Atypical pneumonia in adults in southern Africa

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The true incidence of *Legionella pneumophilia, Mycoplasma pneumoniae, Chlamydophila pneumoniae* and *Coxiella burnetti*, the so-called atypical pathogens that cause adult community-acquired pneumonia in southern Africa, is unknown. Although there are a lack of community-based studies, hospital-based studies suggest that the incidence may be as high as 30% in patients admitted to, but not requiring, an intensive care unit. A lack of specific clinical features that differentiate atypical pathogens, plus the lack of reliable, simple diagnostics, compound the uncertainty regarding the contribution of atypical pathogens to the sum total of community-acquired pneumonia in southern Africa. Without reliable diagnostic tests, macrolide or azalide antibiotics are widely used for in-patients with pneumonia, potentially fuelling the rise of antibiotic resistance to macrolides in other bacteria.

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Introduction

Since its original description in the 1930s, use of the term "atypical pneumonia" has been refined from "any community-acquired pneumonia (CAP) that is different to that caused by *Streptococcus pneumoniae*", to indicate "a CAP caused by one of several identified pathogens including *Legionella pneumophilia, Mycoplasma pneumoniae, Chlamydophila pneumoniae,* and *Coxiella burnetti*". More recently, some authors have included new pathogens, such as avian influenza and the severe acute respiratory syndrome (SARS) virus. This, and the awareness of a greater overlap in the clinical presentation between "typical" and "atypical" pathogens, has raised questions around the validity and utility of the term "atypical pneumonia". Murdoch and Chambers have advocated that atypical pneumonia be restricted to "pneumonia that is unusual in clinical presentation, epidemiology, or both", a definition that would help in identifying new trends in incidence, outbreaks, and recognition of novel respiratory pathogens.[1] This review will focus on traditional atypical pathogens, as well as highlight other important organisms in the southern African context.

Epidemiology

Atypical pneumonia caused by *L. pneumophilia, M. pneumoniae, C. pneumoniae* or *C. burnetti*, accounts for 8-63% of all cases of CAP worldwide, depending on the geographical location of the study, whether it is community or hospital based, and the type of cohort, i.e. general ward vs. intensive care unit (ICU) admission.[2]

Few studies have reported on the incidence of atypical pathogens causing CAP in southern Africa, and those that have, have mostly originated from South Africa. None of these studies were carried out in community cohorts. Limited financial resources, lack of sampling, and the predominant reliance on serology for diagnosis, has hampered epidemiological studies.

In-patient studies from South Africa suggest that the prevalence of atypical pathogens causing CAP ranges from 1-36%.[3-6] *M. pneumoniae* caused 10% of CAP in 81 in-patients admitted to Tygerberg Hospital.[3] Another prospective serological study of 92 consecutive patients admitted to Groote Schuur Hospital, Cape Town, with CAP, found 36% to be infected with an atypical pathogen, 20.7% with *C. pneumoniae*, 8.7% with *L. pneumophilia,* and 1.1% with *M. pneumoniae*.[4] Elsewhere in South Africa, a study from KwaZulu-Natal found 21% of isolates in patients with CAP to be due to atypical pathogens. *M. pneumoniae*, *C. pneumonia,* and *L. Pneumophilia,* accounted for 13%, 8% and 1% respectively.[5] Lastly, in an 11-year retrospective review of 259 patients admitted to the Hillbrow Hospital ICU in Johannesburg with severe CAP, of the 26 patients who had *Legionella* and *Mycoplasma* serology, sent on suspicion of an atypical pneumonia, two patients were diagnosed with *M. pneumoniae* and one with *L. pneumophilia*.[6] Taken together, these studies suggest that, although the rate of atypical pneumonia in hospitalised adults in South Africa may be as high as one-third of all CAP, their contribution to severe disease requiring ICU admission, may be minimal.

Further ICU studies in different locations are required to confirm this suspicion. Furthermore, the incidence of *M. pneumoniae* requiring ICU is likely to vary in a cyclical manner, in line with its epidemic cycles.

