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Impact of respiratory virus infection in patients with chronic chest disease

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SUMMARY

This study investigated the morbidity associated with respiratory virus infections in patients with well-documented chest disease, and the risk of transmission between close contacts. Patients informed the study team if they were exposed to a family member or colleague with a cold. Patients and symptomatic index cases recorded respiratory symptoms during the study period. Acute nasopharyngeal swabs and paired sera were obtained for viral diagnosis.

Twenty-five (43%) of 58 recorded exposures resulted in a symptomatic illness and 16 (28%) patients developed lower respiratory tract symptoms. Sixteen (64%) of the 25 symptomatic patients contacted their general practitioner, 14 (56%) received antibiotics and 4 (16%) were hospitalized. Mean duration of illness was 10·6 days in symptomatic patients and 5·7 days in their corresponding index cases ($P < 0{\cdot}005$). Mean symptom scores were 100·6 in symptomatic patients and 62·2 in index cases ($P < 0{\cdot}01$). Respiratory viruses were identified in 19 (33%) episodes. Rhinovirus, coronavirus and respiratory syncytial virus infections were all associated with lower respiratory tract exacerbations.

Respiratory tract symptoms following exposure to a cold were comparatively severe in these patients with chronic chest disease. This group of patients might gain particular benefit from the introduction of effective vaccines or antiviral therapy.

INTRODUCTION

Respiratory virus infections are frequently associated with exacerbations of chronic bronchitis [1–4] or asthma [5–10], and patients with chronic chest disease appear to have an increased susceptibility to respiratory tract infections when compared to their spouses [11] or siblings [12]. Annual influenza vaccine is recommended for high-risk patients, including those with respiratory disease [13]; however, vaccines are not currently available against other respiratory viruses. In order to assess the potential benefits of future vaccines or antiviral drugs it is important to establish the impact of respiratory virus infection.

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Although many patients with chronic respiratory disease will deliberately avoid individuals with symptomatic colds this is not always possible, and the *consequences of such exposure have not been investigated. This study aimed to determine the risk of transmission of respiratory viruses to patients with asthma,* bronchitis and bronchiectasis who were in close contact with symptomatic family members or colleagues. The study also examined the relative severity of illness in symptomatic patients with chest disease and previously healthy index cases during the same episode, when each was likely to have been infected by the same virus.

PATIENTS AND METHODS

Patients and study design

The patients with chronic chest disease described in this study took part in a recently reported trial of prophylactic intranasal α_2-interferon [14]. However, the present paper considers only those episodes in which the placebo was administered. The selection of patients and study design have been described previously [14]. Subjects entering the study were adults with an established history of chronic airways disease. Asthma was defined as variable wheezy breathlessness with a documented forced expiratory volume in one second/forced vital capacity (FEV_1/FVC) ratio of $< 60\%$ at least once in their illness and a change in FEV_1 or peak flow rate of at least 15% either spontaneously or as a result of bronchodilator treatment. Chronic bronchitis was defined as a history of sputum production on most days for at least 3 consecutive months for at least two successive years, an FEV_1/FVC ratio of $< 60\%$ and a change of $< 15\%$ in peak flow rate or FEV_1 either spontaneously or as a result of bronchodilator treatment. Patients with bronchiectasis had a characteristic history of chronic purulent cough usually accompanied by radiographic changes. Subjects were examined, and gave written informed consent. Baseline full blood count, electrolytes, liver function tests, peak flow rate, FEV_1/FVC and chest X-ray appearance were recorded.

Patients were instructed to contact a member of the study team if they were in close contact with someone having an upper respiratory tract infection (URTI). URTI was defined as the presence of either one respiratory symptom (rhinorrhoea, nasal congestion, sore throat, cough, hoarseness) for 2 days, two symptoms for one day, and/or the appearance of symptoms suggestive of influenza (fever, chills and muscle aches).

Patients recorded the presence and severity of any upper or lower respiratory symptoms on a symptom diary card for as long as symptoms persisted. Peak flows were documented twice daily, before breakfast and at 18.00 h. The index cases completed similar symptom diaries. Nasopharyngeal swabs and acute blood samples were taken from patients and index cases within 24 h. The investigators were notified if the subject developed upper or lower respiratory tract symptoms or if any secondary cases occurred. Further visits were then made to confirm symptoms and take diagnostic samples. Subjects were reviewed at 7 and 21 days, and convalescent blood samples were taken from the patient, index case and any secondary cases on day 21. Symptom diary cards were collected on day 21.

