

A Prospective Study of Infections with Atypical Pneumonia Organisms in Acute Exacerbations of Chronic Bronchitis

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Abstract

The objective of this paper was to study the incidence of 6 atypical pneumonia pathogens or atypical organisms in local patients admitted for acute exacerbation of chronic bronchitis. This is a prospective observational study. Over a period of 3 years (1995 to 1997), 90 patients admitted to a large general hospital in Singapore for acute exacerbation of chronic bronchitis were tested for the following infections: Legionella, Mycoplasma, Chlamydia, influenza A, influenza B and parainfluenza viruses, using paired serological examination.

The antibiotic prescribing pattern by the attending physicians in these cases were also examined. Positive serologies were found in 31 patients (34%), of whom 26 patients (28%) had viral infections. The most common organism was influenza A with 18 positive serologies (20%). Five patients were tested positive for Legionella. There was no evidence of acute infections by Mycoplasma pneumoniae or chlamydia using serological tests.

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Introduction

Chronic obstructive pulmonary disease (COPD) is a disease state characterised by the presence of airflow limitation that is generally progressive, partially reversible and caused by either intrinsic airway disease (bronchitis) or parenchymal destruction (emphysema).¹ COPD is a leading cause of death and a major medical and economic problem.^{1,2} Various investigators have described the association between viruses and *Mycoplasma pneumoniae* and the acute exacerbation of COPD.³⁻⁷ These organisms are often referred to as atypical pneumonia pathogens as they produce a different clinical syndrome from classical bacterial pneumonia-insidious onset, non-productive cough and no response to β -lactam antibiotics.⁸ The most common of these organisms are *Mycoplasma pneumoniae*, *Legionella* spp, *Chlamydia pneumoniae* and influenza types A and B. Parainfluenza types 1 to 3 are among the less common organisms. The incidence of these infections ranged from 18% to 64% in these studies. Presently there are no local figures for the incidence of infections with viral and organisms such as *Legionella*, *Mycoplasma pneumoniae* and *Chlamydia*

pneumoniae in this common cause of hospital admissions. Prospective studies of adult community acquired pneumonia in Singapore⁹ and Hong Kong¹⁰ have looked at the incidence of atypical pneumonia organisms but not specifically as a cause of exacerbations in COPD patients. Most investigators³⁻⁷ found that the viruses most frequently involved in COPD exacerbations were influenza and parainfluenza. *Mycoplasma pneumoniae* was also reported to be present in some studies.^{5,7}

Cigarette smoking and chronic lung disease, both characteristics of COPD, are also known risk factors for *Legionella* infections.¹¹ Since its identification in 1986, *Chlamydia pneumoniae* has emerged as the most common chlamydial infection in humans world-wide.^{12,13} Its incidence locally is presently still under study. Although serology by complement fixation for chlamydia is not specific for *Chlamydia pneumoniae*, it nonetheless provides indirect evidence of the incidence of the organism in COPD patients.

The aim of this prospective and observational study, which was conducted over three years (1995 to 1997), was to study the incidence of influenza A and B,

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parainfluenza 1, 2, 3, *Legionella* spp, *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* in patients admitted to a local general hospital for acute exacerbations of chronic bronchitis.

Materials and Methods

Over a period of three years, 137 patients who were admitted to a large general hospital in Singapore for the clinical diagnosis of acute exacerbation of chronic obstructive airway disease were recruited for this study. An acute exacerbation is defined as an increase in any two of the following symptoms, i.e. dyspnoea, cough, sputum production or wheezing in a patient with a history of COPD. The case histories were reviewed by one of the investigators to ensure that they satisfy the diagnosis for COPD and the study's definition of acute exacerbation. The chest X-rays of the patients were reviewed for evidence of changes consistent with COPD (hyperinflation, pulmonary oligoemia), pulmonary infiltrates, and evidence of other aetiologies such as heart failure, pneumothorax, malignancies bronchiectasis and tuberculosis. Spirometry was performed wherever possible to confirm the presence of airflow obstruction and assess its severity. The antibiotics prescribed by the attending physician were noted.

Paired serologies for *Mycoplasma*, *Chlamydia*, influenza A, influenza B and parainfluenza were taken on admission and two weeks later. Paired serologies for *Legionella* were taken on admission and 4 to 6 weeks later. In most cases the second specimen was taken during follow-up visits at the outpatient clinic.

