

Effect of Respiratory Infections on Exacerbation of Asthma in Adult Patients

A Six-Month Follow-up

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The peak expiratory flow values and asthma symptom scores of 92 adults with extrinsic and intrinsic asthma were recorded daily from September 1981 to April 1982 in order to study the effects of symptomatic respiratory infections (SRI) on the course of asthma. During the follow-up, 253 exacerbations of asthma were observed in 67 patients. 68 subjects had 141 episodes of SRI. 63 of 253 exacerbations (25%) were found in association with SRI. The mean duration of the exacerbations associated with SRI was 11.4 days, significantly different ($P < 0.01$) from the mean duration of 8.1 days recorded for the other exacerbations. The results confirm the high incidence of asthmatic exacerbations during respiratory infections and suggest that the recovery from an exacerbation is slower in association with infection.

Key words: adults; atopic bronchial asthma; nonatopic bronchial asthma; PEF; respiratory infections.

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CLINICAL ASPECTS

Acute viral infections of the respiratory tract are frequent triggering factors of exacerbations leading to hospitalization of asthmatic patients. The purpose of this survey was to study the relationship between symptomatic respiratory infections and exacerbation of asthma in adult outpatients with mild to severe asthma. The results suggest that respiratory infections are important precipitants of asthmatic attacks in both atopic and nonatopic asthma in adults. In addition, exacerbations associated with infection seemed to follow a slower recovery pattern than other exacerbations. Nevertheless, the majority of exacerbations were due to triggering factors other than infections.

Acute viral infections of the respiratory tract are known to precipitate attacks of asthma in children (17-20, 22). Respiratory infections are also associated with exacerbations of asthma in adult patients, leading to hospitalization (11). However, the role of infection in adult outpatients with asthma is less well known (24).

The present study was undertaken to determine the occurrence of symptoms suggesting a respiratory infection during exacerbation of asthma in adult atopic and nonatopic outpatients. The effect of symptomatic respiratory infection (SRI) on the mean duration of exacerbation was also studied.

An exacerbation of asthma was defined on the basis of changes in daily asthma symptom score and peak expiratory flow (PEF) measurements. The frequency of exacerbations provoked by SRI was investigated in 92 adults with mild to severe asthma during a 6-month follow-up.

MATERIAL AND METHODS

The study was carried out between September 1981 and April 1982, with the monthly mean temperature ranging from $+4.2$ to -15.8°C .

Patients

The study was performed at the departments of pulmonary diseases of three centres (Ounasrinne Hospital, Rovaniemi; Tiuru Hospital, Tiurunemi and University Central Hospital, Helsinki) in Finland in conjunction with the evaluation of influenza virus vaccine. The results from the vaccine evaluation will be reported separately.

Initially 111 outpatients with asthma were selected for the study. 19 patients were excluded from the follow-up because of an acute respiratory illness or the lability of their disease during a 2-week run-in period. The study group proper thus consisted of 92 asthmatics (38 men) with a mean age of 46 years (range 15-77). The asthma of 44 of the patients was defined as atopic on the basis of the patients' medical history and the obtainment of at least two positive reactions on skin prick testing.

Judged by their clinical history and their need for bronchodilating drugs, the severity of asthma was considered mild in 49, moderate in 30 and severe in 13 patients. Eighty patients required daily medication, 21 of them being on continuous oral steroid treatment. 29 (31%) patients were of the opinion that the onset of their asthma was associated with a respiratory infection and 65 (71%) patients always experienced exacerbation of asthma during a respiratory illness.

The subjects had suffered from asthma for 10.4 years on average (range 1-50 years). Six

patients were smokers. For the study, written informed consent was obtained from the patients. The study was approved by the Ethics Committees of each participating hospital.

Methods of observation

The patients evaluated the severity of their disease daily by recording a symptom score in a follow-up chart. The score consisted of points given on four separate items (cough, sputum production, daytime breathlessness, nighttime breathlessness), each quantified using a scale from 0 to 3 (Table 1). PEF was measured by the patients on a mini-Wright peak flow meter twice a day at about 7 a.m. and 7 p.m.

