

'Atypical' bacteria are a common cause of community-acquired pneumonia in hospitalised adults

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Objectives. To assess the proportion of cases of community-acquired pneumonia caused by 'atypical' bacteria, including the recently discovered *Chlamydia pneumoniae*, and to compare the clinical, radiographic and laboratory features of patients with and without 'atypical' bacteria.

Methods. A prospective serological study was carried out on consecutive adult pneumonia patients from July 1987 to July 1988. Acute and convalescent sera were tested in batches for antibodies against *Legionella pneumophila* serogroup 1, *C. pneumoniae*, *Chlamydia psittaci*, *Coxiella burnetii* (phase-2 antigen) and *Mycoplasma pneumoniae* (IgG and IgM). Records and chest radiographs were examined retrospectively.

Results. Acute and convalescent sera were available from 113 patients. The records of 4 patients could not be traced and 17 patients did not fulfil the inclusion criteria. Thirty-two of these 92 patients (35,9%) were found to be infected with 'atypical' bacteria. The two most common organisms were *C. pneumoniae* (20,7%) and *L. pneumophila* (8,7%). There were no differences in the clinical and radiographic features of patients with and without 'atypical' bacteria. Clinicians prescribed erythromycin or tetracyclines with equal frequency in the two groups.

Conclusions. 'Atypical' bacteria, especially *C. pneumoniae*, are a common cause of community-acquired pneumonia in adults in South Africa. This is the first demonstration of an aetiological role of *C. pneumoniae* in this country. We confirmed the finding of other studies that there are no clinical, radiographic or laboratory features characteristic of 'atypical' bacterial infection in hospitalised patients. This has major implications for therapy, as these organisms respond to erythromycin and tetracyclines, but not to β -lactam antibiotics.

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Atypical pneumonia is a clinical syndrome first described by Reimann in 1938.¹ There is no precise definition of this syndrome,² but the illness has a subacute onset with constitutional symptoms and a dry cough. Radiographic shadowing is characteristically non-segmental and more extensive than the physical examination would suggest. Leukocytosis is absent or moderate. The course is generally benign. *Mycoplasma pneumoniae* is the most common aetiological agent of atypical pneumonia. Other bacteria that cause atypical pneumonia are *Chlamydia psittaci*, *Legionella* spp. and *Coxiella burnetii* (the agent that causes Q fever).² These organisms share three characteristics: they are not visible on Gram stain, they do not grow on conventional culture media and they do not respond to penicillins or cephalosporins.

There is a widespread belief that pneumonia caused by these organisms can readily be differentiated from pneumonia due to conventional bacteria. However, the most common radiographic finding in pneumonia due to these four 'atypical' bacteria is unilateral consolidation, often lobar or segmental,³⁻⁸ and the clinical features are generally indistinguishable from those found in pneumonia caused by conventional bacteria.^{2,7-10}

Table I summarises four recent studies which show that 'atypical' bacteria cause a significant proportion of cases of community-acquired pneumonia in adults. The major differences in these studies are the incidence of mycoplasma pneumonia, which occurs in cyclical epidemics every few years,¹¹ and legionella pneumonia which varies geographically and temporally.¹²

A fifth 'atypical' bacterium that causes pneumonia has recently been discovered. *Chlamydia pneumoniae* (formerly known as *Chlamydia* strain TWAR) was found to be responsible for 12% of cases of mild pneumonia in college students.¹⁷ Studies of hospitalised patients with community-acquired pneumonia showed that *C. pneumoniae* caused 6 - 10% of cases.¹⁸⁻²⁰ It was also shown that there were no differences in clinical or radiographic features of patients with pneumonia caused by *C. pneumoniae* and those in whom other pathogens were responsible.¹⁸⁻²⁰ A chlamydia complement fixation test is widely used to diagnose psittacosis. This test is not species-specific and can be positive in primary infections (but not re-infections) with *C. pneumoniae*.²¹ It is therefore likely that some cases of psittacosis found in earlier pneumonia studies were in fact caused by *C. pneumoniae*. Even so, roughly 20 - 40% of patients with community-acquired pneumonia will have infections caused by 'atypical' bacteria. To date there is no commercially available test to detect *C. pneumoniae* antibodies; this has hindered the investigation of the aetiological role of this agent in community-acquired pneumonia.

All of the studies quoted so far were performed in developed countries. A previous study from this institution²² showed that 10% of cases were due to *M. pneumoniae*. Other 'atypical' bacteria were not tested for in that study. The aim of the current study was to assess the proportion of cases of community-acquired pneumonia due to *M. pneumoniae*, *Legionella pneumophila*, *C. psittaci*, *C. pneumoniae* and *C. burnetii* in a developing country. A secondary objective was to compare the clinical, radiographic and laboratory features of patients with and without 'atypical' bacteria.