Microbiology

Respiratory virus infection was established by virus isolation from nasal or throat swabs or by a significant fourfold rise in specific antibody titre between acute and convalescent serum samples. Nasal swabs were placed high in the anterior nares, and throat swabs were passed firmly over the pharynx and tonsils. Swabs were placed together in 2·5 ml of viral transport medium containing nutrient broth with 10% foetal calf serum, penicillin, streptomycin and amphotericin B. Samples were frozen immediately by plunging into liquid nitrogen and subsequently stored at −70 °C for later analysis. When thawed 0·2 ml volumes were inoculated on to monolayers of Ohio HeLa cells, MRC-5 human lung fibroblasts, C16 cells (a cell line susceptible to coronavirus, derived from MRC-5 fibroblasts [15]) and Madin Darby canine kidney (MDCK) cells (susceptible to influenza and parainfluenza). All cell lines were cultured in roller tubes at 33 °C with 5% CO_2 and observed for 14 days. Specimens inoculated on to Ohio HeLa cells were routinely passaged once after 7 days, and equivocal specimens were passaged up to three times. Rhinovirus infection was diagnosed after observation of characteristic cytopathic effect (CPE), and confirmed by demonstrating characteristic acid lability at pH 3. Influenza and parainfluenza viruses were identified by haemadsorption-inhibition on MDCK cells.

Acute and convalescent paired sera were tested for complement-fixing antibodies to adenovirus, influenza A and B, respiratory syncytial virus, *Mycoplasma pneumoniae*, *Coxiella burnetti* and *Chlamydia psittaci*. Antibodies to coronavirus 229E and OC43 were determined by enzyme-linked immunosorbent assay (ELISA) as described previously [14, 16].

Sputum was taken from all patients who were able to provide a specimen. Routine sputum bacteriology was performed in the Leicester Public Health Laboratory.

Symptom assessment and data analysis

Subjects scored each possible symptom daily on their diary cards as 0 (nil), 1 (mild), 2 (moderate) or 3 (severe). When a patient had constant symptoms (e.g. cough) only a change in the severity of that symptom was recorded. Only those upper or lower respiratory tract episodes beginning in the 10-day period following contact with the index case were analysed. The outcome of patients with chest disease after close exposure to an index case with a cold was classified as either nil; doubtful cold; upper respiratory tract infection (URTI) or lower respiratory tract infection [14]. These outcomes were defined as follows; 'nil', asymptomatic subjects; 'doubtful cold', symptoms scoring no more than 1 (mild) or involving only one of nose, throat or cough; 'upper respiratory tract infection' (URTI), symptoms involving two or more of nose, throat, cough or systemic features with at least one symptom scoring 2 (moderately severe) or worse; 'lower respiratory tract infection', symptoms in at least two of cough, sputum, wheeze or chest tightness lasting at least 2 days.

'Symptomatic days' were defined as days in which two or more symptoms were recorded, with at least one symptom moderately severe or worse. The reduction in peak flow associated with symptomatic illness was determined by comparing

the mean of the morning and evening peak flow recordings on the day of exposure with the mean of the peak flow recordings on the worst day of each episode.

Statistical analysis

Unpaired *t* tests were used to compare ages of patients with asthma and chronic bronchitis. Paired *t* tests were used to compare ages, symptom days and symptom scores in patients and index cases. Proportions of patients with symptoms were compared by χ^2 analysis. Values of $P \leqslant 0{\cdot}05$ were considered significant.

RESULTS

Characteristics of patients exposed to respiratory virus infections

Forty-nine patients with chronic chest disease recorded a total of 58 exposures to close contacts with symptomatic colds. Forty-one patients were exposed to infection on one occasion only, 7 had two exposures and 1 had three exposures. Thirty-five (60%) episodes involved patients with asthma, 15 (26%) involved patients with chronic bronchitis and 8 (14%) involved patients with bronchiectasis. Table 1 compares the age and respiratory history of patients with asthma, chronic bronchitis and bronchiectasis who were exposed to symptomatic contacts. Although all patients had a history of chronic airways disease, the majority were ambulant. Two patients were maintained on domiciliary oxygen. The overall mean forced vital capacity was 2308 ml (S.D. = 673, range 800–3650).

Outcome of exposures

Of the 58 exposures, 25 (43%) resulted in the patients developing definite respiratory symptoms; 16 (28%) were associated with an exacerbation of the underlying chest disease (6 asthmatics, 7 bronchitics and 3 with bronchiectasis) and a further 9 (15%) exposures resulted in symptoms which were confined to the upper respiratory tract (6 asthmatics and 3 bronchitics). Doubtful colds resulted from 12 (21%) exposures, and 21 (36%) exposures were not associated with any recorded symptoms. Of the 15 exposures involving patients with chronic bronchitis, 10 (67%) resulted in symptoms of upper or lower respiratory tract infection compared to 12 (34%) of the 35 episodes involving patients with asthma and 3 (38%) of the 8 episodes involving patients with bronchiectasis. Differences between groups were not statistically significant.

