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The Incidence of Respiratory Tract Infection in Adults Requiring Hospitalization for Asthma*

Harry Teichtahl, MBBS, FCCP; Nicholas Buckmaster, MBBS; and Eric Pertnikovs, MBBS

Acute respiratory tract infections (RTI) are known to worsen asthma particularly in children. There are few studies in adults assessing the incidence of RTI in patients hospitalized with acute asthma.

Aim: **To document the incidence of RTI in adults hospitalized with acute asthma.**

Methods: **A prospective study of patients with acute asthma admitted to the Department of Respiratory Medicine, Western Hospital Footscray, over a 12-month period. A control group was studied from elective surgical inpatients. Patients were investigated with serologic tests for Chlamydia, Mycoplasma, Legionella, and influenza A and B. Nasopharyngeal aspirate (NPA) samples were cultured for influenza, respiratory syncytial virus (RSV), adenovirus, parainfluenza, rhinovirus, and herpes simplex virus. If sputum was available, it was assessed with microscopy and culture. Blood cultures were taken if patients were febrile and all patients had a chest radiograph. Control subjects completed serologic tests and NPA.**

Results: **Seventy-nine patients (33 male and 46 female) and 54 control subjects (26 male and 28 female) were studied. Two patients were enrolled twice. Mean (±SD) age of patients was 35±15 years (range, 16 to 66 years), and mean age of control subjects was 37±15 years (range, 18 to 69 years). In the patient group, 29 (37%) had evidence of recent RTI of which 23 were viral. Five of the control subjects (9%) had evidence of recent RTI ($p<0.001$). Twenty-four patients were positive on serologic and/or NPA culture. Five patients had positive serologic test results and/or NPA culture to two or more agents. Two patients tested positive on sputum, radiograph, and temperature criteria. Three patients tested positive on the basis of radiographic evidence of consolidation, blood neutrophilia, and temperature. Influenza A (13) and rhinovirus (9) were the most common infectious agents. Other agents identified were RSV (one), influenza B (two), adenovirus (one), and Mycoplasma (one). Influenza and rhinovirus infections occurred predominantly in late and early winter, respectively. Summer hospitalization did not relate to RTI.**

Conclusion: **Thirty-seven percent of adult patients with acute asthma admitted to the Department of Respiratory Medicine over a 12-month period had evidence of recent RTI.**

(CHEST 1997; 112:591-96)

Key words: adult; asthma; exacerbation; respiratory infection

Abbreviations: CFT=complement fixation test; NPA=nasopharyngeal aspirate; PEFR=peak expiratory flow rate; RSV=respiratory syncytial virus; RTI=respiratory tract infections; VIDRL=Victorian Infectious Diseases Reference Laboratory, Fairfield Hospital, Victoria, Australia

The role of respiratory tract infections (RTI) in the evolution of acute exacerbations of asthma is continuing to be defined. There are many studies in children that have shown an association of RTI with a deterioration of asthma symptoms. Between 14% and 45% of acute asthma exacerbations in children are thought to be related to viral RTI.[1-5] The situation in adults is less clear with older studies showing RTI associated with asthma exacerbation in only 10 to 21%.[6,7] There have been few recent studies assessing the rate of RTI in acute exacerbation of adult asthma. Beasley et al,[8] in a longitudinal outpatient study, have shown an incidence of viral RTI of 36% in acute severe adult asthma exacerbations and 10% in mild asthma exacerbation. Nicholson et al,[9] also in a longitudinal study of adult asthmatics in the home, have shown objective evidence of RTI in 44% of asthma exacerbations.

Our prospective study was performed over a 12-

*From the Department of Respiratory Medicine, Western Hospital, Melbourne, Australia.

Supported in part by Abbott (Aust) Pty Ltd.

Manuscript received February 16, 1996; revision accepted April 18, 1997.

Reprint requests: Harry Teichtahl, MBBS, FCCP, Director, Respiratory Medicine, Western Hospital, Gordon Street, Footscray, Victoria, Australia 3011

month period and assessed the incidence of RTI in adults with acute asthma exacerbation requiring admission to a general hospital in metropolitan Melbourne, Australia.

