Treatement of Community-Acquired Pneumonia and Pitfalls

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Introduction

Community-acquired pneumonia (CAP) continues to be a leading cause of mortality among the world’s population, despite the development and availability of new and potent antibiotics in its management. Important issues that help effective management of CAP are correct diagnosis of pneumonia, identification of the exact causative pathogen, and appropriate empirical treatment. Factors guiding the choice of antimicrobial agent include the spectrum of activity, efficacy, pharmacokinetics, cost, safety profile, and whether or not a specific pathogen is identified. While many pathogens are said to be associated with CAP, a small range of key pathogens are responsible for most of the cases, with the predominant pathogen implicated being Streptococcus pneumoniae (S. pneumoniae). Other pathogens implicated in CAP in order of frequency are Klebsiella pneumoniae, Pseudomonas aeruginosa, α-hemolytic streptococci, Escherichia coli, β-hemolytic streptococci, and atypical coli. Data from western countries show S. pneumoniae, Mycoplasma pneumoniae, Chlamyphila pneumoniae, Legionella spp., and Haemophilus influenzae to be significant pathogens. However, data from Asia region revealed that Gram-negative bacilli (GNBs) and Mycobacterium tuberculosis were more relevant. Klebsiella pneumoniae, Escherichia coli, Enterobacter cloacae, Proteus mirabilis and Serratia marcescens are common GNBs implicated in CAP. Gram-negative bacilli were also the most common pathogens identified among patients with severe CAP (21.5%). Gram-negative bacilli were identified in 13.0% of all hospitalized patients among Asian studies with the most common GNB isolated being Klebsiella pneumoniae (6.3%).

The emergence of drug-resistant pathogens has complicated the empiric management of CAP. Drug-resistant and multidrug-resistant bacteria, particularly S. pneumoniae are a major concern in the effective treatment of these infections. A growing concern also exists on the lack of new antibiotics, especially in the treatment of multidrug-resistant Gram-negative bacteria, which produce extended spectrum β-lactamases (ESBLs). Extended spectrum β-lactamases are primarily produced by Enterobacteriaceae family of Gram-negative organisms particularly Klebsiella pneumoniae, and Escherichia coli with high rates being seen in Asia. As the inactivate cephalosporins they have the potential to render empiric antibiotic treatment ineffective. These organisms also have the capacity to acquire resistance to other antimicrobial classes, such as the quinolones, tetracyclines, cotrimoxazole, trimethoprim, and aminoglycosides that further limit therapeutic options.

Treatment based on empirical antibiotic use is recommended to ensure adequate coverage of both typical and atypical pathogens. Conversely, the judicious use of antimicrobials is also constantly being adopted to prevent further increases in the development of resistance. However, unless there is an improvement in the rapid diagnostic methods to define causative pathogens and allow specific, directed therapy, patients will continue to be treated empirically. Also, CAP as a condition itself is an increasing threat in the future given the projected increase in the number of patients at risk (elderly and those with comorbid conditions). Efforts are, therefore, on to assess the efficacy of preventive strategies in CAP.

Management of Community-Acquired Pneumonia

Following the diagnosis of CAP and assessment of disease severity, the first step in the management of the condition involves prescription of appropriate antibiotics as bacteria are the common pathogens. The guidelines developed for CAP management need to be followed in tandem with clinical judgment. Other than the commonly observed American Thoracic Society (ATS) and British Thoracic Society (BTS) guidelines, practice guidelines from the Post Graduate Institute of Medical Education and Research (PGIMER), Chandigarh provide an Indian perspective to the management of this condition. Few highlights from the Indian guideline recommendations on CAP management include:

- **The use of tetracycline derivatives as monotherapy is not recommended as most S. pneumoniae show a high rate of resistance to them.**

- **Limiting the use of fluoroquinolones is stressed upon, as it leads to a delay in tuberculosis diagnosis that happens to be a common mimic of CAP in India.**

- **The use of fluoroquinolones is also recommended, as it can lead to an increase in multidrug organisms resistant to both fluoroquinolones and other antibiotics.**

The most appropriate treatment approach in the Indian setting is suggested to be a β-lactam and a macrolide in the outpatient setting. An intravenous β-lactam along with a respiratory fluoroquinolone is proposed to be appropriate in the Indian inpatient setting. Intravenous antibiotics are indicated in the hospitalized patient who is hemodynamically unstable, is unable...
Supportive management

• Inpatients may be prescribed antibiotics to be prescribed for
• Patients need to be afebrile and

Antibiotics – Initiation and duration of prescription

An early administration of antibiotics can decrease mortality in patients with a confirmed diagnosis of CAP. Suggestions for the time of initiation and duration of antibiotic use in patients presenting with symptoms of CAP confirmed with a chest radiograph are as listed below:

- The first dose of antibiotic to be administered within 4 to 6 hours of radiographic confirmation of CAP.
- Antibiotics to be prescribed for 5 to 7 days for outpatients based on clinical response.
- Patients need to be afebrile and clinically stable for 48–72 hours before the discontinuation of antibiotics.
- Inpatients may be prescribed antibiotics for 7 to 10 days.
- Treatment may be prolonged for 14–21 days in inpatients based on clinical assessment.