Of the 25 patients who developed definite upper or lower respiratory tract symptoms, 16 (64%) consulted their general practitioner and 14 (56%) received antibiotics. Four (25%) of the 16 patients with lower respiratory tract symptoms required hospital admission for the exacerbation of their chest disease but no death occurred. The mean number of recorded symptomatic days was 13·9 (S.D. = 8·2, range 4–33) for the 16 patients who had an exacerbation of their chest disease, and 6·9 (S.D. = 5·0, range 2–16) for the 9 patients who developed an URTI. The mean symptom score was 113·7 (S.D. = 78·3, range 33–316) for those who had an exacerbation of their chest disease and 77·2 (S.D. = 37·6, range 39–153) for those who developed an URTI. The mean initial peak flow for all patients was

Table 1. *Characteristics of patients (numbers of episodes) exposed to close contacts with symptomatic colds*

	Chronic bronchitis (15)	Asthma (35)	Bronchiectasis (8)	Total (58)
Mean age (years)	62·5*† s.d. 6·6 Range 47–72	42·7* s.d. 13·7 Range 17–68	50†‡ s.d. 5·5 Range 42–56	48·4
Male	11 (73%)	11 (31%)	4 (50%)	26 (45%)
Mean history of respiratory symptoms (years)	18·5§ s.d. 15·4 Range 1–51	16·5‡ s.d. 14·8 Range 1–60	39·6‡§ s.d. 12·4 Range 11–50	19·5
History of smoking**	14 (93%)	16 (46%)	3 (37·5%)	33 (57%)
Current smoker	3 (20%)	1 (3%)	0	4 (7%)

s.d., standard deviation.
* Ages in chronic bronchitis and asthma compared, $P < 0{\cdot}0005$.
† Ages in chronic bronchitis and bronchiectasis compared, $P < 0{\cdot}005$.
‡ Length of history in bronchiectasis and asthma compared, $P < 0{\cdot}0005$.
§ Length of history in bronchiectasis and chronic bronchitis compared, $P < 0{\cdot}005$.
** Difference in proportions of smokers not significant ($P > 0{\cdot}1$).

288 l/min (s.d. = 99, range 80–445). Comparison of initial and lowest peak flows for symptomatic episodes showed a mean reduction in peak flow of 72 l/min in patients with lower respiratory tract symptoms and 22 l/min in those with upper respiratory tract symptoms (unpaired t test, $P < 0{\cdot}05$).

Comparative severity of episodes in patients and corresponding index cases

Comparison of the overall severity of illness during each episode in the 25 symptomatic patients and their corresponding index cases showed that the mean number of symptomatic days in patients was 10·6 days (s.d. = 8·0, range 2–33) compared to 5·7 days (s.d. = 2·7, range 0–10) in index cases ($P < 0{\cdot}005$), and the mean symptom score in patients was 100·6 (s.d. = 68·0, range 33–316) compared to 62·2 (s.d. = 35·2, range 5–15) for index cases ($P < 0{\cdot}01$). The mean age of the patients was 50 years (s.d. = 14, range 17–71) compared to 33 years (s.d. = 19·8, range 3–62) for the index cases ($P < 0{\cdot}05$).

Fig. 1 shows mean upper and lower respiratory tract symptoms recorded each day in index cases and symptomatic patients. In the index cases symptoms were most severe at the onset of illness and declined rapidly over 10 days, whereas symptoms in patients persisted for longer periods of up to 33 days. Mean upper respiratory symptom score associated with each episode was 52·7 (s.d. = 44·9, range 11–185) in patients compared to 52·2 (s.d. = 33·7, range 10–153) in index cases. These scores were not significantly different. In contrast, mean lower respiratory symptom scores associated with each episode were 47·9 (s.d. = 39·1, range 5–162) in patients compared to 10·0 (s.d. = 8·4, range 0–28) in index cases (paired t test, $P < 0{\cdot}0005$). Most patients did not have a sequential pattern of symptoms (upper respiratory symptoms followed by lower respiratory tract symptoms), as upper and lower respiratory tract symptoms were both recorded at the onset of illness.