Legionellosis is not only a community-acquired infection. There have been over 300 reports of outbreaks of hospital-acquired legionellosis worldwide, the largest having occurred in a veterans administration hospital in Los Angeles, with 218 confirmed cases between 1977-1982.[7] In South Africa, a number of small outbreaks have been recorded, including an outbreak at a Johannesburg teaching hospital, in which two of 12 cases were hospital acquired.[8] The vast majority of hospital-acquired Legionnaires' disease outbreaks are not due to water cooling towers or air conditioning units, as previously thought, but rather to potable water supplies within the hospital.[9,10] Obtaining routine environmental cultures of hospital water supplies is an effective strategy for the prevention of hospital-acquired legionellosis, yet this practice is seldom carried out. Rather, the approach of the Centers for Disease Control and Prevention (CDC) of using environmental cultures, only in the event of discovery of cases of hospital-acquired infections, is adopted.[11] Not surprisingly, studies show that if the water supply is known to be colonised with *Legionella*, hospital-acquired legionellosis can be found, if proper surveillance and laboratory testing of all patients with hospital-acquired pneumonia is undertaken. With the financial implications that this would have in the state sector in southern Africa, such screening is not, and will not, be undertaken. However, it has important implications for the choice of empiric antibiotic therapy for hospital-acquired infections.

Although not traditionally regarded as an atypical pathogen, nor a predominant pathogen, in adults, the clinical presentation and increasing incidence of *Bordatella pertussis* needs to be recognised in adults presenting with CAP. Classically an infection of children, respiratory symptoms in adults more often lack the characteristic whoop seen in young children, and presents as a prolonged cough that commonly continues for more than two weeks. Unlike tuberculosis, which would be the predominant differential diagnosis of a chronic cough in southern Africa, pertussis rarely presents with the classic constitutional symptoms associated with *Mycobacterium tuberculosis* infection. Approximately 17% of cases of pertussis reported in South Africa between 1998-2002 were seen in adults.[12] Interestingly, a rising incidence in age distribution has been seen in some countries outside of southern Africa, with 12-32% of cases of a cough lasting longer than two weeks in Australia, being due to pertussis.[13] Due to a lack of awareness and missed opportunities for diagnosis in resource-limited settings such as southern Africa, the true incidence of pertussis in adults presenting with a prolonged cough is unknown. However, with the heavy burden of tuberculosis, and the increasing use of empirical therapy in smear negative pulmonary tuberculosis, it is likely that a substantial number of cases is being missed. Treatment with a macrolide reduces the duration and severity of symptoms, and transmissibility.[14]

Despite the introduction of antiretroviral therapy, human immunodeficiency virus (HIV) remains a risk factor for CAP, with increased nasopharyngeal colonisation by *S. pneumonia,*[15] and an association with cigarette smoking.[16] There is an inverse correlation between risk of CAP and cluster of differentiation 4 T (CD4) cell count, although introduction of antiretroviral treatment (ART) does reduce the incidence of CAP, even at CD4 counts of up to 500 cells/mm.[3,17,18] An aetiological diagnosis is made in approximately one-third of HIV-infected patients with CAP,[17] and it would seem from the limited studies elsewhere in the world to date, that the incidence of atypical pathogens is low. Two studies from Spain found that *Legionella* infections were particularly uncommon,[19,20] and it is hypothesised that this may be due to the intrinsic activity of cotrimoxazole against *L. pneumophilia*. Cotrimoxazole is used as primary prophylaxis in HIV patients.[21] A further study from Spain found no difference in clinical features between HIV-infected and uninfected patients with legionellosis.[22]

Clinical presentation of atypical pneumonias

The incubation period for atypical pathogens varies from two to 21 days. None of the clinical features common to atypical pneumonias, including fever, a cough (dry or productive) and myalgia, are unique to atypical pathogens. However, the presence of extra-pulmonary features is common, including cardiac, neurological, dermatological, musculoskeletal, renal and haematological features. *C. burnetti* and *L. pneumophilia* infection are more commonly associated with headache, confusion (rare with *M. pneumoniae*), and pleuritic chest pain. In addition, abdominal pain and diarrhoea are more commonly reported in *L. pneumophilia* infections.[23]

Respiratory signs, e.g. crepitations, may be minimal or absent. Relative bradycardia has been associated with *L. pneumophilia* and *C. burnetti*, although this sign is more commonly absent. Splenomegaly may be a feature of Q fever due to *C. burnetti*. Radiographic findings are often non-specific, and could include patchy infiltrates, consolidation, circumscribed lesions, or round infiltrates and pleural effusions, the latter having been described in association with *C. burnetti*, *M. pneumoniae* and *L. pneumophilia*. Hilar adenopathy and cavitation have been

