Reversible airflow limitation in adults with respiratory infection

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ABSTRACT: The aim of the study was to determine the occurrence of airflow limitation and the frequency of significant reversibility in respiratory infections in adults without known asthma or chronic obstructive pulmonary disease (COPD). We also wanted to study the association between airflow limitation and aetiological agents diagnosed by serological analyses.

Spirometry was performed in 574 adult general practice patients with upper or lower respiratory tract infection, and follow-up measurement was obtained in 429 of them. In the latter group, we also obtained paired sera for analysis of antibodies against respiratory viruses, chlamydial and mycoplasmal agents.

Median forced expiratory volume in one second (FEV_1) in all patients included was 90% of predicted; significantly lower in patients with an established diagnosis of asthma or COPD, compared to those without, 77 and 91% predicted, respectively. Among the patients without known asthma or COPD there was a strong association between low FEV_1 and the symptoms cough and dyspnoea. Both acute-phase and follow-up FEV_1 was measured in 395 of the patients without known asthma or COPD, and a significant increase in median value from 92 to 96% was registered. A reversibility of FEV_1 of >15% was measured in 23% of the 395 patients, uninfluenced by anti-asthma treatment in the great majority. Patients with an established viral, mycoplasmal or chlamydial infection had a significantly lower FEV_1 at entry and a greater reversibility, compared to those without such aetiological diagnosis.

We conclude that reversible obstruction was particularly common in the patients diagnosed as having acute bronchitis, but that it was also found in the patients diagnosed as having upper respiratory tract infection. The high frequency of spontaneous reversibility in otherwise healthy adults calls for caution when response to anti-asthma treatment is interpreted in patients with possible asthma.
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It has been established that healthy persons may experience an impairment of bronchial airflow in association with respiratory infection [1, 2]. Respiratory viruses and *Mycoplasma pneumoniae* do not only cause exacerbation of asthma and chronic obstructive pulmonary disease (COPD) [3–5], but also airflow limitation and bronchial hyperreactivity in otherwise healthy persons [6–8]. Significant reversibility of airway obstruction has been shown in patients diagnosed as having acute bronchitis in two clinical studies [9, 10]. We wanted to find out whether these results could be confirmed in a larger population of adults with respiratory infection who consult a primary care doctor.

Reversibility of bronchial obstruction is a known feature of asthma, and an increase of forced expiratory volume in one second (FEV_1) of more than 15% of the initial level has been considered to be a significant response to a course of oral corticosteroids [11]. We wanted to determine how often such reversibility occurs spontaneously in otherwise healthy adults with respiratory infection.

We also wanted to study the role of respiratory viruses, mycoplasmal and chlamydial agents in airflow limitation, to find out whether certain agents may cause more obstruction than others.

Material and methods

Patients

Consecutive patients aged 18 yrs or more, attending the Municipal Emergency Clinic in Tromsø, between October 1988 and June 1989, and presenting symptoms indicating an upper or lower respiratory tract infection (including cough, dyspnoea, sore throat and concern about having a respiratory infection) were asked by a reception nurse to participate in this investigation, which also dealt with other aspects of respiratory infection [12]. Patients with dyspnoea severe enough to need emergency treatment and pregnant women were excluded. Of 626 patients who were asked, 581 participated. At the Municipal Emergency Clinic, general practitioners in Tromsø manage out-of-hours calls. Forty doctors were sharing the duties at the clinic in this period, and all took part in the examination of the patients.

Examinations

On a self-administered questionnaire, the patients reported smoking habits and symptoms associated with the present illness. Cough and dyspnoea were to be graded as: absent, usual, more annoying than usual, or very annoying. Coryza, sore throat and fatigue were to be graded as: absent, slight or pronounced. In a standardized interview, specially trained nurses asked about previous heart and lung disease and about use of anti-asthma medication. The nurses also carried out spirometry with the patient standing. Vitalograph Alpha, an electronic spirometer with a pneumotachograph type flowhead, was used. Calibration was carried out daily, by the use of a one litre syringe. The best result of FEV_1 after three attempts was registered. Out-prints of the volume-time curves were reviewed by the first author. The doctors, who were not informed about the spirometric results, were told to examine and treat the patients as usual and record main clinical diagnosis and treatment. The doctors were not obliged to follow certain criteria in making their diagnosis. Patients diagnosed as having asthma, COPD or chronic bronchitis by the doctor, or who reported use of anti-asthma medication regularly or on-demand, were classified as having established asthma or COPD.

