Original Article

# Atypical pathogens causing community-acquired pneumonia in adults

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## Abstract

**Objective:** To determine the frequency of community-acquired respiratory pathogens with special focus on atypical organisms in patients presenting to a tertiary care facility with community-acquired pneumonia (CAP).

**Methods:** The descriptive study on adult patients was conducted from February 2007 to March 2008 at the Aga Khan University Hospital, Karachi. It comprised 124 consenting patients of age 16 and above who presentd with a diagnosis of community-acquired pneumonia. The diagnostic modalities used were based on significant changes in antibody titer or persisting high antibody titers in the case of Mycoplasma pneumoniae and Chalmydia pneumoniae infections, or bacterial antigen in urine, in the case of Legionella pneumophila serogroup 1 infection. Pyogenic bacteria were identified on the results of respiratory secretions or blood cultures. Continuous data and categorical variables were worked out using SPSS version 15.

**Results:** Among the 124 patients enrolled, an etiologic agent was identified in 44 (35.4%) patients. The most common organism was Mycoplasma pneumoniae (n=21, 17%), followed by Chlamydia pneumoniae (n=15, 12%), Streptococcus pneumoniae (n=9, 7%), Haemophilus influenzae (n=2, 1.6%), Klebsiella pneumoniae (n=2, 1.6%) and Staphylococcus aureus (n=1, 0.8%). Streptococcus pneumoniae was the most common organism isolated from blood cultures. No cases of Legionella pneumophila serogroup 1 were identified.

**Conclusions:** Mycoplasma pneumoniae and Chalmydia pneumoniae are significant etiologic agents for community-acquired pneumonia occurring in Karachi. Local treatment guidelines for community-acquired pneumonia should include therapy directed specifically at these agents.

## Introduction

Community-acquired pneumonia (CAP) is a common and potentially serious infection that is responsible for a significant number of outpatient visits and hospital admissions each year.[1,2] Despite effective anti-microbial therapy, it is responsible for considerable mortality; ranging from 6.7 to 18 percent in the United Kingdom, and from 6 to 24 percent in the United States.[3]

A considerable seasonal and geographical difference in the type and frequency of organisms that cause CAP has been reported.[2] In most studies, S. pneumoniae has been the most common etiologic agent identified. However, increasingly, atypical organisms such as L. pneumophila, C. pneumoniae and M. pneumoniae are being reported as causes for CAP more frequently than was previously thought.[4] A large-scale study conducted in the United States identified atypical pathogens in 60% of cases.[5]

Available therapeutic guidelines for the empirical treatment of CAP rely on studies from the Western world. There is scarcity of information in the local literature about the prevalence of microbes causing CAP in this part of the world. The only study done in Pakistan on frequency of atypical pneumonia used a clinical approach for diagnosis in hospitalised children which is not reliable in terms of differentiating between etiologic causes of pneumonia.[6]

We conducted this study to determine the frequency of microbial causes of CAP and to provide background data to assist the development of antibiotic therapies for local use.

## Patients and Methods

The descriptive study was conducted prospectively from February 2007 to March 2008. All consenting adult patients (age 16 and above), presenting consecutively to the Aga Khan University Hospital, Karachi, with a CAP diagnosis were enrolled in the study. CAP was defined as the presence of at least two symptoms of lower respiratory tract infection, accompanied by acute infiltrate on chest radiograph or auscultatory findings of consolidation on chest examination.[7] Patients were excluded if they had been transferred from some other hospital, or those who developed symptoms while already hospitalised, or patients with a suspicion of post-obstructive pneumonia and immuno-compromised hosts.

Written informed consent was obtained from all

patients, and the study was approved by the Ethical Review Committee (ERC) of the Aga Khan University. A structured data sheet was used to collect clinical and laboratory data. Results of routine investigations such as complete blood count, serum electrolytes, blood urea nitrogen, creatinine and arterial blood gases were recorded. Patients were assessed for severity of disease using the British Thoracic Society (BTS) guidelines.[7] Blood cultures were collected in Bactec aerobic and anaerobic bottles (Beckton Dickinson, USA).[8] Sputum examination included Gram stain, culture and sensitivity and Ziehl- Neelsen stain if Mycobacterium tuberculosis was suspected. Serum samples were obtained within 24 hours of admission for serologic testing of M. pneumoniae and C. pneumoniae. Convalescent serum sample was obtained at the follow-up visit. The mean interval between two samples was 14 days. For the detection of urinary antigen of L. pneumophila serogroup 1, immuno-chromatographic assay (NOW-BINAX, Inverness medical professional diagnostics) was used. The infection due to C. pneumoniae was determined by enzyme linked immunosorbant assay (ELISA) using a commercial Nova Tec (Dietzenbach, Germany). Using this method, serum antibody titer of immunoglobulin M (IgM) was measured. A four-fold or greater increase in titer between paired samples or a cutoff value of 11 NTU (Novatec unit) or above was considered positive. For M. pneumoniae, EIA (enzyme immuno-assay) Serodia-MycoII, Fujirebio Inc. (Tokyo, Japan) was used. A titer of 1:80 or above in at least one serum sample or four-fold increase in antibodies between the paired serum sample was considered positive.

