Atypical Pneumonia

Introduction

Streptococcus pneumoniae causes up to 70% of community-acquired pneumonia cases and atypical pathogens are responsible for 30–40% of cases. The other bacteria which cause community-acquired pneumonia besides Streptococcus pneumoniae are Haemophilus influenzae, Staphylococcus aureus and Gram-negative bacilli. Legionella, Mycoplasma pneumoniae and Chlamydia pneumoniae are the atypical agents which cause CAP.1,2

Atypical pathogens: Literature Review

A population-based, CAP surveillance study involving non-institutionalized adults hospitalized due to CAP reported that Mycoplasma pneumoniae was the dominant pathogen in one-third of all CAP cases. Chlamydia pneumoniae was responsible in 8.9% of cases whereas Legionella caused up to 3% of cases. In this study, Streptococcus pneumoniae was implicated in 12.6% of cases, which was much lesser than noted in the earlier CAP surveillance studies. However, the authors hypothesized that low rates of S. pneumoniae most likely reflect the insensitivity of sputum Gram’s stain and culture when these tests were performed in the context of routine care.3

A study by Zaki and Godal reported that Chlamydia pneumoniae, Mycoplasma pneumoniae, Legionella pneumophila, Coxiella burnetii, adenovirus, and influenza virus were the pathogens responsible for CAP. Streptococcus pneumoniae (22%) followed by Haemophilus influenzae (18%). Mycoplasma pneumoniae (5%) and Legionella pneumophila (5%) were the most common isolated bacteria. The most common positive serological reaction was for Chlamydia pneumoniae (30%) and adenovirus (30%).4

Arnold et al. conducted a study to correlate the incidence of CAP due to atypical pathogens in different regions of the world with the proportion of patients treated with an atypical regimen in those same regions. Clinical outcomes of patients with CAP treated with and without atypical coverage were also evaluated in the study.5

The study divided the various regions in the world as follows:

- Region I: North America
- Region II: Europe
- Region III: Latin America
- Region IV: Asia and Africa

Outcome measures assessed included:

- Time to reach clinical stability
- Length of hospital stay
- Mortality

It was found that the incidence of CAP due to atypical pathogens in the regions I to IV were 22, 28, 21, and 20% respectively. The proportion of patients treated with atypical coverage were 91%, 74%, 53%, and 10% in regions I, II, III and IV, respectively. The study also showed that compared to those without atypical coverage, patients treated with atypical coverage had:

- Decreased time to clinical stability (3.7 vs. 3.2 days)
- Decreased length of stay (7.1 vs. 6.1 days)
- Decreased total mortality (11.1% vs. 7%)

- Decreased CAP-related mortality (6.4% vs. 3.8%).

It was concluded that empiric therapy for all hospitalized patients with CAP with a regimen that covers atypical pathogens is supported by significant global presence of atypical pathogens and better outcomes.5

In an Indian study conducted by Udwadia et al, the most common atypical organism causing CAP were Chlamydia pneumoniae and Mycoplasma pneumoniae.6 Following organisms were identified:

<table>
<thead>
<tr>
<th>Organisms</th>
<th>%</th>
<th>Organisms</th>
<th>%</th>
</tr>
</thead>
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<td>S. pneumoniae</td>
<td>22</td>
<td>M. pneumoniae</td>
<td>3</td>
</tr>
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<td>14</td>
<td>Pseudomonas aeruginosa</td>
<td>2</td>
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<tr>
<td>Klebsiella pneumoniae</td>
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<td>Salmonella typhi</td>
<td>1</td>
</tr>
<tr>
<td>Legionella pneumoniae</td>
<td>2</td>
<td>Mycobacterium tuberculosis</td>
<td>7</td>
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Need for Covering Atypical Pathogens

The need for antibiotic cover for atypical pathogens is controversial. Although there are not many studies, which show the importance of antibiotic therapy for atypical pathogens, the need-to-treat infection with Legionella has been well-established. Placebo-controlled trials and randomized trials comparing azithromycin, tetracycline, and penicillin show that L. pneumophila is shown to have better survival rate on antibiotic treatment.7

Furthermore, the Medicare database noted statistically significant survival advantage in hospitalized patients with CAP with fuoroquinolone or a β-lactam plus a macrolide as compared to β-lactam alone.7

Despite improvements in microbiological detection, it must be emphasized here that the specific pathogen cannot be isolated in about 30% of cases of CAP.8

It would also be helpful to have brief look at the most common atypical pathogens involved in causing CAP in order to arrive at appropriate treatment regimens for the same.

