CPD Article

The atypical pneumonias: The South African context

Black AD, BSc (WITS), MBBCh (WITS), FCP (SA), Cert Pulmonology (SA)
Division of Pulmonology, Department of Medicine,
University of the Witwatersrand, and Chris Hani Baragwanath Hospital.

Correspondence to: Department of Medicine, Chris Hani Baragwanath Hospital, PO Bertsham, 2013, email: andrew.viv@polka.co.za

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Abstract

Community-acquired pneumonia (CAP) is a common clinical presentation in general practice. The prevalence and burden of disease caused by the atypical bacteria (*Mycoplasma pneumoniae, Chlamydophila pneumoniae* and *Legionella pneumophila)* are not well defined in South Africa. Each of the atypical bacteria is discussed individually with regard to clinical presentation, diagnosis and treatment. A unified approach to CAP and its management is discussed.

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Introduction

Lower respiratory tract infections are a common problem in general practice. Since its isolation more than 120 years ago, *Streptococcus pneumoniae* has remained the most common organism responsible for community-acquired pneumonia (CAP).[1] Historically, *S. pneumoniae* pneumonia was considered to have a "typical" clinical presentation, with the patient experiencing chills, rigors, cough productive of sputum containing Gram-positive cocci, and segmental or lobar consolidation on chest X-ray. Prior to antibiotics, infection resulted in death or resolution by crisis (hectic fevers and delirium) or lysis (gradual decrease in fever).[2]

In the late 1930s, cases of pneumonia, which were different to 'typical' pneumococcal pneumonia, appeared in the medical literature. These pneumonias often occurred as outbreaks, were associated with an insidious onset and a prodrome of a low-grade fever, photophobia and headache, with a worsening cough. Sputum Gram's stain failed to demonstrate pneumococci, and the chest X-ray showed a broncho-pneumonia rather than a lobar or segmental consolidation. These pneumonias were designated as

Case Study

A 26 year-old male presents with a generalised rash. He gives a history of having 'flu' for the past week with a fever and headache; he has also developed a dry cough, which has worsened over the past few days. Other than paracetamol he has taken no other medication. He is allergic to penicillin. His six-year-old daughter had the 'flu' a month ago and is now well. Examination reveals a healthy-looking male with a generalised rash involving the palms of the hands and the soles of the feet (**Figure A and B**). There is no mucosal involvement. He has a temperature of 37.9°C, no lymphadenopathy and minimal crackles over the left lower zone of his chest. His chest X-ray is shown in **Figure C.** He has a normal full blood count.

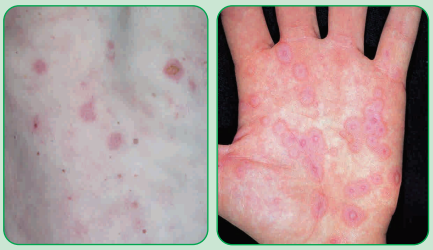


Figure A and B
(1B with permission www.dermnet.com)

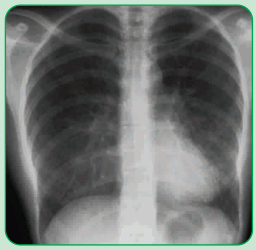


Figure C: Chest X ray showing patchy bi-basal infiltrates

Questions:

1. What is the probable diagnosis in this patient?
2. What simple bedside test may help confirm the diagnosis?
3. What is the appropriate therapy in this patient?
4. What specific diagnostic tests are available for the diagnosis of this disease?