Results were worked out as mean ± SD for continuous data and as frequency (percentage) for categorical variables. All analyses were conducted by using the Statistical Package For Social Sciences (SPSS), version 15.0.

## Results

Among the study population of 124, the mean age was 56.5 ± 19.5 years (range 16-90 years), while 69 (55.6%) were male. Three (2.4%) were treated as outpatients, while 121 (97%) patients were admitted. Of the total, 93 (75%) were non-smokers, 27 (21.8%) were ex-smokers, while 3 (2.4%) were current smokers with a mean exposure of 22 ± 20 pack years. One patient had a history of alcohol abuse. Besides, 22 (18%) patients gave a history of travel; 9 (7%) had travelled internationally to the western hemisphere, while 6 (5%) had travelled to the rural areas in Sindh. None of the patients gave a history of exposure to domestic pets (rabbits, birds) or wildlife (squirrels, ducks). Also, 74 (59%) patients had underlying diseases in addition to pneumonia (Table-1).

With respect to presentation, 124 (92%) patients presented with fever, 107 (86%) cough, 55 (44%) chest pain and 23 (19%) with altered mental status. The mean duration of symptom prior to presentation was 8 ±6.3 days. Admission serum WBC counts ranged from 3 to 60,000 cells, with mean (Confusion-Urea-Respiratory Rate-BP) CURB-65 score of 1.5 (range 1-4); 73 (60%) patients had consolidation on chest X rays; with para-pneumonic effusions developing in 44 (36%) patients and cavitation in 7 (6%). Bilateral interstitial infiltrates were present in 49

**Table-1: Characteristics of the study population (n=124).**

| Characteristic | n | % |
|---|---|---|
| **Mean age, range (years)** | **56.5±19.5** | **16-90** |
| **Age group (years)** | | |
| 16 – 44 | 30 | 24 |
| 45 – 64 | 46 | 37 |
| 65 and above | 48 | 39 |
| **Gender** | | |
| Male | 69 | 56 |
| Female | 55 | 44 |
| **CURB-65** | | |
| 0 | 40 | 32 |
| 1 | 24 | 19 |
| 2 | 38 | 31 |
| 3 | 17 | 13.6 |
| 4 | 3 | 2 |
| 5 | 2 | 1.6 |
| **Smoking Status** | | |
| Current smokers | 4 | 2.4 |
| Ex-smokers (>6 months) | 27 | 21.8 |
| Never smokers | 93 | 75 |
| **Co morbid illnesses** | | |
| Asthma /Chronic Obstructive Pulmonary Disease (COPD) | 23 | 18 |
| Bronchiectasis | 1 | 0.8 |
| Pulmonary fibrosis | 1 | 0.8 |
| Hypertension | 39 | 31 |
| Congestive heart failure (CHF) | 2 | 1.6 |
| Ischaemic heart disease (IHD) | 25 | 20 |
| Diabetes mellitus (DM) | 23 | 18 |
| Chronic kidney disease (CKD) | 8 | 6 |
| Chronic liver disease (CLD) | 6 | 4 |
| Treated Tuberculosis (TB) | 5 | 4 |
| None | 30 | 24 |
| Antibiotics taken prior to hospital admission | 26 | 21 |

CURB-65: Confusion-Urea-Respiratory Rate-BP-Age <65.

**Table-2: Etiologic agents of community-acquired pneumonia identified by culture and serological testing.**

| | |
|---|---|
| Organism identified | 52 (42%) |
| **By Serology:** | |
| Mycoplasma pneumoniae | 21 (17%) |
| Chlamydia pneumonia | 15 (12%) |
| **By Culture:** | |
| Streptococcus pneumoniae | 9 (7%) |
| Haemophilus influenzae | 2 (2%) |
| Klebsiella pneumoniae | 2 (2%) |
| Mycobacterium tuberculosis | 2 (2%) |
| Staphylococcus aureus | 1 (0.8%) |
| No organism identified | 72 (58%) |

**Table-3: Age, CURB-65 score and etiologic agent of those patients who died.**

| Age in years | CURB-65 score | Organism | Cause of death |
|---|---|---|---|
| 85 | 5 | Mycoplasma pneumoniae | Respiratory failure |
| 81 | 5 | Pseudomonas aeruginosa | Septic shock |
| 75 | 4 | Chlamydia pneumoniae | Respiratory failure |
| 60 | 4 | None identified | Septic shock |
| 38 | 4 | None identified | Septic shock |

CURB-65: Confusion-Urea-Respiratory Rate-BP-Age <65.