All patients were invited for follow-up spirometry after 4–5 weeks, carried out by the same nurses. From the patients who attended, paired specimens of sera were obtained. Serological analyses for immunoglobulin G (IgG) antibodies were carried out against the following agents: *Mycoplasma pneumoniae, Chlamydia* spp., influenza virus A and B, parainfluenza virus 1 and 3, respiratory syncytial (RS)-virus, and adenovirus. A fourfold change in titre or a single high titre (≥ 80) was used as evidence of infection [13]. Throat specimens were cultured for the detection of Group A streptococci and serological analysis for antistreptolysin 0 and anti-deoxyribonuclease (DNase) B was also carried out. A chest radiograph was taken when requested by the doctor, and according to certain other criteria [12], and was thus obtained in 319 patients. Twenty patients were radiographically diagnosed as having pneumonia [12].

Patients with pronounced discomfort from cough or dyspnoea after 10 days of illness, or who had FEV_1 <85% predicted at the first consultation, were asked to attend the Chest Clinic at the University Hospital of Tromsø for further examinations and treatment. Eligible patients were asked to participate in a one week placebo-controlled trial with fenoterol, a study presented previously [14].

The study was approved by the Regional Committe of Medical Research Ethics.

Analysis

Median FEV_1% predicted and 5–95% percentiles were calculated in all patients with a valid spirometry at the first consultation. Reference values from a Norwegian urban population [15] were used. The change in FEV_1% predicted between the first consultation and the follow-up control after 4–5 weeks and the association with micro-

biological agents was analysed in those patients with valid spirograms at both consultations. The patients with an established diagnosis of asthma, COPD or chronic bronchitis were analysed separately. Statistical significance of differences between groups were tested with Chi-squared test and Wilcoxon's rank sum test, and the differences between paired results with signed rank test. SAS software package was used in all the statistical analyses.

Results

Of the 581 participating patients, spirometry was successfully carried out in 574, 335 women and 239 men, median age 28 yrs (range 18–78 yrs). Reasons for unsuccessful recordings in seven patients were technical problems (twisted tube), poor co-operation and chest pain (one of the pneumonia patients).

Of the 574 patients, 24 were diagnosed as having an aggravation of asthma or COPD at entry, and as an additional 21 reported to have asthma and use anti-asthma medication regularly or on demand, 45 patients could be classified as having an established diagnosis of asthma or COPD. Of these 45 patients, 40% reported very annoying cough and 25% very annoying dyspnoea. The corresponding frequencies in the remaining patients, classified as the patients without known obstructive disease, were 26 and 6%, respectively.

Airflow limitation

The median FEV_1 in all 574 patients was 90% predicted, and the 5–95% percentiles were 60–112. Significantly higher FEV_1 was found among the 529 patients without known obstructive disease, 91% predicted (median value), than among the 45 patients with an established diagnosis of asthma or COPD, 77% predicted (p<0.0001). Among the patients without known obstructive disease, there was no significant difference between men and women, and habitual smokers had lower FEV_1 % predicted than nonsmokers only when aged 40 yrs or more (table 1). The patients who reported very annoying cough or dyspnoea had a significantly lower median FEV_1 than

Table 1. – FEV_1 % predicted according to age and smoking habit in 519* adults without known obstructive disease, who had a respiratory infection

Age yrs	n	Smoking n	%	FEV_1 % pred Nonsmoker	Smoker	All
18–29	289	156	54	89	92	91
30–39	113	65	58	91	92	92
40+**	117	54	46	99	88	93
All	519	275	53	92	91	91

Data for FEV_1 % predicted are median values. FEV_1: forced expiratory volume in one second. *: 10 of the 529 patients, with median FEV_1 86% predicted, did not answer the questions about smoking; **: the difference between smokers and nonsmokers is statistically significant p<0.05.

Table 2. – FEV_1 % predicted according to reported symptoms in 529 adults with respiratory infection

Symptom	n	Median FEV_1 % pred	FEV_1 % pred 5–95% percentiles
Very annoying cough	137	87*	51–111
Very annoying dyspnoea	30	81*	41–106
Coryza (pronounced)	217	91	67–113
Sore throat (pronounced)	194	92	65–112
Fatigue (pronounced)	174	92	65–108
Previous/chronic heart disease	15	91	53–107
Previous/chronic lung disease	26	94	65–110
All patients	529	91	64–113

FEV_1: forced expiratory volume in one second. *: the difference between patients with and without the symptoms is statistically significant, $p<0.0001$.