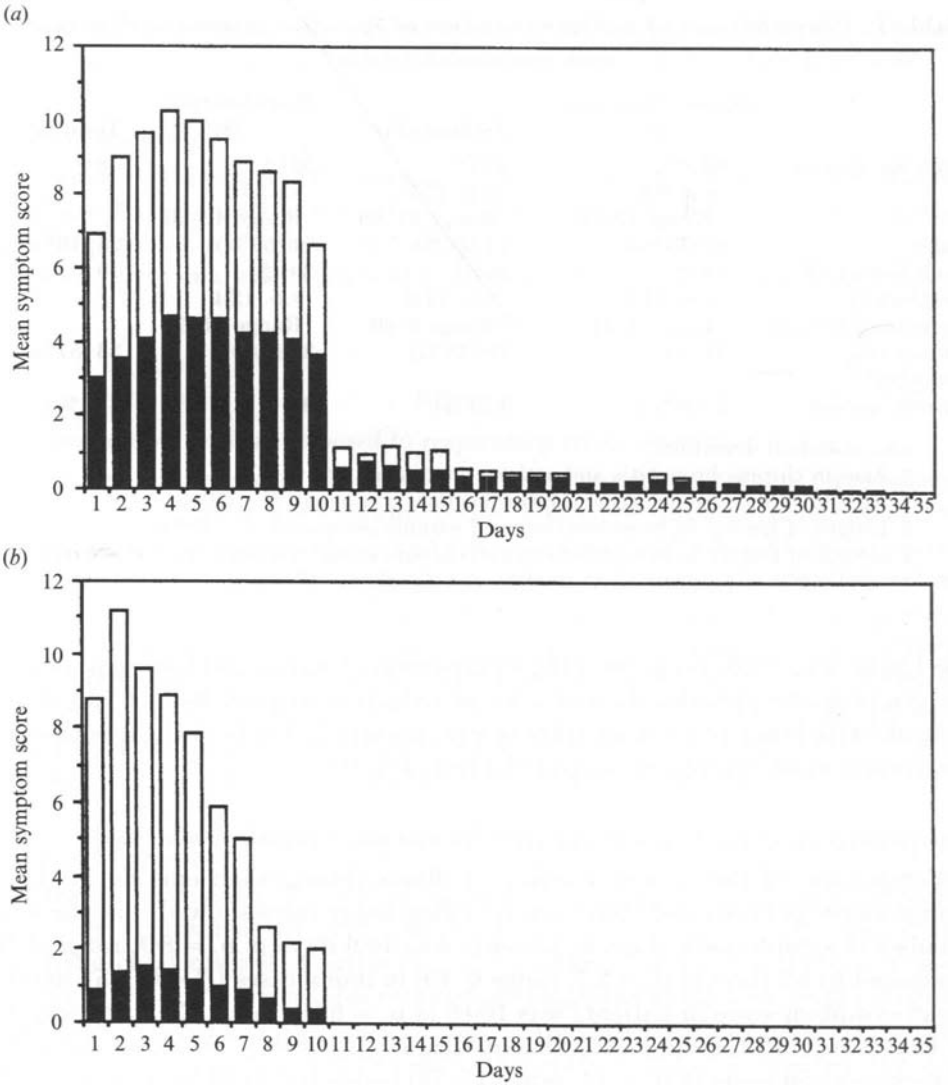

Figure 1. Comparison of mean daily upper (□) and lower (■) respiratory tract symptoms in (*a*) symptomatic patients and (*b*) index cases.

Microbiology

Acute nasal and throat swabs and acute and convalescent serum samples were obtained from the patients and index cases in all 58 respiratory episodes. The results of virus diagnosis are shown in Table 2. Rhinoviruses were isolated from 5 (4·7%) of the total of 116 nasopharyngeal swabs taken from patients and index cases. No other virus was isolated. Of the 116 paired serum samples taken from index cases and patients, 17 (15%) showed evidence of a recent respiratory virus infection (6 coronavirus 229E, 7 coronavirus OC43, 1 influenza A, 2 influenza B, 1 respiratory syncytial virus). In addition, one individual had a significant rise in complement-fixing antibody titre to *Mycoplasma pneumoniae*.

The viral aetiology was identified in 12 (21%) of the 58 index cases and 9 (16%)

Table 2. *Positive viral diagnosis and outcome of exposure to upper respiratory tract infections (Episodes where virus infection was not established in either the index case or patient are not shown)*

Outcome	Virus diagnosis in Patient	Index case
Nil	—*	229E†
	—	229E
	—	229E
	—	229E
	229E	—
	—	Rhinovirus
	—	Rhinovirus
	OC43†	OC43
	—	Influenza B
Doubtful cold	OC43	OC43
	—	Inf A and 229E
	—	Inf B and rhinovirus
	Rhinovirus	—
	—	*M. pneumoniae*
URTI	OC43	—
	OC43	—
Lower RTI	OC43	—
	Rhinovirus	—
	RSV	—

* No laboratory evidence of virus infection. † Coronavirus serotypes 229E and OC43.

patients. A respiratory virus infection was diagnosed in the patient and/or index case in 19 (33%) episodes. There was no obvious correlation between the viruses diagnosed in each episode and the subsequent outcome. Exacerbations of respiratory disease were associated with coronavirus, rhinovirus and respiratory syncytial virus infections.