Answers:

1. Mycoplasma pneumonia with erythema multiforme.
2. Bedside cold agglutinin test.
3. A respiratory fluoroquinolone (moxifloxacin or gatifloxacin). Clinical differentiation between the causes of CAP is unreliable and, even in classic cases, *S. pneumoniae* should be covered. Monotherapy with a tetracycline or macrolide is not recommended due to increasing *S. pneumoniae* resistance. Addition of a ß-lactam to these agents is not possible in this patient, as he is allergic to the ß-lactams. The duration of therapy should be 14 days. No specific treatment is required for erythema multiforme, and the lesions usually heal without scarring within two weeks.
4. Serology for *M. pneumoniae* is available, but as antibodies only develop late in the disease, they are of little diagnostic benefit in the acute illness.

atypical pneumonias.[2]

The atypical pneumonia syndrome was initially considered to be sufficiently distinct from typical *S. pneumoniae* pneumonia to allow for accurate clinical diagnosis. With the development of the sulphur- and penicillin-based antimicrobials, the atypical pneumonias were further characterised as a lower respiratory tract infection that did not respond to antimicrobials (penicillin- and sulphur-based antimicrobials) and no organism could be identified on sputum Gram's stain or culture. The prefix primary was used to indicate that no causative agent could be determined.[2] It has since been established that clinical findings are insufficient to distinguish between typical and atypical pneumonias.[3,4] Improved diagnostic techniques have allowed for the identification of the previously unknown pathogens. The term primary atypical pneumonia is thus of little medical relevance today.

The original use of the term atypical pneumonia now covers a wide range of ever-growing agents, including SARS and avian influenza. In this article, the more limited use of the term atypical pneumonia will be used, namely that which recognises the atypical bacteria (no true cell wall), *Chlamydia pneumoniae, Legionella pneumophila* and *Mycoplasma pneumoniae*, as the cause of atypical pneumonias in immunocompetent adults.

Internationally, the prevalence of the atypical pathogens in CAP ranges from 8% to 63%.[5] This broad range is due to multiple factors that differ in the various studies, including severity of pneumonia in the series, outpatient with pneumonia vs. inpatient with pneumonia vs. ICU patients with pneumonia, geographic differences, method of identification and temporal variation in the frequency of these organisms as a cause for CAP. Large differences in the prevalence of Chlamydia pneumonia may in part be attributed to the fact that Chlamydia pneumonia tends to occur in mini-epidemics

A series from Cape Town, South Africa identified an atypical pathogen as a cause of CAP in 36% of adult patients admitted to hospital.[4] *C. pneumoniae* was identified in 21% of cases and *L. pneumophila* in 9%, while *M. pneumoniae* was only found in 1% of the cases.[4] In another series from Cape Town that looked at patients admitted to ICU for pneumonia, the aetiology was found to be 5% for legionella and 1% for mycoplasma, in cases of primary pneumonia where a diagnosis was established.[6] Chlamydia was not tested for in the ICU series.

These studies confirm that the atypical pathogens do play a role in CAP in South Africa; however, several factors make it impossible to infer their actual prevalence and importance in CAP in South Africa.

Mycoplasma pneumoniae

Clinically

M. pneumoniae causes illness ranging from mild upper respiratory tract infection to severe pneumonia. Disease is usually of low severity and mortality and is invariably self-limiting. It is often the cause of mini-outbreaks, especially in family units and closed communities, where it tends to cause pneumonia in the age range of five to 25. Cyclic epidemics occur every three to four years. *M. pneumoniae* is often referred to as 'walking pneumonia', as the patients are usually not very ill. There is a prodrome of low-grade fever, headache and progressive dry cough, which may become debilitating. As the pneumonia progresses, patients may produce small quantities of white or blood-flecked sputum. Rigors, myalgias and gastrointestinal complaints are not features of mycoplasma infection.

Auscultation of the chest is usually unremarkable, with no or minimal crackles. Systemic examination may reveal a number of extra pulmonary manifestations, the most frequent being bullous myringitis (Figure1) and a wide range of rashes, including erythema multiforme (Figure 2 A and B), erythema nodosum (Figure 3 C and D), Raynaud's phenomena and polyarthralgias. Major organ involvement, especially of the cardiac and central nervous systems, is well described, but tends to occur in sicker, hospitalised patients and carries a worse prognosis.[7]

Figure 1: Bullous myringitis: large fluid filled bullous arising from the posterior wall of the left tympanic membrane (Source: www.EAC.Hawkelibrary)