The study protocol was approved by the Ethics committee of the hospital.

Inclusion Criteria: Patients who were admitted with the clinical diagnosis of COPD and satisfied the study criteria of acute exacerbation were included in the study. COPD, a disorder characterised by chronic airflow obstruction, includes both chronic bronchitis and emphysema.

Chronic bronchitis was defined as chronic or recurrent excess mucus secretion into the bronchial tree occurring in most days for at least 3 months of the year for at least 2 years. As emphysema is strictly a pathological diagnosis, we were unable to make a clinical diagnosis of emphysema in this study.

Exclusion Criteria: The following patients were excluded from the study: those with other co-existing pulmonary pathologies such as bronchial asthma, bronchiectasis or pulmonary tuberculosis; patients with co-existing malignancy, pneumothorax and acute heart failure; non-smokers; patients whose chest X-rays or lung function tests were not suggestive of COPD; and COPD patients admitted for problems other than acute exacerbation.

Serologic Procedures

Serial serum specimens were tested by complement fixation for antibodies to influenza A and B viruses, parainfluenza 1,2,3 viruses, *Mycoplasma pneumoniae* and *Chlamydia*. Serologic evidence of infection was defined as a four-fold increase or greater in antibody titre between acute and convalescent phase sera or a single value of $\geq 1/128$ in the case of viruses. Serologic evidence for *Legionella* infection was defined as a four-fold rise of serial indirect fluorescent antibody test or the presence of a single titre $\geq 1/1028$.

Other respiratory viruses such as respiratory syncytial virus, adenovirus, coronavirus and rhinovirus were not tested.

Results

Patient Characteristics (Table I)

During the 3-year study period 90 patients who were admitted for acute exacerbations of chronic bronchitis were studied for the presence of the 6 atypical pathogens. The remaining 47 patients who were recruited did not show up for their second blood sampling and were excluded from the study. Their median age was 71.5 years. There were 85 male and 5 female patients. All the patients had a positive smoking history. Spirometry was performed in 60 of these patients and of these, 37 (62%) patients had an FEV1 of less than 40% predicted, indicating severe disease. Another 12 (20%) had a FEV1 between 40% and 60% predicted indicating moderately severe disease. Only 2 patients had diabetes mellitus.

TABLE I: CHARACTERISTICS OF STUDY POPULATION

	Positive serology (n = 31)	Negative serology (n = 59)	Total (n = 90)
Median age (y)	76	71	71.5
Sex			
Male	27	59	86
Female	2	2	4
Mean FEV1 (L)	0.84	0.94	0.91
Mean FEV1 (% predicted)	39	41	40
FEV1	(n = 19)	(n = 41)	
<40%	13	24	37
40% to 60%	3	8	11
>60%	3	9	12
Mean white cell count (mm ³)	10,348	11,904	10,051
Fever	11/31 (35%)	15/59 (25%)	26/90 (29%)
Chest X-ray infiltrates	12/31 (39%)	25/59 (42%)	37/90 (41%)
Diabetes mellitus	1	1	2

Serologic Results (Table II)

Positive serologies were found in 31 patients (34%). Influenza A was the most common organism comprising 18 positive serologies (20%). Influenza B and parainfluenza group 3 viruses were found in a smaller number of patients. Positive serologies of the 3 viruses investigated made up 28.8% of the total population. Eleven patients or 35% of the seropositive cases had a fever on initial presentation. Twelve patients or 39% of seropositive cases were found to have infiltrates on chest X-ray.

Ten or 38.5% of the seropositive patients had a polymorpholeukocytosis (leukocyte count $>1,000\text{mm}^3$). Five patients had positive Legionella serologies (5.5%) and of these, only 2 had radiological evidence of pneumonia and none were treated initially with macrolides. Only 1 out of the 5 cases were taking oral steroids.

None of the patients were tested positive for Mycoplasma and Chlamydia.

The antibiotic prescribing patterns of the medical team managing the patients conformed to standard practice (Tables III and IV). In those patients who were found to have infection with the study organisms, 22 patients or 24.4% were prescribed penicillin, 3 with sulphonamides, 5 with cephalosporins and 1 with erythromycin. There were no distinguishing features between patients with positive serologies from those with negative serologies, except that the positive serology group had a higher median age (Table I).

