of PIC may be associated with the variation of cough sensitivity between individuals.

The pathogenesis of PIC remains unclear. Airway mucosa injury, airway inflammation, BHR and heightened cough sensitivity caused by viral infection might contribute to the onset of PIC (7, 22, 23). The transient enhancement of cough sensitivity was observed in patients with upper respiratory infection, and then back to normal after acute phase in previous studies (7, 8). Ryan *et al.* reported that cough sensitivity was three to ninefold greater in patients with post H1N1 infectious cough than patients without PIC and healthy subjects (21). Similarly, heightened cough sensitivity in patients with PIC was observed in our study as well. However, we did not measure the cough sensitivity during acute phase, the dynamic change of cough sensitivity could not be identified in the current study. We originally expected that heightened cough sensitiv-

ity could be observed in all patients, and then back to normal in patients without PIC, but become persist in patients with PIC. We think that PIC could be explained neither by BHR, nor the level of airway inflammation, as they seemed irrelevant to PIC. Influenza may result in extensive shedding of epithelial cells closed to the basement membrane in lower airway, the exposure of subepithelial nerve endings, and release of neuropeptide might be an important mechanism of cough hypersensitivity (24). Little *et al.* found that non-pneumonitic influenza infection was associated with transient bronchial hyperreactivity (23). According to the results of our study and Ryan's study, the pathogenesis of PIC was not related with BHR.

In summary, we exclusively observed the duration of cough following H1N1 influenza and the prevalence of PIC. We found that most of the patients with H1N1 influenza presented with acute cough (<3 weeks), but only a few of patients developed PIC or chronic cough. There was no BHR in patients with PIC. PIC was frequently occurred in the subjects with previous history of PIC and heightened cough sensitivity, but was not related with acute symptoms, BHR and the level of airway inflammation.

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