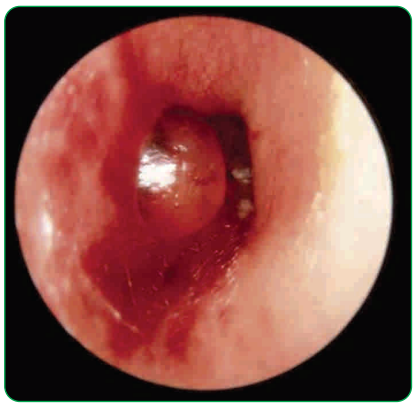
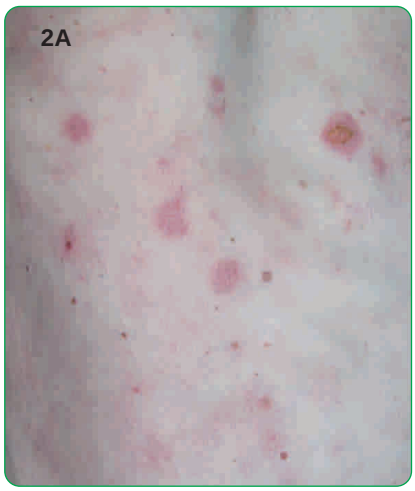


Figure 2 A & B: Erythema multiforme



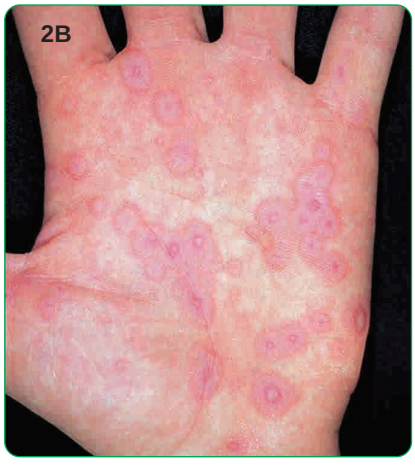
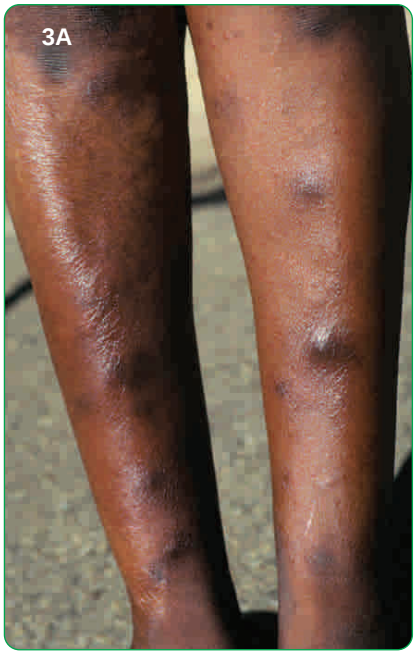
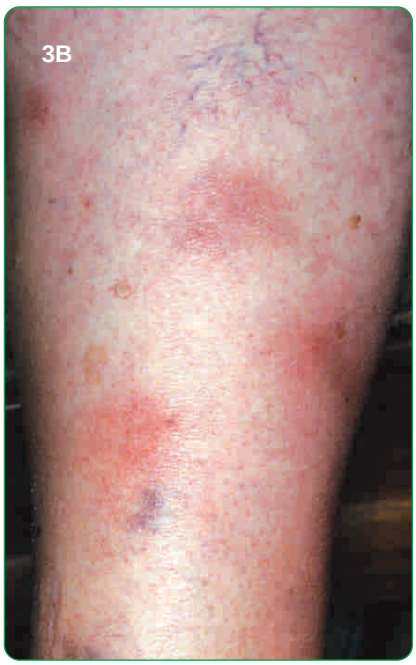