TABLE II: ATYPICAL PNEUMONIA ORGANISMS ASSOCIATED WITH ACUTE EXACERBATIONS OF CHRONIC BRONCHITIS

Organism	No.	%
<i>Legionella</i> spp	5	5.5 (90% CI 1.58-9.53)
<i>Mycoplasma pneumoniae</i>	0	0
<i>Chlamydia</i> spp	0	0
Influenza A	18	20 (90% CI 13.1-26.9)
Influenza B	4	4.4 (90% CI 0.87-8.02)
Parainfluenza group 3	4	4.4 (90% CI 0.87-8.02)
Total	31	34.4 (90% CI 26.2-42.7)

TABLE III: ANTIBIOTIC PRESCRIBING PATTERN IN STUDY POPULATION COMPRISING ALL PATIENTS WITH EXACERBATION OF CHRONIC BRONCHITIS (n = 90)

Antibiotic	No.	%
Penicillin	68	75.5
Macrolide	6	6.7
Cephalosporin	11	12.2
Sulphonamide	5	5.6

TABLE IV: ANTIBIOTIC PRESCRIBING PATTERN IN PATIENTS WITH ACUTE EXACERBATIONS OF CHRONIC BRONCHITIS CAUSED BY ATYPICAL PNEUMONIA ORGANISMS (n = 31)

Antibiotic	No.	%
Penicillin	22	71
Macrolide	1	3
Cephalosporin	5	16
Sulphonamide	3	10

Discussion

Acute bronchitic exacerbations have a detrimental effect on the clinical course of COPD. In the late stages of the disease infections become increasingly common and may contribute to the underlying pathogenesis. Bacterial infections contribute to oxidative stress in patients with COPD by facilitating the recruitment and activation of phagocytic cells in the lung.¹⁴ While viral infections have not been shown to contribute to disease progression, they cause damage to the airway epithelium and mucociliary apparatus, thus predisposing the lung to bacterial colonisation.¹⁵

Cigarette smoking, chronic lung disease and immunosuppression especially caused by corticosteroid therapy have been consistently implicated as risk factors for Legionellosis. The incidence of Legionella in this study, although small, is higher than recent prospective studies on community acquired pneumonia in Singapore⁹ and Hong Kong¹⁰ where no positive cases of Legionella were detected. In a recent surveillance study of Legionellosis in Singapore, Heng et al¹⁶ found that 8.7% of 241 cases of Legionellosis reported between 1989 and 1996 have coexistent COPD.

The negative finding for *Mycoplasma pneumoniae* in this study corroborated with those of Smith et al,³ (5 out of 1030 exacerbations), Buscho et al,⁵ (4/166) and Gump et al,⁴ (1/116) where low incidences were found.

The results of these studies suggest that while *Mycoplasma pneumoniae* may be associated with exacerbations of chronic bronchitis, it is not of great importance in relation to the disease.

Chlamydia pneumoniae was first identified in 1986 and has since gained attention as an important respiratory pathogen. The illness produced by *C. pneumoniae* is usually mild but may be severe in patients with pre-existing chronic diseases or in immunocompromised patients.¹² Blasi et al¹⁷ reported that *C. pneumoniae* infection was a relatively frequent event in COPD with at least 4% of exacerbations associated with it. Similarly Beaty et al¹⁸ reported acute *C. pneumoniae* infection in 5% of their patients with COPD exacerbations. Beaty's study also showed that at the time of low incidence in the community, acute *C. pneumoniae* infection is uncommon

in patients with acute exacerbations of COPD. *C. pneumoniae* infections are periodic with several years of higher incidence followed by years of low incidence; this may explain the absence of positive Chlamydia serology in our study population. The more recent Spanish Multicentre Study¹⁹ on community-acquired pneumonia in COPD found *C. pneumoniae* to be present in 9% of the aetiological diagnoses made.

The viral seropositivity rate of 28.8% correlates well with that of the major studies done on the incidence of viral infections in acute exacerbations of COPD. The study by Gump et al⁴ found that one third of 116 exacerbations observed could be related to viral infections, the predominant viruses being influenza and parainfluenza viruses with a smaller incidence of respiratory syncytial virus, coronavirus and adenovirus. Buscho et al⁵ found serologic evidence of viral infections in 22.6% of 166 exacerbations observed over 5 years; the predominant organisms in this study were influenza A, parainfluenza type 3 and coronavirus OC43. The largest study by Smith et al³ reported that viral infections were associated with 17.5% of 1030 illnesses studied.