Table I: Characteristics of atypical pneumonias

	Mycoplasma pneumoniae	*Legionella pneumophilia*	*Chlamydophilia pneumoniae*	*Coxiella burnetti*
Microbiological characteristics	Fastidious, difficult to grow in the laboratory	Gram-negative bacillus found in fresh water	Gram-negative obligate intracellular bacterium	Gram-negative intracellular bacterium
Risk groups	Children or young adults (5-25 years old). Cyclical epidemics occur every three to five years.	Elderly with co-morbidities and immune-compromised individuals. Sporadic infection or outbreaks are associated with water aerosols.	Asthmatics and patients with cardiovascular disease[25]	Exposure to contaminated body fluids of infected cattle, goats and sheep (farmers, abattoir workers, vets). Endocarditis risk in patients with pre-existing valve lesions.[13]
Diagnostic tests	Acute and convalescent serology. Cold agglutinins (poor sensitivity and specificity). Real-time PCR. Direct isolation on specialised media rarely used.	Acute and convalescent serology (IFA or ELISA). Urinary antigen (subgroup 1) in first 7-10 days of symptoms. Direct isolation on specialised media rarely used.	Fourfold increase in IgG three weeks apart, or a single IgM titre ≥ 1:64.[26] Cell culture and PCR not routinely available.	Acute and convalescent serology. Isolation of the organism requires biosafety 3 facility PCR from sputum.
Antibiotics used in management	Macrolides, azalides, doxycycline or fluoroquinolones are active			

PCR: polymerase chain reaction, IFA: immunofluorescent assay, ELISA: enzyme-linked immunosorbant assay, IgG: immunoglobulin G, IgM: immunoglobulin M

identified in immunocompromised patients,[24] which in the southern African context evokes the differential diagnosis of tuberculosis in HIV-infected patients.

Table I describes individual characteristics of the atypical pneumonias.

Diagnosis

Historically, the diagnosis of atypical pathogens, as a cause of CAP, has relied on demonstrating a serological response in acute and convalescent blood samples, as the fastidious nature of the organisms makes culture difficult. Outside of trial conditions, the loss to follow-up rate is such that convalescent serology is rarely sent, and, in the context of southern Africa, it remains an expensive and impractical test. Approximately 85% of cases of Legionnaires' disease are due to *L. pneumophilia* subtype 1, which is the target for the *Legionella* urinary antigen test. Although relatively simple to use, in practical terms, this test is rarely used in southern Africa due to resource limitations, and the fact that the test's sensitivity reduces with the time from symptom onset, with late presentation being common in our setting. Molecular tools are a promising advance for the diagnosis of bacterial (including atypical pathogens), and viral, causes of pneumonia. A full description of molecular diagnostics is outside the scope of this review, but real-time polymerase chain reaction (PCR) on sputum is perhaps the most promising advance to date.[27]

Treatment

International and society-generated guidelines for the treatment of CAP differ subtly in their emphasis on the place of antibiotics that cover atypical pathogens with regard to the regimen and the timing of their introduction.

Macrolides, or the azalide azithromycin, are the major class of antibiotics used to treat proven or suspected atypical infections, although the ketolide telithromycin, doxycycline, and a number of fluoroquinolones, are also known to be active. The use of fluoroquinolones in areas with a high prevalence of tuberculosis in southern Africa should be discouraged, due to their anti-mycobacterial action. If tuberculosis was present, either as the primary diagnosis, or as a co-infection, monotherapy with a fluoroquinolone, may lead to rapid resistance of the mycobacterium.

Whether anti-atypical cover is given orally or parenterally, as monotherapy or in combination with a β-lactam or other antibiotic, will depend on the known resistance patterns for common causes of CAP in a particular region or institution, and the severity of infection. The standard severity of illness score used to assess patients with CAP is the Confusion, Urea, Respiratory rate, Blood pressure (CURB)-65 score (Table II), which is easy to use, and correlates with more complex scoring systems.