Materials and Methods

Subjects

This was a prospective study performed at a community hospital in the western suburbs of Melbourne, Australia. The study was approved by the hospital's Research and Ethics Committee. Patients and control subjects were recruited between August 1993 and July 1994. Each patient was matched on the basis of sex and age with a control subject and control subjects were recruited simultaneously with patients to avoid potential seasonal bias. Asthma patients received standard therapy with IV and/or oral steroids, bronchodilators, and antibiotics as required. Asthma patients were recruited via the Emergency Department of the hospital if admitted to the respiratory medical unit. Control subjects were recruited from elective surgical admissions. All subjects gave informed consent to enter the study. The diagnosis of asthma was defined on history and variability of peak expiratory flow rate (PEFR) and/or of FEV_1 of at least 20% either with therapy or spontaneously.

Tests Performed

All patients and control subjects underwent a detailed history, including questioning for subjective evidence of recent RTI and asthma symptoms. Nasopharyngeal aspirate (NPA) was performed on each subject and the aspirate was cultured for influenza A and B, respiratory syncytial virus (RSV), adenovirus, parainfluenza virus, rhinoviruses, coronaviruses, and herpes simplex virus at the Victorian Infectious Diseases Reference Laboratory (VIDRL), Fairfield, Victoria, Australia. The NPAs were performed with the patient in upright position. A fine sterile nasal cannula was attached to a sterile suction trap and passed to the posterior nasopharynx via a nostril and suction applied. The cannula tip was withdrawn from the nasopharynx, inserted into sterile saline solution, and 5 mL of saline solution was suctioned into the trap container. All NPA specimens were examined within 24 h of sampling. All subjects underwent an initial first bleed serologic test and where possible had a further convalescent serum sample taken 2 to 3 weeks following admission to the study. Serum samples were examined for evidence of acute infection for Legionella species, *Mycoplasma pneumoniae*, Chlamydia infection via chlamydial common antigen, and influenza A and B. The patients also had a chest radiograph, full blood examination, and sputum microscopy and culture assessment looking for eosinophils, neutrophils, and pathogens. If febrile at the time of hospital admission, the asthma patients had blood cultures taken.

Viral Culture Procedures

The NPAs were cultured for viruses at the VIDRL. Culture for and identification of viruses were performed by techniques previously published.[10,11]

Sputum Microscopy and Culture Procedures

Sputum was obtained from asthma patients if the patient had a productive cough. Microscopy was performed on all sputum after Gram's stain both at low power (×100) and with oil immersion lens. A qualitative report on leukocytes, squamous cells, and organisms was made on smear. Sputum was then cultured on horse blood agar (HBA) with Optichon disc {Becton-Dickinson; Sparks, Md), chocolate blood agar (CBA) with bacitracin and MacConkey agar at 35°C in CO_2. The HBA and CBA plates were incubated for 48 h. If fungal elements were seen, the sputum was also cultured on a Subouraud dextrose agar with antibiotics for 7 days at 30°C. Cultures were reported as positive for pathogens if *Streptococcus pneumoniae* and *Haemophilus influenza* were cultured. *Pseudomonas aeruginosa* and streptococci of groups A, B, C, or G, *Staphylococcus aureus*, and *Klebsiella pneumoniae* were considered pathogens on culture if the organism was predominant on smear, there were leukocytes present in the smear, and there was a clinical history of pneumonia.[12-14]

Blood Culture Procedures

Blood cultures were performed in an incubation and fluorescent reading system (Bactec 9240) as per manufacturer's hand book (Becton-Dickinson; Sparks, Md). Blood was injected into bottles for culture (Bactec Plus Aerobic F and Bactec anaerobic F).