To detect respiratory infection, the occurrence of the following symptoms was recorded: fever (axillary temperature $> 37.5^{\circ}\text{C}$), sore throat and symptoms of rhinitis such as running or stuffy nose, and sneezing. These symptoms were called symptoms of "flu" in the daily record cards. A patient was considered to be suffering from SRI if at least two of these symptoms (fever, sore throat or rhinitis) were present for 2 or more consecutive days after having been absent for at least 4 days (22).

There was a 2-week run-in period. Exacerbation of asthma was defined as an increase in symptom score by at least four points or as a decrease in the morning or the evening PEF values by at least 20% during 3 or more consecutive days, compared with the average val-

Table 1
Asthma symptom scores

Score	Breathlessness (day)	Breathlessness (night)	Cough	Sputum
0	none	none	none	none
1	slight, does not prevent normal activity	slight, does not disturb sleep	occasional coughing	occasional scanty sputum
2	moderate, impossible to walk at normal speed	awake with wheezing 1-3 times during the night	bouts of coughing	moderate amount of sputum (1/2-2 spoonfuls/day)
3	continuous asthma, normal activity severely impaired	awake on more than 3 occasions or awake through the night with asthma	disturbing cough most of the time	profuse sputum (more than 2 spoonfuls/day)

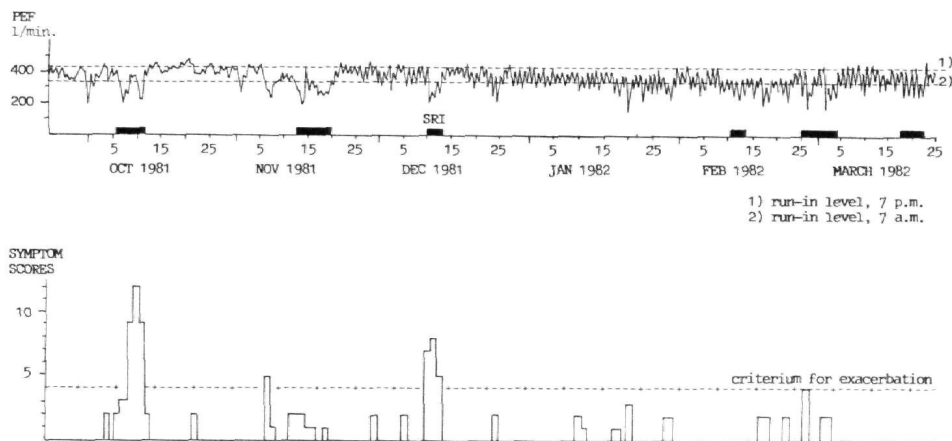


Fig. 1. Daily PEF values and symptom scores of a 46-year-old man with intrinsic asthma. The patient had six exacerbations (= ■) with a decrease in PEF; during two of these (in October and December 1981) a significant increase in symptom score also occurred. One SRI was observed in December 1981 in association with a brief exacerbation of asthma. The patient was admitted to hospital once, in November 1981, on the 7th day of an exacerbation; the duration of the hospitalization was 6 days.

ues observed during the run-in period. The minimum time interval accepted between exacerbations was 3 days.

Exacerbation of asthma was considered to be associated with SRI if it occurred during a SRI or not more than 1 day after it.

The daily self-observation by the patients was augmented by monthly examinations by a physician and an interview by a nurse. During these visits the daily recordings were checked and need for special medication (e.g. corticosteroids or antibiotics) evaluated. In addition, the patients were allowed to contact the personnel if they acquired symptoms beyond their own control.

Statistical methods. Statistical analyses were performed using Student's *t*-test.

RESULTS

In the course of the study, 253 exacerbations of asthma were observed in 67 patients. 228 of these episodes showed a bronchial obstruction pattern with changes in PEF. An increase in

symptom score in combination with a decrease in PEF values was found during 57 episodes. The average duration of all exacerbations was 8.9 days (range 3–55 days).