Mycoplasma pneumoniae6

Mycoplasma pneumoniae is the smallest of all free-living organisms. It does not have a peptidoglycan wall. However, it has a sterol plasmic membrane. This parasitic organism attaches to the respiratory epithelium, acquires essential exogenous nutrients for growth and may become intracellular. It causes injury to epithelial cells and their associated cilia by producing hydrogen peroxide and superoxide. This facilitates co-infection with other pathogens. Most of minor respiratory illnesses are caused by Mycoplasma pneumoniae.

A report by the Center for Disease Control and Prevention (CDC) of an outbreak in Colorado highlights the importance of CAP caused by M. pneumoniae. The infection has an incubation period of 1-3 weeks, followed by gradual symptom onset. Patients may not seek medical attention until a few days or even a week has passed as the onset of illness is gradual.

Symptoms such as headache, malaise, fever and cough may be prominent at this stage of the illness where no identifiable signs are observed during physical examination. The chest radiograph may reveal an infiltrate.
The second week of the illness progression may show sputum production and localized crackles or wheezes. These symptoms may extend for over a month beyond the incubation period. However, these general symptoms do not provide any clue to the likely diagnosis. Confirmation of M. pneumoniae infection can be provided by culture or serology, but most clinical laboratories do not culture for the organism, and serologic response can take weeks to peak. Consequently, antimicrobial therapy for CAP is initiated empirically before infection with M. pneumoniae is confirmed.

It was previously thought that M. pneumoniae pneumonia was only a mild illness primarily affecting older children and young adults, but there is now mounting evidence that it is a frequent cause of hospitalization among children as young as 2 years of age and can even necessitate ventilatory assistance. Chlamydia pneumoniae

Chlamydia pneumoniae has emerged as an important cause of pneumonia in both adults and children as young as 2 years old. Over 50% of adults worldwide have antibodies against the pathogen, indicating prior infection. Unfortunately, immunity is not long lived.

Chlamydia pneumoniae, an intracellular bacterium damages host cells by releasing antigens onto epithelial cell surfaces. This stimulates host immune (inflammatory) responses and ciliostasis. The incubation period of Chlamydia pneumoniae is about 2–4 weeks. The disease is usually mild but may be prolonged. The common symptoms are fever and cough. Crackles are usually revealed on chest examination. The only reservoir for Chlamydia pneumoniae is human beings. The signs and symptoms are seen in a prodromal phase. Sputum is scanty and pulmonary infiltration is minimal. About 9% of mortality is seen with Chlamydia pneumoniae infections.

Chlamydiaceae has two genera (Chlamydia and Chlamydophila) under the new taxonomic classification. Chlamydia genera include C. trachomatis, C. muridarum, and C. suis. Chlamydiophila includes the newly renamed strains of C. abortus, C. felis, C. pecorum, C. pneumoniae, C. caviae, and C. psittaci. Chlamydiophila psittaci has eight known serovars; six have been primarily isolated in birds and two strains have been isolated in mammals. Identification of serovar may help to determine the source of infection.

There are many specific occupational and recreational activities that could increase the risk of acquiring psittacosis. A few of the at-risk professions are laboratory workers, veterinarians, avian quarantine workers, zoo workers, farmers, pregnant women, bird fanciers (pigeon fanciers too), bird owners, pet shop employees, poultry slaugher and processing workers and wildlife rehabilitation workers.

The common modes of transmission of Chlamydia pneumoniae infection to humans is inhalation (dried infective droppings, secretions or dust from feathers), mouth-to-beak, direct contact (handling plumage or of infected birds) and person-to-person transmission. Legionnaires’ Disease

Legionellosis is an infectious disease caused by Legionella pneumophila and presents in two distinct forms. One is pontiac fever which is an acute, febrile and self-limited illness. The other form is Legionnaires’ disease, which is a severe form of infection and leads to pneumonitis.

Legionella pneumophila is an aquatic, aerobic, thin and Gram-negative bacillus. At least 46 species of Legionella have been identified to date. About 80–90% of infections are caused by Legionella pneumophila. Serogroups 1, 4 and 6 are the most common causative pathogens. Legionella micdadei is the first most common causative pathogen. The second most common is Legionella pneumophila. Legionella bozemanii is more virulent or resistant than Legionella pneumophila.

Legionella pneumophila is an intracellular organism. Infection in humans is caused by serotype 1. The mode of transmission is environment-to-human and human-to-human transmission.

Moist soil, heating and cooling water system, respiratory therapy equipments and showers are the common sources of infection. Overnight stay outside home, recurrent plumbing in house, chronic renal failure, malignancy, diabetes mellitus, liver failure and immunocompromised state are the risk factors for Legionella pneumophila infection.