Table II: CURB-65 score for severity of illness

Variable	CURB-65 score and interpretation
Confusion (C)	0-1: Mild community-acquired pneumonia, potentially suitable for home care. 2: Moderately ill, observe in hospital initially. > 3: Severe community-acquired pneumonia. Consider admission to high care unit, or intensive care unit.
Urea ≥ 7 mmol/l (U)	
Respiratory rate ≥ 30 bpm (R)	
Low blood pressure: systolic < 90 mmHg and diastolic ≤ 60 mmHg (B)	
Age ≥ 65 years (65)	

As it may not be possible to measure urea, an abbreviated CRB-65, based solely on clinical criteria, may also be used. A score of 0 indicates a very low mortality risk, and does not require hospitalisation. Hospitalisation should be

considered for a score of 1-2, and any person with a CRB-65 score of 3 or 4 requires urgent hospitalisation.

The current South African guidelines for the management of CAP in adults were published by a working group of the South African Thoracic Society in 2007.[28]

Although it is suggested in the document that the incidence of atypical pathogens as a cause of CAP in South Africa is low, the guidelines recommend the use of antibiotics that cover atypical pathogens in the following situations:

- As monotherapy for a proven atypical pathogen, or as combination therapy for any patient with a suspected atypical pathogen. Due to the increasing resistance profile of *S. pneumoniae* to macrolides or azalides in South Africa, monotherapy with a macrolide or azalide is not recommended in cases where the cause of the CAP is not proven to be due to an atypical pathogen.
- As there is emerging evidence of the benefit of combination therapy for severely-ill patients who are admitted to hospital with CAP, a macrolide is indicated in combination with a β-lactam. Hence all patients with CURB-65 of ≥ 3 should receive an intravenous macrolide or azalide, or fluoroquinolone with a β-lactam.

The South African guidelines share some similarities with international guidelines, such as the joint Infectious Diseases Sociey of America (IDSA)/American Thoracic Society (ATS) guidelines from North America[29] and the European guidelines.[30] In keeping with the American guidelines, the South African guidelines also advocate β-lactam and macrolide combinations for patients admitted to hospital who do not require ICU management, or in combination with a β-lactam and aminoglycoside in ICU patients. In out-patient treatment settings, macrolide monotherapy is also advocated, but unlike the South African guidelines, this includes treatment for patients in whom an atypical pathogen is not confirmed. However, if the patient has co-morbidities, it is necessary to revert to the combination of a β-lactam and macrolide. The European guidelines, published in 2005, echo much of what is recommended in the joint American guidelines, although outpatient treatment of CAP with amoxicillin, or a tetracycline, is preferred over a macrolide.[30]

Furthermore, a greater emphasis is put on differentiating between patients with acute exacerbations of chronic obstructive pulmonary disease, and those with CAP.

Caution should be adopted when choosing macrolide or azalide cover for HIV-infected patients on ART. Azithromycin is preferred over clarithromycin for patients on a non-nucleoside reverse transcriptase inhibitor, such as nevirapine or efavirenz, due to significant drug-drug interactions.[31]

One omission from the South African guidelines is a discussion of the use of neuraminidase inhibitors for suspected influenza infection, either as a primary cause of pneumonia, or as a co-infecting pathogen. Both the American and European guidelines advocate early oseltamivir or zanamivir for patients suspected of having influenza. As this infection is seasonal outside of a pandemic situation, we would advocate the immediate use of oseltamivir in any patient admitted to hospital with serious CAP during the influenza season, and would have a very high index of suspicion for influenza as a diagnosis, or co-infecting organism, in any person with severe acute respiratory illness in the months before the usual median onset of the influenza season, which for South Africa is week 23, i.e. the second week in June. This is in line with the guidelines of the National Institute for Communicable Diseases (NICD) on influenza.[32]

Conclusion

A lack of studies defining the burden of atypical pathogens causing pneumonia in the community setting undermines our ability to determine optimal antibiotic guidelines for CAP. The perception that atypical pathogens are a rare cause of CAP, is not necessarily borne out by in-patient studies, which suggest that up to 30% of cases are due to these organisms in patients not requiring ICU. A large community-based national study of the incidence of atypical pneumonia would help considerably towards rationalising our approach to these atypical pathogens, and further ICU-based studies would also be of benefit.

Lack of reliable, point-of-care tests hampers diagnosis, and requires the use of combination antibiotics that include a macrolide or fluoroquinolone. Unfortunately, this can only drive macrolide resistance, and in private practice, where a greater amount of fluoroquinolones are prescribed as empiric therapy for CAP, drive fluoroquinolone resistance in *M. tuberculosis*, threatening the tuberculosis programme. Such prescribing should be discouraged vigorously.

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