Sixty-three of 253 exacerbations (25%) were found in association with SRI. There were 32 febrile and 31 afebrile infections in association with these 63 exacerbations. The mean duration of the exacerbations associated with SRI was 11.4 days (range 3–55 days), showing a significant difference ($P < 0.01$) from the mean duration of 8.1 days (range 3–52 days) of the other exacerbations.

Altogether 141 episodes of SRI with a mean duration of 4.9 days were observed in 68 subjects during the follow-up. The percentage of SRIs associated with exacerbation of asthma was thus 45.

The follow-up of a patient with six exacerbations of asthma and one SRI is summarized in Fig. 1.

Of all exacerbations, 64% occurred in patients with moderate or severe asthma. This group also acquired more than half (60%) of all exacerbations associated with SRI.

When the data were analysed separately for patients with extrinsic and intrinsic asthma, the proportion of exacerbations with SRI was 29.2% among atopic patients and 19.8% among nonatopic patients. In patients with a history of consistent exacerbation of asthma during respiratory infections, 27.2% of exacerbations were associated with SRI. These patients had a total of 113 episodes of SRI. 53 of these 113 episodes (47%) were found in association with exacerbation of asthma.

Oral steroid treatment was used during 50 exacerbations and antibiotics during 22 exacerbations. The mean duration of exacerbations treated with steroids was 9.6 days and of those treated with antibiotics 9.2 days. The number of exacerbations leading to hospitalization was 11. The mean duration of these exacerbations was 8.2 days (range 3–26 days); five of them (45%) were associated with SRI. Nine patients displayed neither exacerbations nor respiratory infections during the follow-up.

DISCUSSION

In the present study, about 25% of exacerbations of asthma in adult outpatients were associated with an episode of SRI. Although it is not possible definitely to exclude other provoking factors besides SRI in these exacerbations, such influence is unlikely on the basis of the patients' follow-up records. This study confirms the high incidence of asthmatic exacerbations during respiratory infections. On the other hand, about half of all episodes of SRI failed to cause exacerbation of asthma, even in patients whose asthma had previously always been aggravated by respiratory infections.

The diagnosis of SRI in this study was based on daily recordings by the patients and on examinations by a physician. The fact that no attempt was made to elucidate the etiology of SRIs may be considered a major disadvantage. On the other hand, the reported results of bacteria identification by sputum culture have not been unambiguous (16), and viral diagnosis by isolation in tissue culture involves many technical difficulties. Serological methods of diagnosing viral infection are in turn inapplicable to

viruses with numerous serotypes, such as the rhinoviruses (4). In addition, it is possible that a high proportion of all viral infections are subclinical (26). Therefore no effort was made to determine the specific etiology of SRI in the present survey.

In view of the results of earlier studies (3, 9, 10), it seems reasonable to assume that a substantial proportion of the episodes of SRI in the present study was caused by rhinoviruses. Influenza viruses can hardly have been the cause of the SRIs because there were no real epidemics of influenza in Finland during the years 1981–1982 (unpublished observations of the National Influenza Centre, National Public Health Institute, Helsinki).

The course of recovery in exacerbations associated with SRI appeared to differ from that in exacerbations without SRI. In asthmatic exacerbations with SRI, patient recovery was slower (mean 11.4 days) than in the other exacerbations (mean 8.1 days). Similar differences in recovery pattern were observed by Jones (12) who studied adults admitted to hospital for acute asthma; patients with proven influenzavirus infection displayed a slower recovery (10.7 days) compared with other patients (4.9 days).

Symptoms of respiratory infection also seemed to prolong the exacerbation of asthma in a study by Smith (23). He investigated the rate of recovery and factors precipitating asthmatic attacks in a group of 41 patients admitted to hospital for acute severe asthma. Three types of patients were identified: the "accelerated", the "normal" and the "slow" type with a mean duration of hospitalization of 5.3, 9.2 and 12.5 days, respectively. Compared with the "normal" recovery type, fewer patients of the "accelerated" type had experienced a coryzal illness (18.8 and 28.5%, respectively) or purulent bronchitis (18.8 and 38.4%, respectively).