The classic clinical manifestations of Legionnaires’ disease were confirmed by two comparative studies by Gupta et al. and Helms et al. The clinical manifestations include:

- Temperature more than 39°C
- Diarrhea
- Neurologic findings especially confusion, hyponatremia and hepatic dysfunction (transaminase and bilirubin elevations).
- Hematuria

A retrospective case-control study was conducted by Gupta et al. to evaluate sensitivity and specificity of Winthrop-University Hospital (WUH) criteria to identify Legionella pneumoniae vs. bacteremic pneumococcal pneumonia at the time of hospitalization for community-acquired pneumonia involved about 37 patients with Legionella pneumophila and 31 patients with bacteremic pneumococcal pneumonia. A subgroup of patients were analyzed further. The study noted that:

- The sensitivity and specificity of WUH criteria was 78% and 65%, respectively.
- Positive and negative predictive values were 42% and 90%, respectively.
- In the subgroup analysis, sensitivity of 87% and specificity of 50% was noted; positive and negative predictive values were 37% and 92%, respectively.
- Although the sensitivity was relatively high, 13–22% of patients with Legionnaires disease were missed by the WUH score.

The study concluded that given the high mortality rate, the WUH score cannot be used to focus antibiotic therapy since the specificity was low (50 to 65%), the application of the WUH score also could lead to unnecessarily broad coverage. The WUH score might be used to screen patients for specialized Legionella testing. If the WUH score were fulfilled, the patient could receive anti-Legionella antibiotics as empiric therapy without Legionella laboratory testing. But, if the criteria were not fulfilled, Legionella testing could be performed on these patients to cover the 13–22% of patients who do not have the classical syndrome.

Viral Pneumonia

Viral pneumonia occurs in young children and older adults and is caused by adenovirus, influenza, H1N1, parainfluenza and respiratory syncytial virus (RSV).

- Influenza A and B usually occur in the winter and spring. Respiratory symptoms, headache, fever, and muscle aches are the main symptoms of this condition.
• Respiratory syncytial virus (RSV) is most common in the spring and infects children.
• Adenovirus and parainfluenza viral pneumonias are often accompanied by cold symptoms (runny nose and conjunctivitis).
• Post-influenza pneumonia is usually secondary bacterial infection caused by *Staphylococcus pneumoniae* and *Staphylococcus aureus*.

Infectious causes of pneumonia in immunocompromised patients include measles, HSV, CMV, HHV-6 and Influenza viruses. Viruses cause partial paralysis of ‘mucociliary escalator’. There is also an increased risk of secondary bacterial lower respiratory tract infection (LRTI). The known complication following influenza infection is *Staphylococcus aureus* pneumonia.

### Treatment of Atypical Pneumonia

Therapy for pneumonia is empiric because specific pathogens usually are not identified at the time the treatment is initiated. Several classes of antibiotics are effective against atypical pathogens. However, because *C. pneumoniae* and *Legionella* spp. are intracellular organisms and *M. pneumoniae* lacks a cell wall, β-lactams are not effective. The traditional choices for the treatment of atypical pneumonia are erythromycin and tetracycline.1

In Legionella infection erythromycin is effective as demonstrated in some trials and in case of *Mycoplasma pneumoniae*, erythromycin and tetracycline are effective. They also reduce symptom duration in *Chlamydia pneumoniae* infection.

Azithromycin and clarithromycin are very effective against *Mycoplasma pneumoniae*, *Chlamydia pneumoniae* and *Legionella* spp. and show better tolerability profile as compared to erythromycin. Doxycycline is also effective and is associated with fewer gastrointestinal side-effects. Fluoroquinolones are highly effective against *Mycoplasma pneumoniae*, *Chlamydia pneumoniae* and *Legionella* spp. The advantage of fluoroquinolones is once-daily dosing and excellent bioavailability (intravenous or oral).12

The basic dosage of antibiotics prescribed is given follows:12

1. **Macrolides**
   - Azithromycin: 500–1000 mg daily
   - Clarithromycin: 250–500 mg BID
   - Erythromycin: 500 mg QID

2. **Doxycycline**: 100 mg daily

3. **Fluoroquinolones**
   - Levofloxacin: 500–750 mg daily
   - Moxifloxacin: 400 mg daily
   - Gemifloxacin: 320 mg daily
   - Gatifloxacin: 400 mg daily

The combination of rifampin plus a macrolide or a quinolone can be used for initial treatment in severely ill patients with Legionnaires’ disease. Initial therapy should be given by the intravenous route. Usually, a clinical response occurs within 3–5 days, after which oral therapy can be substituted. The total duration of therapy in the immunocompetent host is 10–14 days; a longer course (3 weeks) may be appropriate for immunosuppressed patients and those with advanced disease.12