Figure 3 A & B: Erythema nodosum



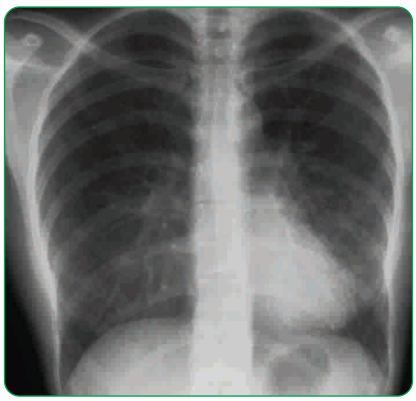


M. pneumoniae causes mucociliary dysfunction, which may predispose these patients to infection with a 'typical' pathogen. Co-pathogens, often *S. pneumoniae*, are well described and their presence may alter the clinical picture.[8]

Chest X-ray

A large disparity usually exists between clinical and X-ray findings. The X-ray changes range from patchy shadowing to lobar consolidation (Figure 4).

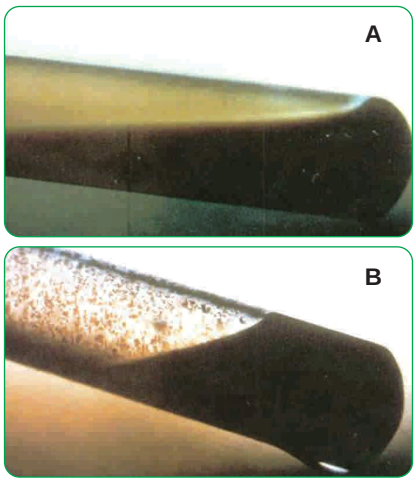
Figure 4: Patchy infiltration



Diagnostic tests

1) **Cold agglutinins** – although not very sensitive or specific, their presence is strongly suggestive of mycoplasma infection. A cheap, rapid bedside test can detect the presence of cold agglutinins. One millilitre of the patient's blood is put in a PI/PTT tube; at room temperature, the red cells coat the entire tube surface. When cooled to 4°C for 3-5 minutes, macroscopic agglutination is visible in the presence of cold agglutinins (Figure 5).[9]
2) **Serology** for *M. pneumoniae* IgM and IgG is sensitive and specific, but is negative in early disease and cannot be used for early diagnosis.
3) **Culture and PCR** techniques are not routinely available.

Figure 5: Bedside cold agglutinin test for confirmation of mycoplasmal pneumonia. **A,** Patient's blood before exposure to the cold. **B,** Patient's blood after 3-minute exposure to 4° C. On rewarming the sample to 37° C, the appearance reverts to that shown in **A**.
With permission. Elsevier[9]



Treatment

The macrolides, ketolides, tetracyclines and fluoroquinolones all show activity against *M. pneumoniae*, but do not eradicate the organisms completely. Treatment does shorten the course and lessens the severity of the illness and should continue for two weeks.[7]

Chlamydophila pneumoniae

Clinical

C. pneumoniae infection is wides-pread, with sero-epidemiological studies showing up to 50% of young adults having been infected. Most infections are probably subclinical, or mild and self-limiting. As with *M. pneumoniae*, *C. pneumoniae* is a frequent co-pathogen in CAP, making its relative importance difficult to interpret. Clinically, the disease may be biphasic, starting with upper respiratory tract symptoms that settle for 24-72 hours, only to be followed by a dry cough and mild pneumonia or prolonged bronchitis.

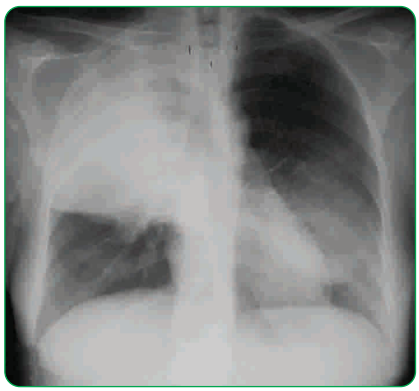
Chest X-ray

The chest X-ray frequently shows a patchy segmental infiltrate, but all patterns have been described.