Few guideline-recommended antibiotics in CAP management of the hospitalized patient are as in Table 1.

Supportive management

Supportive measures in CAP management may include rest, adequate hydration, and symptomatic treatment for fever, body aches, and pleuritic chest pain. Hospitalized patients need regular monitoring of vital parameters, oxygen, nutritional support, and mechanical ventilation as required.

Treatment Challenges

Under ideal circumstances, the treatment for CAP should be planned after identification of the organism by culture or serology and based on the sensitivity pattern. However, particularly in India, no specific causative agent is identified owing to a variety of reasons. Treatment, therefore, is empirical and is based on surveillance data and “best guess” method. It is, thus, considered essential to check on the underlying background of the patient and the epidemiological surrounding while taking the decision on the antibiotic to be prescribed.

An early initiation of antibiotics in CAP management is seen to abbreviate the illness and also decrease complications and mortality. Antibiotic therapy is usually empirical as the organism is not isolated in a large proportion of patients at the onset and neither is the clinical and radiological picture a good predictor of the pathogen. Choosing an appropriate antibiotic is further complicated by the emergence of multi-drug resistant organisms in the community. Other factors that influence the effectiveness of the antibiotic selected include the likely pathogen, the community resistance pattern, risk of antibiotic resistance, the severity of pneumonia, and the presence of comorbid illnesses.

An inappropriate use of antibiotics can lead to an increase in healthcare associated infections, the emergence of multi-drug resistant organisms, and an overall increase in healthcare costs.

Table 1: Guideline-recommended antibiotics for CAP treatment in hospital

<table>
<thead>
<tr>
<th>Patient group</th>
<th>BTS</th>
<th>ERS/ESCMID</th>
<th>IDSA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-ICU patients</td>
<td>• Amoxicillin ± clarithromycin</td>
<td>• Penicillin ± macrolide</td>
<td>• A respiratory fluoroquinolone.</td>
</tr>
<tr>
<td>ICU patients (severe CAP)</td>
<td>• Amoxicillin-clavulanate ± clarithromycin</td>
<td>• Cephalosporin ± macrolide</td>
<td>• A β-lactam plus a macrolide</td>
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Streptococcus pneumoniae was supposed to be a very sensitive organism to routinely prescribed antibiotics, particularly penicillin. However, after the first clinically significant penicillin-resistant Pneumococcus was isolated in the year 1967, many studies have reported an increase in the emergence of the resistant strain. Currently, in addition to reports of strains resistant to β-lactam group of antibiotics, there is also an emergence of multi-drug resistant strains.

The increased prevalence of drug-resistant strains of S. pneumoniae is of primary concern in CAP treatment. Over the past decade, the approach to empirical therapy for CAP has changed owing to the emergence of S. pneumoniae strains that are resistant to penicillin and other antimicrobials. The risk factors for drug-resistant S. pneumoniae infections are age greater than 65 years, the use of β-lactams or fluoroquinolones in the last three to six months, medical comorbidities, alcoholism, and an immunosuppressed state.

Risks of Penicillin Resistance in Pneumococci

Historically, clinicians have been prescribing penicillin as a part of the empiric treatment of S. pneumoniae infection. This approach was bereft of any concern regarding the susceptibility of the Pneumococcus to the chosen antimicrobial. However, in the early 1990s, a sharp increase in the prevalence of penicillin-resistant S. pneumoniae was noted. Over the last ten years, there has been a greater increase in the high-level penicillin resistance [minimum inhibitory concentration (MIC) of penicillin, ≥ 2.0 µg/mL], as compared to intermediate resistance (MIC, 0.12–1.0 µg/mL) among the pathogen. From isolates collected between 2000 and 2004 in the US,
21.2% of resistance to penicillin has been reported. Studies from other places, such as Europe, Australia, and Malaysia, observed penicillin resistance in 24.6%, 6.7%, and 21.6% of _S. pneumoniae_ isolates, respectively. Studies from other countries have also reported varying levels of resistance to other antibiotics. A collaborative study from eight Asian countries, including India, has revealed 35.1% of total resistance in _S. pneumoniae_. Surveillance for resistant strains of _S. pneumoniae_ across Indian states has noticed the upsurge of intermediate resistance (4.6%) from CMC Vellore in the South and 2.3% (total resistance) and 15.2% (intermediate resistance) to penicillin in a study from North India. A study by Chawla et al. depicted a 4% total resistance and a 10% intermediate resistance to penicillin among the _S. pneumoniae_ isolates. A difference in the resistance pattern between South and North India is attributed to the high genetic diversity existing among strains isolated from various geographical areas within India. An increase in the number of intermediate resistant strains as observed in studies can result in a greater spread of resistant strains in the near future.9