Although the mechanisms by which respiratory viral infections cause exacerbations of asthma are not completely understood, at least two host factors may be postulated (5). One such factor may be an increased bronchial reactivity, aggravated by viral infection, as Empey et al. (2) proposed in their study. This hyperreactivity of the airways can in turn be due to disruption of

tight junctions between the epithelial cells, rendering the subepithelial tissue more accessible to specific and nonspecific stimulants (8). Furthermore, we have shown that local detachment of the bronchial epithelium sometimes occurs in patients with asthma (14). Viral infections of the respiratory tract may enhance this shedding of epithelium (7, 25). Epithelial damage is thought to bring about stimulation of the vagally mediated "irritant" receptors (2) which are located in and beneath the epithelium (13). The slower recovery from exacerbations associated with infection may thus be due to increased bronchial reactivity caused by epithelial damage. Several studies have shown that bronchial hyperreactivity and epithelial damage persist for several weeks after viral infections (2, 6, 7, 15, 25).

Another host factor potentially causing exacerbation of asthma may be the impairment of defence mechanisms which normally prevent viral infections from extending into the bronchi. The results of a recent study by Carson et al. (1) suggest that viral infections may disturb the ciliary function in the respiratory tract and cause transient impairment of mucociliary clearance. We have observed similar ciliary dysfunction (14) even in asthmatic patients without a concomitant respiratory infection.

When the data of the present study were analysed separately for patients with extrinsic and intrinsic asthma, the proportion of exacerbations provoked by SRI was greater among the atopic patients (29.2 and 19.8%, respectively). This result appears to contradict the general view that respiratory infections are harmful mostly in intrinsic asthma. The present findings suggest that infections can cause exacerbation of asthma regardless the type of asthma. Consequently, the label "infectious asthma" is obviously misleading and should be abandoned.

The exacerbations treated with steroids did not differ in recovery pattern from the other exacerbations. This appears to be due to the method of the study. In most cases, oral corticosteroid medication was started in conjunction with a monthly visit to the clinic if exacerbation seemed to be imminent. In fact, an exacerbation had often lasted many days before the initiation of oral steroid medication. Because in the majority of

exacerbations no special medication was used, it seems probable that in most episodes resolution occurred spontaneously.

The role of infection in the pathogenesis of asthma has three main aspects: the initial onset of asthma, and the provocation and persistence of acute episodes (4). In the present study, 29 patients (31%) attributed their first episode of wheeze to a respiratory infection. In a study by Pearson (21), 48% of adult patients with late-onset asthma gave a similar history. These results are in agreement with the clinical and empiric view that the onset of asthma is often associated with a respiratory infection.

As only about every second episode of SRI provoked an exacerbation in the present study, it is evident that symptoms of respiratory infection do not always lead to exacerbation of asthma. This may be due to individual properties of different viruses or to different stages of asthma during infection.

In conclusion, acute respiratory infection appears to be the triggering factor in a substantial portion of exacerbations in adult outpatients with extrinsic or intrinsic asthma. In addition, the recovery from exacerbation is slower in association with respiratory infections. Nevertheless, the majority of exacerbations seem to be caused by other factors than infections.

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REFERENCES

1. Carson, J. L., Collier, A. M. & Hu, S. S.: Acquired ciliary defects in nasal epithelium of children with acute viral upper respiratory infections. *N. Engl. J. Med.* 3122, 463-468, 1985.
2. Empey, D. W., Laitinen, L. A., Jacobs, L., et al.: Mechanisms of bronchial hyperreactivity in normal subjects after upper respiratory tract infection. *Am. Rev. Resp. Dis.* 113, 131-139, 1976.
3. Gregg, I.: The role of viral infection in asthma and bronchitis. In Proudfoot, A. T. (ed.): Symposium on