### Community-Acquired Pneumonia, Tuberculosis and Fluoroquinolones

*Mycobacterium tuberculosis* and community-acquired pneumonia

*Mycobacterium tuberculosis* causes infection in about one-third of the world’s population and causes 1.6 million deaths worldwide.13 It is estimated that about 3.3–7% CAP cases are due to *M. tuberculosis*.6 Fluoroquinolones are resistant to streptococci in about less than 3% of cases. They have excellent activity against atypical organisms and *Mycobacterium tuberculosis*. Fluoroquinolones are used for the treatment of multidrug-resistant tuberculosis, shortening the duration of AKT and as replacement drug.14

**Impact of Empirical Therapy of CAP on Treatment of M. tuberculosis Infections**

Initiation of empirical therapy of CAP is known to have two important concerns of *Mycobacterium tuberculosis*.13 These are:

1. Delayed initiation of anti-TB treatment
2. Resistance to fluoroquinolone

Dooley et al. conducted a retrospective cohort study to evaluate the effect of empiric fluoroquinolone therapy on delays in the treatment of tuberculosis. About 33 patients with culture-confirmed tuberculosis were included in the study. Sixteen patients received fluoroquinolones for presumed bacterial pneumonia and the rest did not receive fluoroquinolones. Median time between presentation to the hospital and initiation of antituberculosis treatment in patients who received fluoroquinolones and patients who did not receive was 21 days and 5 days, respectively.15

It was concluded that initial empiric therapy with a fluoroquinolone and delay in the initiation of appropriate antituberculosis treatment were associated. Empiric fluoroquinolone therapy delays the diagnosis of tuberculosis by 21 days, prolongs patient’s infectivity, morbidity and mortality, and develops fluoroquinolone-resistant mycobacteria.15

Yoon et al. evaluated the effect of empiric fluoroquinolone therapy on delay in diagnosis in patients with pulmonary tuberculosis initially misdiagnosed as bacterial pneumonia.14

Patients with pulmonary tuberculosis initially treated with fluoroquinolones for more than five consecutive days were enrolled in the study group. Patients with pulmonary tuberculosis initially treated with non-fluoroquinolones were enrolled in the control group.

The study found that both clinically and radiologically improvement in fluoroquinolone group (89%) was significant as compared to non-fluoroquinolone group (42%). Delay in initiation of antituberculosis treatment was longer in fluoroquinolone group (43.1 days) as compared to non-fluoroquinolone group (18.7 days).14

These studies indicate that newer fluoroquinolones should be restricted in tuberculosis endemicity because of its potential to mask active tuberculosis and emerging drug-resistant tuberculosis.

Ruiz-Serrano et al. compared the activities of the fluoroquinolones, ciprofloxacin, ofloxacin, levofloxacin, grepafloxacin, trovafloxacin, and the novel compound gemifloxacin (SB-265805) against 250 clinical isolates of *Mycobacterium tuberculosis* with different levels of susceptibility to first-line antituberculosis drugs. Overall, levofloxacin (MIC<sub>90</sub> 1 μg
mL) showed the greatest activity against the *M. tuberculosis* strains tested, with 96.4% of the strains inhibited at 1 μg/mL. Ciprofloxacin (MIC$_{90}$ 1 μg/mL; 92.0%), grepafloxacin (MIC$_{90}$ 1 μg/mL; 90.4%), and ofloxacin (MIC$_{90}$ 2 μg/mL; 88.8%) also showed good activity. Trovafloxacin (MIC$_{90}$ 64 μg/mL; 0%) and gemifloxacin (MIC$_{90}$ 8 μg/mL; 6.4%) were inactive against most of the strains tested.16

**Prevention of Resistance**

The common approach for preventing the emergence of resistance is to administer the drug at doses that produce blood concentrations that continuously exceed the resistance level of all spontaneous mutants. This prevents the selective amplification of any mutant population. The greater the activity of the agent, the less likely they will select for mutants that have reduced susceptibility. The duration of exposure of the *M. tuberculosis* infecting organisms to the fluoroquinolone may also be a risk factor for the development of resistance.17

**Recommendations**

- Atypical coverage is a must in moderate-to-severely ill patients with pneumonia requiring hospitalization and intensive care unit care.
- The only acute respiratory tract infection in which delayed antibiotic treatment has been associated with increased risk of death is CAP, hence prompt and accurate diagnosis of CAP is important.
- Tuberculosis should always be considered while treating CAP in India. Therefore fluoroquinolones (levofloxacin and moxifloxacin) though effective in the treatment of CAP should be used cautiously.
- Newer macrolides are the drug of choice for the treatment of CAP.
- Viral pneumonias, especially influenza and H1N1 should be considered in the clinical setting.

**References**