Patients and methods

We evaluated consecutive adults with an admission diagnosis of pneumonia from July 1987 to July 1988 at Groote Schuur Hospital, a large community-based university hospital. Pneumonia was defined as an acute respiratory illness with compatible shadowing on chest radiograph (performed on admission or within 48 hours). Patients with pulmonary tuberculosis or severe immunosuppression (e.g. in cases of AIDS) were excluded. Folders were retrospectively reviewed for demographic data, underlying illnesses, symptom duration, blood pressure values, respiratory rate, presence of confusion, laboratory features (PO₂, urea values, white cell count) and whether the chest radiograph showed a segmental or non-segmental pattern of pulmonary shadowing.

Microbiological methods

Acute and convalescent (2 - 4 weeks) sera were collected. The study was originally set up to assess the incidence of *L. pneumophila*. Paired sera were tested simultaneously for *L. pneumophila* serogroup 1 by an indirect fluorescent antibody test (IFAT) method using antigen prepared in our laboratory. Positive results were checked with control antigen from the Centers for Disease Control (CDC), Atlanta USA. The sera were then frozen at -20°C and subsequently tested in batches (avoiding multiple freeze-thaw) for IgM and IgG antibodies against *M. pneumoniae* (IFAT, Diagnostic and Technical Services), Q fever phase-2 antigen (IFAT, bio-Merieux), *C. psittaci* (IFAT, bio-Merieux), and *C. pneumoniae* (IFAT, antigen supplied by professor C. C. Kuo, Washington University, USA). Definite infections were indicated by a 4-fold rise in titre or a titre of > 16 for *M. pneumoniae* IgM. Probable infections were diagnosed when a single titre was ≥ 64 for mycoplasma IgG, ≥ 256 for *C. psittaci*, Q fever and *L. pneumophila*, and ≥ 512 for *C. pneumoniae*.²¹

Results of sputum and blood cultures were recorded if the clinicians looking after the patient had requested these tests.

Table I. Proportion of community-acquired pneumonia cases caused by 'atypical' bacteria in studies of hospitalised adults

Country	No. of patients	<i>Legionella</i> spp.		<i>M. pneumoniae</i>		Q fever		<i>C. psittaci</i>		'Atypical' bacteria (%)
		No.	%	No.	%	No.	%	No.	%	
UK ¹³	127	19	15	3	2	1	< 1	7	6	24
UK ¹⁴	453	9	2	81	18	5	1	13	3	24
Spain ¹⁵	462	64	14	16	3	3	< 1	1	< 1	18
Australia ¹⁶	106	3	3	8	8	0		5	5	15

Statistical methods

Clinical, laboratory and radiographic features of patients with and without 'atypical' bacteria were compared. The χ^2 -test was used to analyse the categoric variables, while Student's *t*-test (two-tailed) was used to analyse the continuous variables.

Results

One hundred and seventy-three patients with an admission diagnosis of pneumonia were entered in the study, but convalescent serum was not obtained from 60 of these. The records of the remaining 113 patients were reviewed. The records of 4 patients could not be traced and 17 patients did not fulfil the entry criteria for the study. This left 92 patients, 8 of whom were white, 23 black and 61 coloured.

We personally reviewed the radiographs of 72 patients. Our reports correlated very closely with those of the radiologists which were relied upon for the remaining 20 patients whose radiographs had been destroyed.

The results of the serological tests are shown in Table II. The patient with a 4-fold rise in titre to both *C. pneumoniae* and *C. psittaci* presumably represents a cross-reaction. Five of the patients with serological evidence of 'atypical' bacterial infection also had sputum cultures positive for conventional bacterial pathogens (3 *Haemophilus influenzae*, 2 *Streptococcus pneumoniae*). In the patients without serological evidence of 'atypical' bacteria there were 5 positive blood cultures (4 *S. pneumoniae* and 1 *Pseudomonas aeruginosa*) and sputum cultures were positive in an additional 9 (3 *H. influenzae*, 2 *S. pneumoniae*, 3 both *S. pneumoniae* and *H. influenzae*; and 1 *Staphylococcus aureus*).

Table II. Patients with positive serological findings for 'atypical' bacteria

Organism	Definite/probable	(%)
<i>L. pneumophila</i>	8/0	(8,7)
<i>M. pneumoniae</i>	1/0	(1,1)
<i>C. psittaci</i>	2/3	(5,4)
<i>C. burnetii</i>	0/0	(0)
<i>C. pneumoniae</i>	19/0	(20,7)
Total	32*	(35,9)

*One patient had a 4-fold rise in titre to both *C. pneumoniae* and *C. psittaci*.