Diagnosis

Serological diagnosis requires testing of acute and convalescent serum (at least three weeks apart) demonstrating a fourfold or more increase in IgG antibodies. A titre of anti-*C. pneumoniae* IgM antibodies ≥ 1:16 is suggestive of acute infection.

Figure 6: Chest X ray of patient with legionella pneumonia showing multilobar involvement



A delay in antibody formation means that only a retrospective diagnosis is possible.

Other means of diagnosis, such as cell culture and PCR, are not routinely available.

Treatment

The macrolides, tetracyclines, third- and fourth-generation fluoroquinolones all show good activity against *C. pneumoniae.* Treatment should continue for 14 days.[10] As for mycoplasma, a co-pathogen is frequently present.[8]

The organism has the ability to cause persistent infection and, consequently, has sparked research into its role in asthma, COPD and atherosclerosis.[10]

Legionella pneumophila

Legionella is capable of causing severe, often fatal pneumonia. It occurs in three different forms: **explosive epidemics** and **endemic infection**, which are often associated with specific environmental reservoirs, and **sporadic cases**, particularly during the summer. The organism is ubiquitous in water and epidemics can often be traced to water systems in buildings, especially hotels and hospitals.

Clinical

Two distinct forms of disease occur:

1) **Pontiac fever**: an acute, flu-like illness without pneumonia, which is self-limiting and occurs after an incubation period of four hours to three days.
2) **Legionnaire's disease**: Legionella pneumonia. More common in men aged 40 to 70. Smokers, alcoholics and diabetics are at increased risk of disease. A history of recent travel, pneumonia in a co-worker, use of a spa or home plumbing should all be sought. After an incubation period of two to10 days, the disease manifests as a sudden onset of high fever, myalgia and rigors, with a severe headache. Confusion is frequent and focal neurological signs may be present. Diarrhoea and abdominal pain may occur. Cough is not a major feature and the initial impression of the patient may not suggest pneumonia. The white cell count is usually under 15.0 10^9/l. Hyponatraemia and deranged hepatic enzymes are frequent but non-specific findings.

Chest X-ray

Usually a homogeneous unilobar consolidation is present. Deterioration and increasing opacification in both lungs often occurs despite treatment (Figure 6).

Legionella urinary antigen – provides a rapid result with good sensitivity and specificity for disease caused by *L. pneumophila* serogroup 1. It is negative in pneumonia caused by other *L. pneumophila* serogroups and other legionella species, which may account for ≥ 20% of cases of legionella pneumonia.[11]

Serology for antibody detection is insensitive and non-specific, unless paired acute and convalescent sera are tested.

Treatment

Given its potential to cause severe disease, early treatment with appropriate antimicrobials is essential in patients with suspected legionella. As with the other atypical bacteria, ß-lactam antimicrobials have no activity against legionella. The macrolides, tetracyclines and fluoroquinolones all have activity against legionella. The fluoroquinolones are the preferred agent in severe legionella pneumonia.[12] Given the frequency of confusion and gastrointestinal symptoms, initial therapy may need to be intravenous. Duration of therapy should be two weeks. Therapy needs to be prolonged if complications such as lung abscess or empyema develop.

Conclusion

When assessed as a group, the atypical pathogens produce a distinct clinical syndrome. On an individual level, however, it is not possible to distinguish between the various aetiological agents that cause CAP on clinical grounds alone. Even with serological diagnosis, the common occurrence of co-infection with other respiratory pathogens, in particular *S. pneumoniae*, makes it difficult to determine the clinical significance of positive serology in all cases.

With the exception of legionella, the atypical pneumonias tend to lead a mild, self-limiting course, even without the use of appropriate antimicrobials. In the series from Cape Town, all the patients who were found to have atypical pneumonia and who were treated with ß lactams responded, despite "inappropriate" therapy.[4]

Clinically, CAP should be viewed as a single syndrome, rather than being divided into typical and atypical. In patients under 60 years of age, who have no co-morbid disease and who are to be treated as outpatients, high-dose amoxicillin remains the first-choice antimicrobial. Patients with co-morbid disease and the elderly should be given amoxicillin-clavulanate or a second-generation cephalosporin if they are treated as outpatients.