Table 3. – Age, gender, smoking habits and FEV_1 % predicted in the patients who attended the second consultation (attenders), or dropped out after the first consultation

	Attenders n=395	Drop outs n=134	p
Age yrs*	29	25	<0.001
Females %	61	54	NS
Smoking %	46	71	<0.0001
FEV_1 % pred*	92	90	NS

*: median values. FEV_1: forced expiratory volume in one second; NS: nonsignificant.

the patients without these symptoms (table 2). Forty patients reported previous or chronic disease of the heart or lung. Among the 15 with previous/chronic heart disease, coronary heart disease was reported in 10, and no patients reported heart insufficiency. Chronic bronchitis was most frequently reported among the 26 patients with previous/chronic lung disease (n=15), followed by pulmonary tuberculosis and pneumonia. The patients with previous/chronic heart or lung disease had similar FEV_1 % predicted to those without (table 2). Among the patients without known obstructive disease, the 16 with radiographically diagnosed pneumonia had a median FEV_1 of 79% predicted.

Reversibility

Valid follow-up spirometry was obtained in 429 of the 574 patients (75%). Of these, 34 could be classified as having established asthma/COPD, and 395 as without known obstructive disease. The patients who attended the follow-up control were older and less frequent smokers than those who dropped out (table 3). The median FEV_1 % predicted among the 395 patients increased from 92% (64–112%) to 96% (73–116%). The median increase was 4% (-13±44%), significantly higher than zero (p<0.0001). The distribution of the results at the first and second consultations is shown in figure 1. The median FEV_1 among the 33 patients with previous/chronic heart or lung disease increased from 93 to 97% of predicted. Ninety one (23%) had a reversibility exceeding 15% of initial value. Among the 87 patients clinically diagnosed as having pneumonia or acute bronchitis, 37 (43%) had such reversibility, compared to 18% of the patients diagnosed as having upper respiratory tract infection (including throat infection and "flu"), (p<0.0001). Among 16 patients with radiographic evidence of pneumonia, five had a reversibility of more than 15%.

The median FEV_1 among the 67 patients diagnosed as having acute bronchitis increased from 86 to 98% of predicted, and the mean values (for comparison with previous studies) from 88 to 98%.

A decrease in FEV_1 between the initial and follow-up spirometry of more than 15% was found in 17 patients (4%).
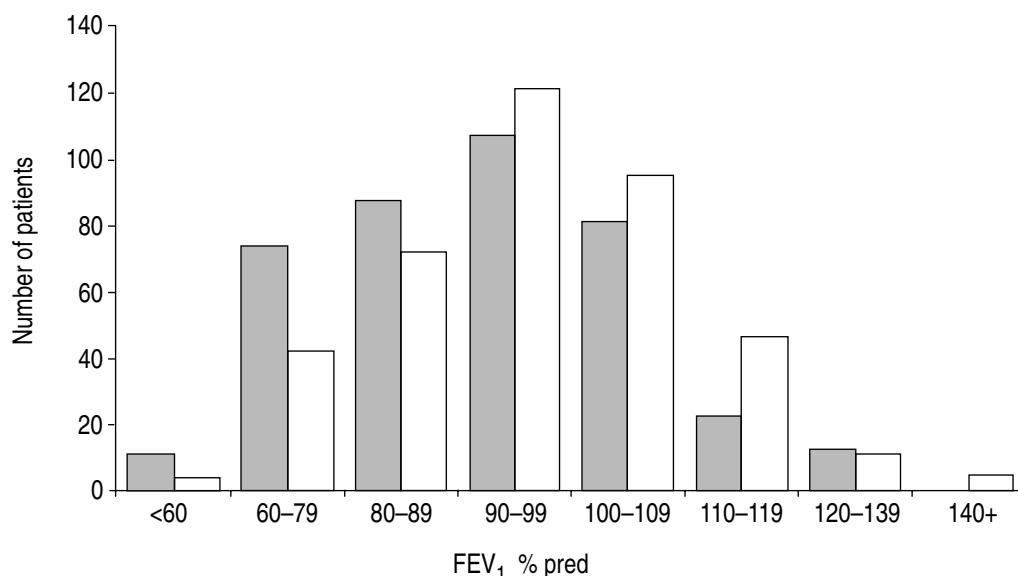

Fig. 1. – Distribution of FEV_1 % predicted in 395 adults without known obstructive disease with respiratory infection. Acute-phase and follow-up values are compared. ▨: first consultation, acute phase; ☐: second consultation, after 4–5 weeks. FEV_1: forced expiratory volume in one second.