Our study did not cover the full spectrum of respiratory viral infections. A more comprehensive study may yield a higher viral seropositivity rate than that obtained in this study.

The high incidence of influenza virus raises the issue of influenza vaccination in local COPD patients. The European Respiratory Society's Consensus Statement on the optimal assessment and management of COPD² recommended that killed influenza vaccines be given parenterally to COPD patients once each autumn. These vaccines are usually trivalent, containing two subtypes of influenza A and one of influenza B; the strains are adjusted each year for best effectiveness.

Nichol et al²⁰ in a study of the efficacy and cost effectiveness of vaccination against influenza among elderly persons (>64 years) living in the community, found that in this subgroup, vaccination was associated with a reduction in the rate of hospitalisation and deaths from influenza and its complications. There was a reduction of 39% of hospitalisation for chronic respiratory conditions among vaccinated elderly patients. A recent meta-analysis by Gross et al²¹ found that despite the paucity of randomised trials, many studies confirm that influenza vaccine reduces the risks for pneumonia, hospitalisation, and death in elderly persons during an influenza epidemic if the vaccine strain is identical or similar to the epidemic strain. The difficulty in implementing large scale influenza vaccination in Singapore stems from the lack of seasonal variation in the climate and the lack of predominance of a particular strain of influenza virus at any point in time. The results of this study resembled

those done in temperate climates in showing that influenza is commonly associated with exacerbation of COPD locally. Hence, future prospective studies on the efficacy of influenza vaccination in the local, elderly COPD population may resolve the issue of influenza vaccination in this group of patients in Singapore.

The role of antibiotics in acute exacerbations of COPD has been re-examined recently.²² Non-bacterial causes account for about half of acute exacerbations of COPD. These include viruses (28% in our study), environmental irritants, intercurrent illnesses and cardiopulmonary events such as heart failure, arrhythmias and pulmonary emboli. Anthonisen et al²³ demonstrated that in patients with increased dyspnoea, sputum volume, and sputum purulence, there was significant benefit associated with empiric broad-spectrum antibiotic usage. Conversely, they found that antibiotics conferred no benefit when only one symptom was present.

The findings of this study form the basis of the recommendations of both the American Thoracic Society Statement¹ and European Respiratory Society Consensus Statement² on COPD.

A meta-analysis²⁴ of randomised trials to estimate the effectiveness of antibiotics in treating COPD exacerbations suggests a small but statistically significant improvement due to antibiotic therapy. More recently Grossman²⁵ stratified treatment of acute exacerbations of chronic bronchitis based on disease severity and risk factors (impairment of lung function, number of exacerbations, age, co-morbidities, oral steroid usage). Under this classification, most of the patients in our study population would fall into the high-risk category in view of their age, co-morbidities and degree of impairment of lung function and hence would require empirical antibiotics regardless of the causative organism detected.

A major difficulty in comparing the results of the different studies on infective exacerbations of COPD stems from the lack of uniform diagnostic criteria of what constitutes an acute exacerbation. Various criteria have been applied by investigators, including subjective worsening of dyspnoea, an increase in the quantity or appearance of sputum, symptoms of upper or lower respiratory tract infections, and the investigator's own clinical impression (which was the most commonly used).²⁶ Most studies, including ours, rely on clinical criteria alone to define acute exacerbation. Exacerbations which require hospitalisations, such as those in this study, are often considered as severe events.²

In conclusion, influenza is a common infection associated with severe exacerbations of chronic bronchitis. The efficacy of vaccination needs to be evaluated in these patients.