Table IV. Clinical, radiographic and laboratory features of patients with and without evidence of infection with 'atypical' bacteria

	Atypical bacteria		P-value
	Absent	Present	
No.	60	32	
Sex (M/F)	38/22	14/18	0,11
Mean age (yrs)	41,8	46,5	0,23
Underlying condition present	23 (N = 60)	14 (N = 31)	0,69
Mean duration of symptoms (days)	5,7	4,9	0,57
Presence of confusion	8 (N = 60)	2 (N = 31)	0,52
Mean blood pressure	124/74 (N = 59)	127/77 (N = 30)	0,56/0,33
Mean respiratory rate	28,4 (N = 21)	26,6 (N = 9)	0,62
Mean Po ₂ (kPa)	9,3 (N = 22)	10,0 (N = 11)	0,66
Mean serum urea level (μmol/l)	8,2 (N = 45)	4,2 (N = 20)	0,01
Mean white cell count (10 ⁹ /l)	13,3 (N = 31)	12,1 (N = 16)	0,06
Radiograph type			
Segmental	38	19	
Non-segmental	22	13	0,88
Length of admission (days)	5,2	4,6	0,61

The seasonal distribution of pneumonia cases is shown in Fig. 1. Underlying medical conditions were present in 37 patients (Table III).

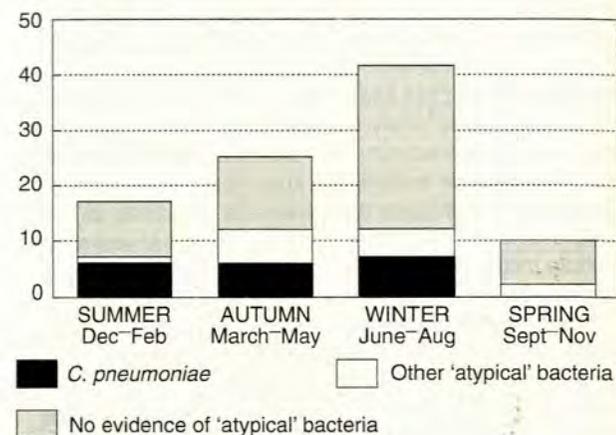


Fig. 1. Seasonal distribution of pneumonia cases.

Table III. Underlying conditions in patients with community-acquired pneumonia

COPD/asthma	13
Alcoholism	8
Cardiac failure	6
Diabetes mellitus	4
Bronchiectasis	2
Miscellaneous*	4

COPD = chronic obstructive pulmonary disease.

* Chronic renal failure, myasthenia gravis, chronic lymphocytic leukaemia, stroke.

There were no differences in the demographic, clinical and radiographic features of patients with and without pneumonia due to 'atypical' bacteria (Table IV). The only laboratory feature that was significantly different between the two groups was the urea level, which was higher in the group without 'atypical' bacteria.

The ability of the attending clinicians to distinguish presence or absence of 'atypical' bacteria was assessed on the basis of the prescription of erythromycin or tetracycline. These antibiotics were prescribed for 6 of the 32 (19%) patients with 'atypical' bacterial infections versus 12 of the

60 (20%) without 'atypical' bacteria. According to the records, they were prescribed because 'atypical' pneumonia was suspected and not because of penicillin allergy. Four patients, 2 from each group, required admission to an intensive care unit, and both patients from the 'atypical' group had *L. pneumophila* pneumonia.

Clinical, demographic and radiographic features of patients with *C. pneumoniae* pneumonia did not differ significantly from patients with other 'atypical' bacteria or from the group without 'atypical' bacteria.

Discussion

We have shown that 'atypical' bacteria cause more than one-third of cases of community-acquired pneumonia in adults. *C. pneumoniae* was responsible for 20.7% of pneumonia cases. This is higher than has been reported in other serological surveys,¹⁷⁻²⁰ but a similar proportion was found in a study using culture and serology.²³ *C. pneumoniae* occurs in cyclical 4 - 6-year epidemics²¹ and our study was presumably conducted during an epidemic year. The proportion of cases of legionella pneumonia (8.7%) in this study is intermediate between areas with a low^{14,16} and a high^{13,15} incidence. Our finding is an underestimate, as we did not test for other *L. pneumophila* serogroups or other *Legionella* spp., which collectively account for about half of legionella pneumonia cases.²⁴ There was no evidence of a legionella outbreak, as the patients came from different geographical areas at separate times.