Serology Procedures

First bleed and where possible second bleed serologic tests were performed at the VIDRL. Mycoplasma IgM titers were measured by reverse enzyme-linked immunosorbent assay technique (Diatech Diagnostics Ltd; Israel). Total antibodies to *M pneumoniae* were measured by passive particle agglutination test (Fujeribio Inc; Japan). *Chlamydia psittaci* antibodies were assessed by complement fixation test (CFT) using virion CFT antigen and Chlamydia control antigen (Virion Ltd; Rueschlikon, Switzerland). Influenza A and B antibodies were assessed by CFT (Whitakers Bioproducts; Md). Legionella antibodies were measured by immunofluorescence using anti-human IgA, IgG, IgM (H & L) with IgG fraction. Fluorescein isothiocyanate-conjugated (Silenus; Hawthorn, Australia) Legionella standard strains were obtained (American Type Culture Collection; Rockville, Md).

Diagnosis of RTI

A diagnosis of recent RTI was made if subjects had one of the following: (1) fourfold increase in antibody titer of paired sera or high IgM antibody titer if only first bleed serologic test available; (2) growth of viruses on NPA culture; (3) positive sputum culture for respiratory pathogen in association with sputum and blood neutrophilia and temperature >37.5°C on admission; and (4) negative serologic test result, NPA, and sputum culture but with chest radiographic evidence of lobar consolidation (not collapse or atelectasis), temperature >37.5°C on admission, and no evidence of allergic bronchopulmonary aspergillosis on sputum sample, full blood examination, total IgE, and specific IgE to aspergillus.

Statistics

Differences between patient and control groups were analyzed either by Mann-Whitney Rank Sum test or z-test to compare proportions with Yates' correction applied to calculations. Results were considered significantly different when $p \leq 0.05$.

Results

Seventy-nine patients with acute exacerbations of asthma who were hospitalized in the respiratory

medical unit and 54 control subjects were recruited. In the study period, 155 adults were admitted to the hospital with acute exacerbation of asthma—118 to the respiratory medical unit and 37 to other medical units of the hospital. We chose to recruit only patients admitted to the respiratory medical unit because the patients admitted with asthma to other medical units also had evidence of other major medical illnesses that may have confounded our results. The 49 patients admitted to the respiratory medical unit and not recruited to trial were missed predominantly because of logistic reasons rather than refusal to enter the study. The major reasons for asthma patient nonrecruitment to the trial was admission to hospital over weekends and a 2-week period in April 1994 when the physicians conducting the trial were on leave. Nonrecruitment into the trial was not related to season. The demographic characteristics of the patient and control groups are given in Table 1.

The monthly patient admission numbers to the hospital and trial are shown in Figure 1. Peak patient admissions to hospital occurred in late winter, all of spring, and early summer with less patient admissions occurring in late summer and autumn.

Twenty-nine patients (37%) had evidence of recent RTI compared with five of the control group (9%) ($p<0.001$). Twenty-three patients (29%) had evidence of recent viral infection, predominantly influenza A and rhinoviruses, on serologic and/or NPA culture criteria (Table 2). Thirteen of the patients had evidence of recent influenza A infection, two had evidence of recent influenza B infection, and nine had evidence of recent rhinovirus infection. Five of the patients had evidence of more than one viral infection (Table 2). There was a peak of influenza in the late winter and early spring period whereas rhinovirus infection occurred predominantly in early winter. Three patients with either influenza A or rhinovirus also grew bacterial pathogens from sputum: *H influenza* and *S aureus*. Six patients (8%) were thought to have a nonviral infection of which three patients were thought to have bacterial infections alone and three had chest radiographic evidence of consolidation, cough, sputum, and fever without isolation of an infective agent. Only one of these patients had evidence of recent Mycoplasma infection (Table 3). We did not find coronavirus or Legionella infection and none of the febrile asthmatic group had pathogens grown from blood cultures. During the summer months, only 4 of 29 patients (14%) had evidence of recent RTI.

The hospital admission temperature was >37.5°C in 34 patients (43%). Five patients did not have admission temperature recorded. Of the febrile patients, 21 (62%) had evidence of recent RTI: 16 viral, 2 were thought to be bacterial, and 3 had consolidation with no organism identified. Conversely, 7 of the 23 patients (30%) with recent viral RTI did not have a temperature >37.5°C on admission. Two of these had influenza A diagnosed on serologic test and one had influenza A on NPA. Four had rhinovirus diagnosed on NPA, and one had both influenza A diagnosed on serologic test and rhinovirus on NPA culture.