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REFERENCES

1. ATS Statement 1995. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1995; 152:S77-S121.
2. Siafakas NM, Vermeire P, Pride NB, Paoletti I, Gibson J, Howard P, et al. Optimal assessment and management of chronic obstructive pulmonary disease (COPD): a consensus statement of the European Respiratory Society (ERS). *Eur Respir J* 1995; 8:1398-420.
3. Smith CB, Golden CA, Kanner RE, Renzette Jr AD. Association of viral and *Mycoplasma pneumoniae* infections with acute respiratory illness in patients with chronic obstructive pulmonary illness. *Am Rev Respir Dis* 1980; 121:225-32.
4. Gump DW, Phillips CA, Forsyth BR, McIntosh K, Lamborn KR, Stouch WH. Role of infections in chronic bronchitis. *Am Rev Respir Dis* 1976; 113:465-73.
5. Buscho RO, Saxtan D, Shultz PS, Finch E, Mufson MA. Infections with viruses and *Mycoplasma pneumoniae* during exacerbation of chronic bronchitis. *J Infect Dis* 1978; 47:377-83.
6. Lamy ME, Pouthier-Simon F, Debacker-Willame E. Respiratory viral infections in hospital patients with chronic bronchitis. *Chest* 1973; 63:336-41.
7. McNamara MJ, Phillips IA, Williams OB. Viral and *Mycoplasma pneumoniae* infections in exacerbations of chronic lung disease. *Am Rev Respir Dis* 1969; 100:19-24.
8. Greenberg SB, Atmar RL. Atypical pneumonia. In: Niederman MS, Sarosi G A, Glassroth J, editors. *Respiratory Infections: A Scientific Basis for Management*. Philadelphia, WB Saunders, 1994:621-33.
9. Hui KI, Chin NK, Chow K, Brownlee A, Yeo TC, Kumarasinghe G, et al. Prospective study of the aetiology of adult community acquired bacterial pneumonia needing hospitalisation in Singapore. *Singapore Med J* 1993; 34:329-34.
10. Chan HS, Cohen M, Pang J. A prospective study of community-acquired pneumonia in Hong Kong. *Chest* 1992; 101:442-6.
11. Stout J, Yu VL. Current concepts: Legionellosis. *N Engl J Med* 1997; 337:682-7.
12. Bourne SJ. Chlamydial respiratory infections [editorial]. *BMJ* 1993; 306: 1219-20.
13. Marrie TJ. *Chlamydiae pneumoniae* [editorial]. *Thorax* 1993; 48:1-4.
14. Repine JE, Bast A, Lankhorst I, and the Oxidative Stress Study Group. State of the art: Oxidative stress in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1997; 156:341-57.
15. Jansen HM, Sachs AP, Van Alphen L. Predisposing conditions to bacterial infections in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1995; 151:2073-80.
16. Heng BH, Goh KT, NgDLK, Ling AE. Surveillance of Legionellosis and Legionella bacteria in the built environment in Singapore. *Ann Acad Med Singapore* 1997; 26:557-62.
17. Blasi F, Legnani D, Lombardo VM, Negretto GG, Magliano E, Pozzoli R, et al. *Chlamydia pneumoniae* infection in acute exacerbations of COPD. *Eur Respir J* 1993; 6:19-22.
18. Beaty CD, Grayston JT, Wang S, Kuo C, Reto CS, Martin TR. *Chlamydia pneumoniae*, strain TWAR, infection patients with chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1991; 144:1408-10.
19. Torres A, Dorca J, Zalacain R, Bello S, El-Ebiary M, Molinos L, et al. Community-acquired pneumonia in chronic obstructive pulmonary disease. A Spanish Multicenter Study. *Am J Respir Crit Care Med* 1996; 154:1456-61.
20. Nichol KL, Margolis MD, Wuorenma RN, Von Sternberg T. The efficacy and cost effectiveness of vaccination against influenza among elderly persons living in the community. *N Engl J Med* 1994; 331:778-84.
21. Gross PA, Hermogenes AW, Sacks HS, Lau J, Levandowski RA. The efficacy of influenza vaccine in elderly persons. A meta-analysis and review of the literature. *Ann Intern Med* 1995; 123:518-27.
22. Grossman RF. The value of antibiotics and the outcomes of antibiotic therapy in exacerbations of COPD. *Chest* 1998; 113:249S-55S.
23. Anthonisen NR, Manfreda J, Warren CPW, Hershfield ES, Harding GK M, Nelson NA. Antibiotic therapy in exacerbations of chronic obstructive pulmonary disease. *Ann Intern Med* 1987; 106:196-204.
24. Saint S, Bent S, Vittinghoff E, Grady D. Antibiotics in chronic obstructive pulmonary disease exacerbations. A meta-analysis. *JAMA* 1995; 273:957-60.
25. Grossman RF. Guidelines for the treatment of acute exacerbations of chronic bronchitis. *Chest* 1997; 112:310S-35.
26. Isada CM, Stoller JK. Chronic bronchitis: Role of antibiotics. In: Niederman MS, Sarosi G A, Glassroth J, editors. *Respiratory Infections: A Scientific Basis for Management*. Philadelphia: WB Saunders, 1994:621-33.