Table 4. – FEV_1 in 393 adults without known obstructive disease who had a respiratory tract infection, related to established infection with mycoplasmal, chlamydial and viral agents; change between the first consultation and follow-up control, and the rate of recovery after 4–5 weeks

	n	FEV_1 at entry[†] % pred	FEV_1 after 4–5 weeks[†] % pred	Increase in FEV_1[†] %	Patients recovered at follow-up %
Influenza virus (A+B)	47	88	96	6	83
RS-virus	19	92	97	7	79
Parainfluenza virus (group 3)	17	90	97	5	94
Adenovirus	12	83	93	11	83
Mycoplasma pneumoniae	13	82	90	16	92
Chlamydia pneumoniae	7	94	89	1	71
Any of these agents	102	90*	96	7**	83
None of these agents	291	92*	97	3**	85

[†]: median values. FEV_1: forced expiratory volume in one second; RS: respiratory syncytial. *, **: the difference between those with and without established infection is statistically significant, p=0.05, p<0.05 respectively.
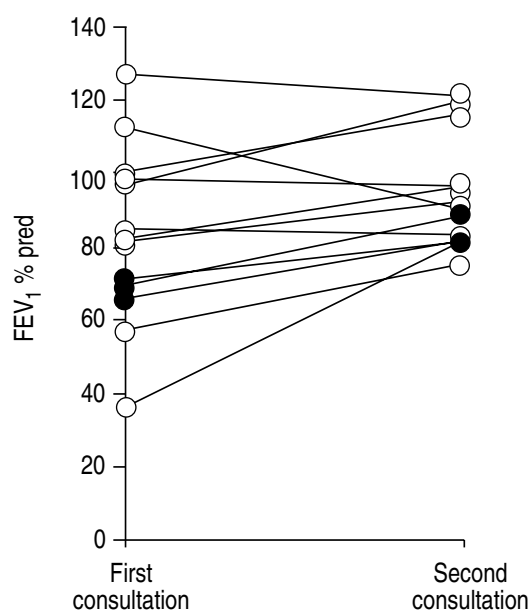

Fig. 2. – Change in FEV_1 % predicted in 13 patients with established infection with *Mycoplasma pneumoniae*. The three patients with radiographic evidence of pneumonia are marked with filled circles (●). FEV_1: forced expiratory volume in one second.

The association with serological evidence of infection

Of the 395 patients with follow-up spirometry, who had no known obstructive disease, paired specimens of sera were obtained in 393. Serological evidence of mycoplasmal, chlamydial or viral infection was found in 102 of these. Infection with influenza virus was most frequently identified (table 4), and 43 of 47 were influenza virus type A. The patients with such serological evidence of infection had significantly lower median FEV_1 % predicted, compared to those without (table 4). This difference was no longer significant at the second consultation, and the median increase in FEV_1 was significantly larger in the 102 with established infection. The greatest median reversibility was found in patients with mycoplasmal infection, and the individual changes in these patients are shown in figure 2.

Ten out of 15 patients with radiographic pneumonia belonged to the 102 with established infection, but the differences in FEV_1 % predicted at entry and the reversibility of FEV_1 remained statistically significant when these 15 patients were excluded from the analysis. The frequency of smoking was 47% in the patients with serological evidence of infection, and 46% among the remaining patients (p=0.9), and there was also similar distribution of age and gender in both groups.

Very annoying cough was significantly more frequent in the patients with established viral, chlamydial or mycoplasmal infection compared to patients without such infection, whilst the opposite was the case for pronounced sore throat (table 5). Very annoying cough was reported particularly frequently in the patients with mycoplasmal infection, whilst coryza was reported particularly infrequently.

Recovery from illness at the follow-up consultation was reported by 84% of the patients, and with similar frequency in patients with and without established infection, as well as in smokers and nonsmokers. The median FEV_1 among the 332 patients who reported recovery was 97% of predicted, significantly higher than among the 61 who had not recovered, 94% of predicted (p<0.05).