Table 1—*Demographics of Asthma Patients and Control Group

	Patients (n=79)	Control subjects (n=54)	p Value
Age, yr, mean±SD (range)	35±15 (17-66)	36±15 (18-69)	NS
Sex, m:f	33:46	26:28	NS
NPA	79 (100)	54 (100)	NS
Paired serology	57 (72)	23 (43)	NS
Single serology	21 (27)	23 (43)	NS
No serology	1 (1)	8 (14)	<0.01
Previous asthma	79 (100)	11 (20)	<0.001

*NS=not statistically different; n=number of subjects recruited; numbers in parentheses=percent of total number of patients or control subjects.

Discussion

We have found evidence of recent RTI in 37% of adult patients admitted to hospital to the respiratory medical unit over a 12-month period with acute exacerbation of asthma. This is in contrast to early previous studies in which 10 to 21% of adult asthmatics have been found to have RTI present at time of acute exacerbations.[15] Indeed, Tarlo et al[16] in 1979 did not find an association between RTI and asthma exacerbation in adults. It has long been postulated that many asthma exacerbations are precipitated by RTI. In children it has been shown that asthma exacerbation is associated with respiratory tract infection in up to 45% of cases, though RTI is present in between 50% and 60% of asthmatic children studied without asthma exacerbation.[5] In the same study, 24% of children hospitalized with asthma had evidence of recent viral infection. Horn et al,[17] however, found 50% of children with acute asthma exacerbation had evidence of rhinovirus infection in sputum. The higher rate of RTI in children with asthma exacerbation compared with adults has been thought to be partly due to the delayed presentation of adults for management and the more rapid clearing of viruses which often occurs in adults, leading to increased difficulty in isolation of viruses in adults.[16]

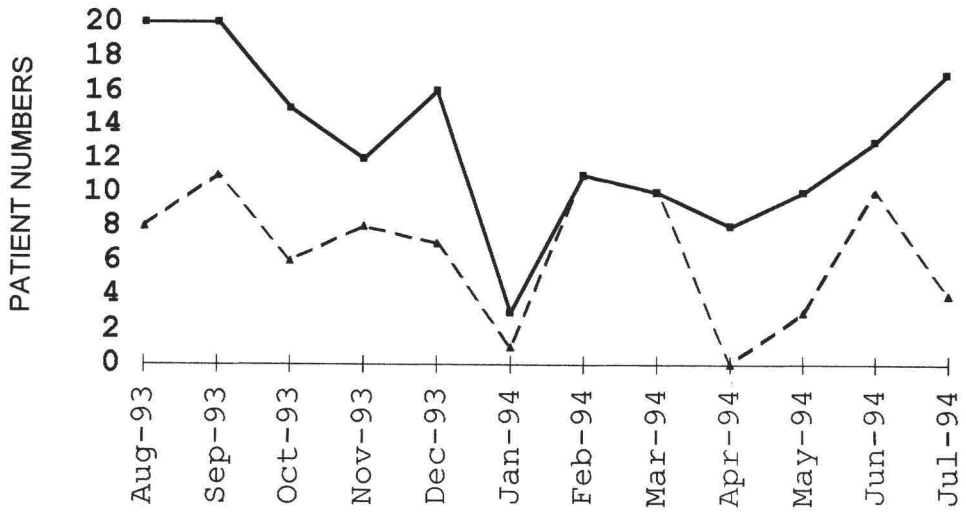

FIGURE 1. Monthly acute asthma admissions. Western Hospital admissions with acute adult asthma (solid line) and recruitment to study (dashed line) plotted by month.