The only significant difference between patients with and without 'atypical' bacteria was in the serum urea level, which was lower in patients with 'atypical' bacteria. An elevated urea level has been shown to be a poor prognostic factor in pneumonia,¹⁴ and is unlikely to help in the identification of specific pathogens. In the current study, erythromycin or tetracyclines were prescribed with the same frequency in patients with and without 'atypical' bacteria; this further emphasises that the two groups are indistinguishable. Antibiotics directed against the enterobacteriaceae were prescribed more frequently, despite the fact that these organisms do not usually cause community-acquired pneumonia.^{13-16, 20,22}

In a recent large prospective study, Fang *et al.*²⁰ found no characteristic features in hospitalised patients with pneumonia due to 'atypical' bacteria and concluded that the term 'atypical pneumonia' should be abandoned. Yung *et al.*² commented that the term 'is only of value in the age group of 10 - 60 years, in previously healthy patients, in those with community-acquired disease and those without a life-threatening illness'.

The majority of infections with 'atypical' bacteria are subclinical, and only a small minority of patients require hospitalisation for pneumonia. An atypical presentation may be associated more strongly with 'atypical' bacteria in mild pneumonia not requiring admission. However, this has not been addressed in a prospective study. Such a study would be difficult to perform as atypical pneumonia is ill-defined, and previous attempts at a definition have focused on characteristics of 'atypical' bacteria.^{25,26}

Patients with pneumonia caused by 'atypical' bacteria generally make a spontaneous recovery as illustrated by the

fact that most of our patients recovered without specific therapy. However, recovery can be prolonged, and appropriate therapy considerably shortens the course of the illness.² Apart from legionella pneumonia, mortality from pneumonia caused by other 'atypical' bacteria is generally low.^{4,7-9,20,28} However, some studies have found that the mortality rate of pneumonia caused by *M. pneumoniae*¹⁴ or *C. pneumoniae*^{18,19} is similar to that of pneumococcal pneumonia.

Appropriate therapy for pneumonia caused by 'atypical' bacteria is erythromycin or tetracyclines. Doxycycline is probably the tetracycline of choice in this situation as it can be taken twice daily and has better intracellular penetration (all of these agents except *M. pneumoniae* are intracellular). Erythromycin and tetracyclines are equally effective in *M. pneumoniae* infections,² but the tetracyclines seem to be more active against chlamydia.^{2,21} Erythromycin is generally regarded as the agent of choice for legionella pneumonia, but tetracyclines are also effective.^{2,27} There are very few controlled trials comparing these two agents in pneumonia caused by 'atypical' bacteria. A recent study has shown that doxycycline is more active than erythromycin in cases of Q fever.²⁸

The specific aetiological agent should be sought in hospitalised adults with community-acquired pneumonia in order to direct antibiotic therapy. An urgent Gram stain of an adequate sputum sample has proved a useful investigation.^{20,22} Tuberculosis can manifest itself as an acute pneumonia in our area,²² and a Ziehl-Neelsen stain should be requested if the Gram stain is negative. If no organism is identified, empirical therapy for patients with mild-to-moderate pneumonia should cover *S. pneumoniae*, which is the most common cause,^{13-15,20,22} or *H. influenzae* if chronic obstructive pulmonary disease is present. Therapy directed against 'atypical' bacteria can be added initially or if response is delayed or incomplete. Patients with pneumonia caused by 'atypical' bacteria may respond to β -lactam antibiotics if secondary bacterial infection is present; this occurred in 5 of our patients and was a frequent finding in other studies.^{14,16,22}

In severe community-acquired pneumonia there is an increased incidence of *Legionella* spp., *S. aureus* and the enterobacteriaceae, although *S. pneumoniae* remains the most common aetiological organism.^{29,31} The mortality rate in this context is very high and some have argued that an early invasive procedure to establish aetiology is justified.³⁰ If no organism is identified, then empirical therapy should cover enterobacteriaceae and *S. pneumoniae*. Specific anti-staphylococcal therapy should be added in an influenza epidemic, or if clinically indicated. The decision to add intravenous erythromycin (which is very expensive) should depend on the local incidence of legionella pneumonia. A retrospective study from this institution found that legionella pneumonia accounted for 5 of 95 patients with community-acquired pneumonia requiring ICU admission.³¹ However, serological tests were only performed in 40 patients and were directed only at *L. pneumophila*. Mortality from severe legionella pneumonia is considerably increased in patients not receiving appropriate therapy.²

The current study has several weaknesses. Firstly, the clinical, radiographic and laboratory data were gathered retrospectively. Secondly, no special attempts were made to

identify conventional bacteria or viruses. Thirdly, more cases of mild-to-moderate pneumonia were studied as convalescent serum was an entry requirement; this resulted in the exclusion of those who died from severe pneumonia. Nevertheless, our conclusion that 'atypical' bacteria are a major cause of community-acquired pneumonia in our area remains valid. This has major implications for therapy.

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