An alternative in penicillin-allergic patients is one of the newer respiratory fluoroquinolones (moxifloxacin or gatifloxacin). Although this is an attractive class of drug covering both atypical and typical pathogens, it should not be used as routine first-line therapy in CAP to prevent the development of resistance.

In cases where an atypical pathogen is suspected or where initial therapy with a ß-lactam has failed, the addition of a macrolide or tetracycline is appropriate. The macrolides and tetracyclines are not recommended as monotherapy for CAP due to emerging *S. pneumoniae* resistance to these antimicrobials. Treatment for suspected atypicals should continue for two weeks.

All patients with severe CAP should have a macrolide as part of empiric therapy to cover for atypical

Table I: Treatment of patients presenting with suspected typical and atypical pneumonia*

Clinical	Treatment of Choice	Comment
Mild CAP Pt < 60 years No co-morbid disease Features of atypical pneumonia or no response to ß-lactam	Amoxicillin 1g 6 hrly plus **Macrolide** Erythromycin 500 mg 6 hrly Clarithromycin 500 mg 12 hrly Azithromycin 500 mg dly or **Tetracycline** Doxycycline 100 mg BD	Fluoroquinolones should be reserved for patients with true ß-lactam allergy Gatifloxacin 400 mg daily Moxifloxacin 400 mg daily
Moderate CAP Pt < 60 years No co-morbid disease Features of atypical pneumonia or no response to ß-lactam	Amoxicillin-clavulanic acid 1 g 12 hrly or Cefuroxime axetil 750 mg 12 hrly plus **Macrolide** Erythromycin 500 mg 6 hrly Clarithromycin 500 mg 12 hrly Azithromycin 500 mg dly or **Tetracycline** Doxycycline 100 mg BD	Fluoroquinolones should be reserved for patients with true ß-lactam allergy Gatifloxacin 400 mg daily Moxifloxacin 400 mg daily
Mild CAP Pt > 60 years and/or co-morbid disease with features of atypical pneumonia or no response to ß-lactam	Amoxicillin-clavulanic acid 1 g 12 hrly or Cefuroxime axetil 750 mg 12 hrly plus **Macrolide** Erythromycin 500 mg 6 hrly Clarithromycin 500 mg 12 hrly Azithromycin 500 mg dly or **Tetracycline** Doxycycline 100 mg BD	Consider hospitalisation Fluoroquinolones should be reserved for patients with true ß-lactam allergy Gatifloxacin 400 mg daily Moxifloxacin 400 mg daily
Severe CAP (confusion, hypotension resp rate >30/min)	Amoxicillin-clavulanic acid 1.2 g iv 8 hrly or Cefuroxime 1.5 g iv 8 hrly or 3rd generation cephalosporin iv plus **Macrolide** plus **Aminoglycoside** Gentamicin 2-4 mg/kg iv daily	Hospitalisation with referral and consider admission to high care or ICU An alternative regimen includes a new fluoroquinolone plus another agent

pathogens, particularly legionella.

With appropriate therapy, clinical improvement should occur within 24 to 72 hours. Failure of response to therapy requires further evaluation of the patient. In South Africa, tuberculosis must be excluded in patients failing to respond.

The routine serological testing for atypical pathogens is not recommended, as it is of limited clinical value. Testing for legionella urinary antigen would be appropriate in the correct clinical situation, but it should be borne in mind that is has shortfalls in the diagnosis of legionella.

The atypical pathogens are responsible for an unknown burden of disease in South Africa. With the exception of legionella, the atypical pneumonias are often mild and have a self-limiting course. As it is not possible to distinguish between the causes of CAP on clinical findings, CAP should rather be regarded as a single entity when these patients are treated (Table I).

Acknowledgements

X-rays courtesy of Prof. E Joseph, Department of Radiology, University of the Witwatersrand.

This article has been peer reviewed

See CPD Questionnaire, page 30

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