(40%) patients. There was no correlation found between radiological presentation and etiological organism.

Of the patients 6 (21%) had received multiple antibiotics prior to hospitalisation and 6 (5%) were started empirically on anti-tuberculous therapy; 2 of these subsequently had microbiological confirmation of M. tuberculosis. Besides, 49 (7%) patients had been hospitalised for CAP in the preceding year.

Among the 124 patients, an etiologic agent was identified in 52 (41.93%). Atypical pathogens were identified in 36 (29%) cases of CAP (Table-2).

All microbial isolates demonstrated sensitivity to macrolides, with only 80% isolates sensitive to fluoroqinolones and 86% sensitive to beta-lactam agents.

Complications occurred in 18 (14%) patients; 6 (4.8%) developed respiratory failure; 6 (4.8%) septic shock; 4 (3%) empyema; and 2 (1.6%) pneumothorax. Only 5 (4%) patients with CAP died, and of these deaths 2 were due to respiratory failure and 3 from septic shock (Table-3). The majority (n=119; 96%) of patients were successfully discharged, with the average length of hospitalisation being 5 ± 3.3 days (range 1-22).

## Discussion

The results of the study indicated a predominance of atypical organisms - M. pneumoniae and C. pneumoniae - as etiological agents of mild to moderate CAP requiring hospitalisation. The atypical pathogens causing pneumonias include C. pneumoniae, M. pneumoniae and L. pneumophila; and multiple viruses. Atypical pneumonias were previously regarded as clinically or radiologically distinctive but are now accepted as being no different in their presentations from bacterial causes of the usual CAP. Most atypical pathogens are difficult to isolate and a definitive laboratory diagnosis is based on serological methods like direct fluorescent antibody (DFA) and indirect fluorescent antibody (IFA) detection methods. The morbidity and mortality from CAP can be considerable. A study from Pakistan reported an 11% crude mortality rate on 329 patients hospitalised with CAP.[9] Treatment protocols for CAP as a matter of routine now favour the empiric use of agents against atypical pathogens.[10,11] The added costs of care associated with dual antibiotic therapy (beta-lactams and macrolides) or the more expensive fluoroqinolones and the possibility of inducing resistant strains against anti-bacterials which are also important anti-mycobacterial agents is of special concern to resource-poor, developing countries.

We were unable to find any reports on the prevalence of atypical causes of CAP in adults from Pakistan. The review of the prevalence of atypical CAP from the developing world revealed two studies from India in which the prevalence of M. pneumoniae and L. pneumophila was reported to be 35% and 27.43% respectively.[12,13] Studies from Jordan[14] and Egypt[15] reported that 38% to 40% of CAP cases were due to atypical organisms. The atypical organisms were present in 8 to 25.5% cases cited by studies in Thailand,[16] Japan[17] and South Korea.[18] Other studies[18,19] have also reported 8 to 25.5% CAP cases being due to atypical organisms. Our results are comparable. We found a prevalence of 29% cases due to atypical organisms.

Most studies have reported a greater proportion of patients infected with C. pneumoniae followed by M. pneumoniae.[14,15,19] In contrast, our results identified M. pneumoniae as the leading cause of CAP (17%) followed by C. pneumoniae (12%). These proportions are similar to two studies reporting 12-14% cases due to Mycoplasma and 4% due to Chlamydia.[20,21] This disparity is possibly due to differences in age and severity of pneumonia between the groups. We identified no patients with L. pneumoniae serogroup 1 infection.

An interesting finding in our study was that only 9 samples were positive for Streptococcus pneumoniae. This organism has historically been the most common etiologic cause of CAP in adult patients. S. pneumoniae tends to be isolated more frequently from patients with severe CAP, older patients or in patients requiring hospitalisation. Our patients tended to be younger and had mild to moderate severity of disease as scored by the CURB-65 scoring system. Additionally, 21% of patients had previously received antibiotics which can lead to false negative cultures. All these may be factors that influenced our low culture rates.

Our results are limited by the large number of patients in whom both cultures and serological testing failed to identify an etiologic organism. Researchers from other developing countries have also reported similar numbers; some[15,17] were unable to isolate any organism in 50-57.1% cases. Another limitation of our study is that this was a single-centre study from a large urban hospital and the results may not be nationally representative.

## Conclusion

The results indicate that atypical pathogens play a larger role in the etiology of mild to moderate CAP than was previously considered. The study suggests that local guidelines be modified to include anti-microbial coverage specifically targeting Chlamydia and Mycoplasma, with less concern for Legionella.

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