All purulent sputum samples were sent for bacteriological analysis. *Haemophilus influenzae* was isolated from one specimen, which was taken from a patient from whom rhinovirus was also isolated. All other specimens showed no significant growth.

DISCUSSION

Although other studies have shown that respiratory virus infections may lead to exacerbations in patients with chronic chest disease [1–10], the risk of close exposure to symptomatic contacts and the comparative severity of respiratory virus infections in patients and previously healthy adults has not been documented. In this study we assumed that all individuals with characteristic upper respiratory tract symptoms were likely to have acquired a respiratory virus infection. Transmission occurred readily to close contacts, and 43% of patients with chronic chest disease who were exposed to symptomatic colleagues or family members developed respiratory tract symptoms. The consequences of respiratory virus infection in this group were relatively severe, as almost two-thirds of symptomatic patients had an exacerbation of their chest disease which required a consultation with their general practitioner and treatment with antibiotics. A

quarter of those who developed lower respiratory tract symptoms were admitted to hospital. Patients with chronic bronchitis appeared to be more susceptible to respiratory virus infection than those with asthma, although the numbers of patients were too small for the difference in susceptibility to reach significance.

Comparison of symptomatic episodes in patients and previously healthy index cases showed that people with chronic chest disease recovered more slowly than those with normal chests, and were more likely to develop lower respiratory tract symptoms. Pairs of infections were recorded by similar methods and occurred in similarly matched environments; it is therefore likely that patients and index cases suffered from the same respiratory virus infection. Patients were generally older than their index cases; however, age alone has been shown to have comparatively little effect on the severity of symptoms associated with respiratory virus infection [17].

The reasons for the increased severity of lower respiratory tract symptoms in patients with underlying chest disease are unclear. Active viral replication in the lower respiratory tract has been demonstrated in experimental studies where volunteers were infected with rhinovirus [19]. Conceivably the mucosal damage associated with long-standing pulmonary disease might facilitate the spread of respiratory viruses throughout the airways. Additional factors which might contribute to the deterioration in lung function associated with respiratory virus infection include the release of histamine and other inflammatory mediators [10, 20].

A respiratory virus was isolated from 4·7% of nasopharyngeal swabs taken from patients and symptomatic index cases, and 15% of paired sera showed a significant rise in antibody titre, indicating recent infection. Coronaviruses were the most frequently implicated agents in this study. It was not possible to reach any firm conclusions on the comparative severity of different respiratory viruses due to the small numbers of episodes in which viruses were diagnosed; however, the study showed that rhinovirus, coronavirus and respiratory syncytial virus infections were all capable of causing lower respiratory tract symptoms in this group of susceptible patients. The virus isolation rate was disappointing, but the results were comparable to other similar studies of naturally occurring respiratory tract infections [21–25]. The study did not take place during a major epidemic year for influenza A. The virus isolation rate might have been improved if nasal washes had been used or if specimens had been inoculated directly on to tissue culture; however, these measures were considered impracticable. At the time of the study more sensitive methods of viral diagnosis, based on the polymerase chain reaction (PCR) were not available locally. A semi-nested, reverse-transcriptase-PCR technique, for the diagnosis of rhinovirus infections, has recently been described and evaluated in our laboratory [26]. RT-PCR was found to be at least five times more sensitive than conventional cell culture in detecting rhinoviruses in nasal and throat swabs from adults with naturally occurring upper respiratory tract infections. Such techniques will be of great benefit in future clinical studies of respiratory virus disease. Secondary bacterial infection appeared to be of comparatively little importance in this study; however, antibiotics were routinely prescribed in patients with lower respiratory tract symptoms, and early use of antibiotics may have prevented bacterial infection.

The results of this study illustrate the morbidity and undoubted economic importance of respiratory virus infections. The practical implications of this study are that patients with chronic chest disease should attempt to avoid close contacts with colds, whenever possible. The incidence of influenza infection in this study was very low, and it is not possible to comment on the relative value of influenza vaccination or use of amantadine. The study highlights a need for more effective vaccines and antiviral agents; however, the immediate prospects for further therapeutic advances are small, since such a wide range of viruses is associated with respiratory tract disease.

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