Older studies had difficulty in isolating rhinovirus and coronavirus infection and although we tried to culture for coronaviruses on NPA, we did not find infection with this organism, perhaps because of its fastidious nature. Our study has identified only one patient with evidence of recent Mycoplasma infection. As Mycoplasma infections occur in epidemics, this suggests that little Mycoplasma had occurred in the community during the patient recruitment period. We found that 11% of our patients had rhinovirus cultured from NPA and by combining NPA culture and viral serology, we also found an incidence of 19% influenza A or B infection in our patients. Our results for viral RTI associated with acute asthma exacerbation are lower than those of Nicholson et al[9] who prospectively studied 138 adult outpatient asthmatics. They found an incidence of 44% of nonbacterial pathogens in what they termed severe asthma episodes (mean decrease of PEFR >100 L/min). They also found that 24% of laboratory-confirmed RTI were associated with mean decrease of PEFR ≥50 L/min on days 1 to 7. These authors were also able to identify coronavirus infections by a noncommercial enzyme-linked immunosorbent assay technique and rhinoviruses by semi-nested reverse transcriptase polymerase chain reaction.[9] In a prospective study, Beasley et al[8] assessed recent RTI in acute asthma exacerbations in adults in an outpatient setting. Though overall they found evidence of RTI in only 10% of acute asthma exacerbations, they state that the incidence of viral RTI with severe asthma exacerbation was 36%. The authors, however, did not specify the criteria for severity of asthma. They further found that 60% of those adult asthma patients who had evidence of RTI also had an exacerbation of asthma of varying severity.[8]

Table 2—*Viral Organisms Detected in Asthma Patients and Control Subjects*

	NPA	Serology Paired Sera	Serology High IgM	Total
Asthma				
Influenza A	6	2	10	18
Influenza B	0	1	1	2
Rhinovirus	9	—	—	9
Adenovirus	2	—	—	2
RSV	1	—	—	1
HSV	1	—	—	1
Total				33*
Control				
Influenza A	—	—	1	1
Influenza B	—	—	2	2
Rhinovirus	1	—	—	1
Total				4

*Five subjects had more than one virus detected and some viruses were detected by more than one test. NPA—nasopharyngeal aspirates. HSV=herpes simplex virus.

Table 3—*Nonviral RTI in Asthma Patients*

Patient	Organism	Temperature, °C	Chest Radiograph
9*	*S aureus*	38.2	Normal
17†	Nil	37.5	Lobar consolidation
24*	*H influenzae*	38	BT‡
42†	Nil	39	Lobar consolidation
36*	*M pneumoniae*	37.1	Normal
75†	Nil	38	Lobar consolidation

*All but mycoplasma grown in sputum. Mycoplasma diagnosed on single IgM titer. These patients had blood and sputum neutrophilia.
†These patients did not have evidence of allergic bronchopulmonary aspergillosis.
‡BT=bronchial wall thickening.

To our knowledge, our study is only the second prospective work assessing the association of recent RTI in adults with acute asthma requiring hospitalization. Abramson et al,[18] in a case-control study of 38 patients older than 10 years admitted to hospital with acute asthma, found that 21% had evidence of recent viral RTI. The asthmatic group had 6.2 times more chance of having viral RTI than a control group.[18] Our study has a larger number of patients and we specifically assessed patients older than 18 years.