Group A streptococcal infection was found by culture or significant change in antistreptolysin-0 or anti-DNase-B titre in 57 of the 393 patients, and a reversibility of FEV_1 >15% was found in nine of these.

Among the 34 patients with established asthma/COPD who attended the second consultation, infection with influenza virus was established in 4, RS-virus in 4 and parainfluenza virus in 2. The median FEV_1 % predicted, 68%, was lower, and the median reversibility of FEV_1, 31%, was higher in these 10 patients than in the 24 with no serological evidence of infection, whose corresponding values were 79 and 8%, respectively. These differences were not statistically significant.

Table. 5. – Very annoying dyspnoea, very annoying cough, pronounced sore throat, fatigue and coryza reported by 393 adults without known obstructive disease who had a respiratory tract infection, related to established infection with mycoplasmal, chlamydial and viral agents

	n	Very annoying dyspnoea		Very annoying cough		Pronounced sore throat		Pronounced fatigue		Pronounced coryza	
		n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Influenza virus (A+B)	47	7	(15)	18	(38)*	11	(23)	23	(49)*	15	(32)
RS-virus	19	3		5		6		9	(47)	12	(63)
Parainfluenza virus (group 3)	17	0		8	(47)*	5		4		7	(42)
Adenovirus	12	1		1		5	(42)	3		5	(42)
Mycoplasma pneumoniae	13	1		9	(70)*	4		2		2	(15)
Chlamydia pneumoniae	7	1		3		2		2		5	(71)
Any of these agents	102	10	(10)	36	(36)**	27	(27)*	38	(37)	45	(44)
None of these agents	291	16	(6)	67	(23)	120	(41)	87	(30)	122	(42)

*,**: the difference between patients infected and not infected by the agent is statistically significant, p<0.05, p<0.01 respectively.

Anti-asthma treatment

A bronchodilator for inhalation was prescribed at the first consultation to three of the 395 patients without known obstructive disease, who attended the follow-up consultation. A reversibility of FEV_1 exceeding 15% of initial value was found in one of these three patients. Anti-asthma treatment was prescribed to another six of the 395 patients who had FEV_1 <60% predicted when they attended the Chest Clinic, few days after entry, and a reversibility of more than 15% was registered in all six. Forty four of the 395 patients without known obstructive disease entered the clinical trial with fenoterol/placebo. The median FEV_1 values at entry were similar in those allocated to the fenoterol and the placebo groups, 84 and 83% predicted, respectively, and were still so after 4–5 weeks (93% predicted in both groups). A reversibility of FEV_1 of more than 15% between the first consultation at the emergency clinic and the second consultation after 4–5 weeks was registered in 8 of the 21 patients who were allocated to the fenoterol group, compared to 6 of the 23 allocated to the placebo group, and it may, thus, be assumed that the one week of treatment with fenoterol may have contributed to the reversibility in two patients. Altogether 30, of the 395 patients had anti-asthma treatment, including the participants of the clinical trial, and in nine of these patients this treatment may have contributed to a more than 15% reversibility of FEV_1.

Discussion

The study shows that a transient fall in FEV_1 is a common feature of respiratory infections. The reversible airflow limitation does not necessarily reflect bronchial obstruction in all of the patients. The greater than 15% reversibility of initial FEV_1 in 5 out of 16 patients with radiographic pneumonia indicates that restrictive lung disease may play a role in some patients. But restrictive disease probably did not represent an important source of error, because the patients with chronic/previous heart or lung disease had normal FEV_1 values. Since a reversibility of FEV_1 of more than 15% was found in 9 of the 57 patients diagnosed as having streptococcal pharyngitis, narrowing of the pharynx may also have contributed to the results. General fatigue during the acute illness did not seem to play any important role.

Because a reversibility of more than 15% was found in 23% of the patients, whereas a corresponding fall was found only in 4%, only a minor part of the reversibility may be ascribed to the statistical phenomenon "regression towards the mean". The reversibility may be regarded as spontaneous in the great majority of cases, since anti-asthma treatment probably played a role in only nine of the 91 patients with a reversibility of FEV_1 exceeding 15%.