- viral diseases, pp. 82-98. Royal College of Physicians, Edinburgh, 1975.
4. Gregg, I.: The role of infection: In Clark, T. J. H., Godfrey, S. (eds.): *Asthma*. Chapman and Hall, London, 1983.
 5. Gregg, I.: Provocation of airflow limitation by viral infection: implication for treatment. *Eur. J. Respir. Dis.* **64**, (Suppl 128), 369-379, 1983.
 6. Hall, W. J., Hall, C. B. & Speers, D. M.: Respiratory syncytial virus infection in adults: clinical, virologic, and serial pulmonary function studies. *Ann. Intern. Med.* **88**, 203-205, 1978.
 7. Hers, J. F. P. H.: Disturbances of the ciliated epithelium due to influenza virus. *Am. Rev. Respir. Dis.* **93**, 162-171, 1966.
 8. Hogg, J. C.: Bronchial mucosal permeability and its relationship to airways hyperreactivity. *J. Allergy Clin. Immunol.* **67**, 421-425, 1981.
 9. Horn, M. E. C., Brain, E., Gregg, I., et al.: Respiratory viral infection in childhood. A survey in general practice. *Rochampton 1967. J. Hyg. (Camb.)* **74**, 157-168, 1975.
 10. Horn, M. E. C., Brain, E., Gregg, I., et al.: Respiratory viral infection and wheezy bronchitis in childhood. *Thorax* **34**, 23-28, 1979.
 11. Huhti, E., Mokka, T., Nikoskelainen, J., et al.: Association of viral and mycoplasma infections with exacerbations of asthma. *Ann. Allergy* **33**, 145-149, 1974.
 12. Burge, P. S.: Trigger factors in asthma. In Clark T. J. H. (ed.): *Steroids in asthma. A reappraisal in the light of inhalation therapy*. Adis Press, 1983.
 13. Laitinen, A.: Ultrastructural organisation of intra-epithelial nerves in the human airway tract. *Thorax* **40**, 488-492, 1985.
 14. Laitinen, L. A., Heino, M., Laitinen, A., Kava, T., Haahtela, T.: Damage of the airway epithelium and bronchial reactivity in patients with asthma. *Am. Rev. Respir. Dis.* **131**, 599-606, 1985.
 15. Little, J. W., Hall, W. J., Douglas, R. G. et al.: Airway hyperreactivity and peripheral airway dysfunction in influenza A infection. *Am. Rev. Respir. Dis.* **118**, 295-303, 1978.
 16. May, J. R.: The flora of the respiratory tract in chronic disease. *Postgrad. Med. J.* **51**, 144-146, 1975.
 17. McIntosh, K., Ellis, E. F., Hoffman, L. S., et al.: The association of viral and bacterial respiratory infections with exacerbations of wheezing in young asthmatic children. *J. Pediatr.* **82**, 578-590, 1973.
 18. Minor, T. E., Dick, E. C., Baker, J. W., et al.: Rhinovirus and influenza type A infections as precipitants of asthma. *Am. Rev. Respir. Dis.* **113**, 149-153, 1976.
 19. Minor, T. E., Dick, E. C., DeMco, A. N., et al.: Viruses as precipitants of asthmatic attacks in children. *J.A.M.A.* **227**, 292-298, 1974.
 20. Mitchell, I., Inglis, H. & Simpson, H.: Viral infection in wheezy bronchitis and asthma in children. *Arch. Dis. Child.* **51**, 707-711, 1976.
 21. Pearson, R. S. B.: Natural history of asthma. *Acta Allergol.* **12**, 277-291, 1958.
 22. Roldaan, A. C. & Masural, N.: Viral respiratory infections in asthmatic children staying in a mountain resort. *Eur. J. Respir. Dis.* **63**, 140-150, 1982.
 23. Smith, A. P.: Pattern of recovery from acute severe asthma. *Br. J. Dis. Chest* **75**, 132-140, 1981.
 24. Tuft, L.: The "intrinsic" or "infectious" label. *Ann. Allergy* **38**, 361-362, 1977.
 25. Walsh, J. J., Diettein, L. F., Low, F. N., et al.: Bronchotracheal response in human influenza. *Arch. Intern. Med.* **108**, 98-110, 1961.
 26. Whitehead, J. E. M.: Viral epidemiology: the hidden universality of infection. *Br. Med. J.* **2**, 451-456, 1972.

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