To reduce the likelihood that our findings may have been secondary to a high background incidence of RTI within the general community at the time of our study, we attempted to recruit control subjects who were age- and sex-matched with our patients. Because our control subjects were recruited simultaneously with the patients and were age- and sex-matched, there were some difficulties with recruiting over the entire 12-month period; however, it was clear that the rate of RTI within the control group was lower than the asthmatic patients. Our control subjects, however, were a selected group admitted to the hospital for elective surgery and our finding of 9% incidence of recent RTI may be an underestimation for the general community. Although we do not have incidence figures of RTI agents in the community during the time frame of our study, we have an indication of these pathogens in the community from data collected by VIDRL (N. Lehmann; personal communication; 1995).[19] These data are taken from serologic, NPA, and sputum samples sent to the reference laboratory, from patients who are ill with RTI. Overall during winter, RSV was the predominant pathogen as it was in spring and the influenza viruses were common in early spring. Viral infections were uncommon in summer with adenoviruses and parainfluenza viruses being predominant, and during autumn, rhinoviruses, adenoviruses and parainfluenza viruses were common. From these figures, there did not seem to be an influenza or Mycoplasma outbreak in the community during the 12 months of our study (N. Lehmann; personal communication; 1995).[19] Indeed RSV, adenoviruses, and parainfluenza were noted frequently in the VIDRL data, but they were infrequently associated with asthma exacerbations in our study. The reasons for this are unclear; perhaps the latter infections occurred predominantly in children and/or are less likely to cause increase in bronchial reactivity in adults compared with the influenza viruses.[20] Data regarding pollen counts during the year in Melbourne show that 81% of total grass pollens per annum occur in November and December and tree pollens, mainly elm and cypress, predominate in late winter and early spring.[21] Taken together, these data suggest that in late winter and early spring, the population is exposed to a number of RTI pathogens and tree pollens that could potentially cause asthma. Whereas in summer, though RTI pathogens are less evident, grass pollens are abundant and in autumn and early winter, RTI pathogens are again common in the community. Our hospital admission rates for adult patients with acute asthma show that 55% of the patients were admitted in the five months August 1993 to December 1993 inclusive, whereas in the four months January 1994 to April 1994 inclusive, 20% of the year total number of patients were admitted (Fig 1). It is therefore tempting to suggest that in our group of patients, the worst times for acute exacerbation of asthma are in late winter, all of spring, and early summer and are related to high levels of community RTI pathogens and high environmental pollen counts.

We believe that the incidence of 37% RTI occurring in adult patients with acute exacerbation of asthma requiring hospitalization could be underestimated because a number of the patients failed to return for their convalescent serum sample and as a result some viral infections may have been missed. In addition, we were unable to specifically culture for *Chlamydia pneumoniae* (strain TWAR) infection, an organism that has previously been implicated in asthma exacerbations.[22] Further studies in adults with acute exacerbation of asthma using the polymerase chain reaction technique for viral identification may identify a higher incidence of RTI in adult subjects.[23,24] It is possible that we may have overestimated the frequency of RTI in our patients by using the criteria of chest radiograph consolidation in association with fever and blood neutrophilia as being diagnostic of infection. However, these criteria are used in routine clinical practice to diagnose pneumonia, and in studies of etiology of hospitalized community-acquired pneumonia, an infective organism is not identified in at least 30% of cases.[25] Similarly the isolation of an organism in the sputum is likely to be pathogenic in the setting of associated sputum neutrophilia and fever with or without chest radiograph abnormalities. Alternatively, we may have underestimated the number of patients with bacterial RTI because of antibiotic therapy prior to their admission to hospital. We do not have reliable data to confirm or deny this possibility, though most of the patients in the study denied recent antibiotic therapy.

An interesting clinical observation was the 43% frequency of fever in patients with acute exacerbation of asthma requiring hospitalization. One could postulate that the fever could be secondary to the inflammatory process of asthma alone. However, perhaps not surprisingly, in our population the find-

ing of a fever was more common in those asthmatics with evidence of recent RTI compared to those without. Those patients with evidence of recent RTI but who were afebrile on admission to hospital may have exhibited ongoing increased bronchial reactivity secondary to an RTI that had occurred within the 4 weeks prior to hospitalization. There is evidence from both animal and human experimentation to support the concept that viral RTI cause ongoing bronchial inflammation and bronchial hyperreactivity.[26,27] In addition, as previously stated, adult asthma patients may present to hospital late in the disease severity, so that even if there is evidence of recent RTI, the patients may be afebrile at time of hospitalization.

In summary, we believe this study demonstrates that there is a strong association of recent RTI with severe acute exacerbation of asthma in adults requiring hospitalization for their asthma. The 19% incidence of influenza infection in this group supports the view that in adults with significant long-term asthma, influenza vaccination on a yearly basis would be advisable.[28] As 79% of RTI found in our patient group were viral, we suggest that antibiotic therapy be withheld in acute severe exacerbation of asthma unless there is a high clinical and microbiologic suspicion of acute bacterial infection.

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