The distinct reversibility among the patients diagnosed as having acute bronchitis, and the strong association between reduced FEV_1 and the symptoms dyspnoea and cough, indicates that bronchial obstruction is a main explanation for the transient airflow limitation described in this study. The findings of WILLIAMSON [9] and BOLDY *et al.* [10] concerning patients with acute bronchitis have been confirmed, as the increase in mean FEV_1 from 88 to 98% predicted was close to Williamson's finding (84 to 98% predicted). Bronchial obstruction may also be a reason for the reversible airflow limitation found in many patients diagnosed as having upper respiratory tract infection. Bronchial obstruction in this group of patients may, among other things, be explained by a tendency to underdiagnose acute bronchitis when physical chest signs are missing.

The classification of the patients as infected *versus* not infected with respiratory viruses, chlamydials or *M. pneumoniae* may be subject to many sources of error. The sensitivity of the serological analysis for infection is less than 100%. The patients were not examined for rhinovirus and the other viruses causing common cold, and such infections may have been frequent in the patients without established infection [16]. Many patients may thus have been misclassified, and the difference between the two groups may have been underestimated.

Very annoying cough was frequently reported by patients infected with influenza virus or *Mycoplasma pneumoniae*. This association indicates the role of these agents in lower respiratory tract infection. Very annoying cough was also very frequent in parainfluenza virus infection, possibly reflecting the tendency of this virus to affect the larynx and trachea [17].

The airflow limitation and reversibility found in patients infected with *Mycoplasma pneumoniae* was not surprising. It has previously been shown that mycoplasmal infection may cause exacerbations of asthma [18], and bronchial hyperreactivity in nonasthmatics [19]. The patients with mycoplasmal infection in the study by SABATO *et al.* [19] also had significantly lower FEV_1 after one month compared to controls, although they reported to be asymptomatic at that time. The relatively low follow-up FEV_1 in the patients with mycoplasmal infection in our study may reflect a tendency of slow recovery from impairment of lung function in such patients.

The tendency of particularly low FEV_1 and great reversibility found among the patients with known asthma or COPD in whom we could determine an aetiologic agent, supports the conclusion of BEASLEY *et al.* [4] that the most serious attacks of asthma are frequently precipitated by viral infection.

The study population was generally young. We could not find any age trend in airflow limitation and reversibility, but the documentation as regards the elderly must be characterized as fragile. The over-representation of young smokers among the drop-outs is probably of minor importance, since a difference in airflow limitation between smokers and nonsmokers was only found in patients older than 40 yrs of age.

Reduction and reversibility of $FEV_1\%$ predicted was used as measure of airflow limitation. We found that it was difficult to obtain a valid measure of forced vital capacity (FVC) in many patients, since the forced expiratory manoeuvre was frequently interrupted by cough. This could also be read from the volume-time curves. We thus decided not to present FEV_1 values in % of FVC. An increase in FEV_1 of more than 15% of the initial value was used as an indicator of significant reversibility. This arbitrary cut-off point may not be valid in all patients. A reversibility of 9% as response to a bronchodilator was found to be the upper normal value in healthy nonsmokers in one epidemiological study [20]. The reversibility of FEV_1 in percentage of baseline is strongly dependent on the initial value [21], and a reversibility of 15% may, thus, be insignificant in subjects with a low initial FEV_1. In the present study of generally young, otherwise healthy adults, few subjects had a very low initial FEV_1, and error due to the use of percentage change from initial FEV_1 probably plays a minor role.

Clinical implications

Bronchial obstruction may also play an important role in the symptoms of respiratory infections in otherwise healthy persons. However, only a few clinical trials have evaluated the usefulness of bronchodilators or corticosteroids in acute bronchitis. A significant symptomatic effect of a beta$_2$-agonist have been demonstrated in two clinical trials [15, 22], whilst inhaled steroids have not as yet been proved to be more useful than placebo [23]. The smaller increase in FEV_1 in the patients of this study, who had not recovered completely after 4–5 weeks, compared to those who reported to have recovered, may indicate that a bronchodilator should be more frequently prescribed. More studies are needed to assess the usefulness of anti-asthma therapy in acute bronchitis.

It is likely that some patients in our study population without known asthma or COPD, actually had one of these diseases. It has been reported that a considerable proportion of patients diagnosed as having acute bronchitis will be later shown to have asthma [24, 25]. Although the doctor should think of asthma as a possibility when airflow limitation is diagnosed in a patient with respiratory infection, he should also be aware that spontaneous reversibility is a common feature of such infections, as shown by this study. The high frequency of spontaneous reversibility should be taken into consideration when a response to anti-asthma treatment is interpreted in patients with possible asthma.

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