**The Indian scenario**

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**Impact on clinical outcomes**

Penicillin-resistant _S. pneumoniae_ isolates can lead to a higher rate of treatment failures and increase the length of hospital stay. These strains may also possess genes responsible for resistance to other antibiotics.9 The increasing susceptibility of pneumococci to penicillin and its impact on clinical outcomes was noted in a study from the Centers for Disease Control and Prevention. It was found that after day 4 of hospitalization, the risk of death was 7 times greater in patients infected with high-level penicillin-nonsusceptible _S. pneumoniae_ (PNSP) (MIC, ≥ 4.0 µg/mL) than in patients infected with intermediate isolates (MIC, 0.012–1.0 µg/mL). Studies that evaluated the association between PNSP and short-term mortality rate in pneumococcal pneumonia found a significant difference in the mortality rate; 19.4% and 15.7% in the PNSP and penicillin-susceptible _S. pneumoniae_ group, respectively.8

**Macrolide-resistant Streptococcus pneumoniae**

Macrolide antibiotics have been widely prescribed as a part of the empiric treatment of community-acquired respiratory tract infections (RTIs). In 1993, there were concerns raised on the increasing prevalence of pneumococcal resistance to β-lactam antibiotics and an increased awareness of the role of atypical pathogens in CAP. These concerns led to the recommendations by the American Thoracic Society (ATS) to use macrolides as a first-line empiric therapy option in CAP patients treated on an outpatient basis. Although these drugs came to be used worldwide on a large scale, developing high levels of pneumococcal resistance to macrolide antibiotics have raised concerns about the continued clinical efficacy of these agents.10

**Prevalence of macrolide-resistant Streptococcus pneumoniae**

The prevalence of resistance and the distribution of macrolide-resistant genotypes are seen to vary between geographical regions. An increase in the pneumococcal macrolide resistance has been attributed to an increased use of macrolides, inappropriate use of antibiotics for the treatment of nonbacterial or self-limiting infections, and misuse of antibiotics either through an incorrect choice of antibiotic or faulty dose/duration of therapy. In the Alexander project, a global rate of pneumococcal macrolide resistance ranged 16.5% and 21.9% in 1996 and 1997, respectively, with an increase of 24.6% observed from 1998 to 2000. In the PROTEKT study, 29.2% of isolates were seen to be macrolide-resistant from 2002 to 2003. The two primary mechanisms that are considered responsible for macrolide resistance in the majority of _S. pneumoniae_ isolates are as follows9:

- Modification of the drug target site
- Active efflux of the drug from the cell mediated by the product of the _mef_ (A) gene

Bacteria with the _mef_ (A) phenotype exhibit resistance to erythromycin, clarithromycin, and azithromycin. A rise in macrolide MIC among _mef_ (A)-positive _S. pneumoniae_ isolates, with values ranging from 1 to > 256 µg/mL in the PROTEKT study, indicated such increases in MIC to increase the likelihood of clinical treatment failure. Patient groups at risk of macrolide-resistant _S. pneumoniae_ are as shown in Table 2.10

**Impact on clinical outcomes**

Studies have suggested a link between macrolide resistance and treatment failure mostly in patients hospitalized with breakthrough bacteremia. Given the fact that the majority of the patients in an outpatient setting are prescribed macrolides, the actual incidence of pneumococcal macrolide treatment failure is much higher than that observed in published case reports and observational studies.10

**Recommendations to overcome macrolide resistance**

Treatment guidelines by the American Thoracic Society, the Infectious Disease Society of America, and the Centers for Disease Control and Prevention recommend the use of empiric macrolide monotherapy, specifically in patients with no coexisting cardiopulmonary disease and with no risk factors for infection with drug-resistant _S. pneumoniae_ (i.e. recent antibiotic use, age > 65 years, immunosuppressive illness, multiple medical comorbidities, and/or exposure to a child attending a day care center). Recommended alternatives to empiric macrolide therapy include combination treatments such as that of a high-dose β-lactam and a macrolide or a respiratory fluoroquinolone.10

**Fluoroquinolone Resistance in Streptococcus pneumoniae**

Respiratory fluoroquinolones are an effective treatment option for CAP patients.4 The emergence
of fluoroquinolone-resistant *S. pneumoniae* strains, despite a low worldwide prevalence, is a concern to clinicians who manage RTIs. The global prevalence of fluoroquinolone resistance in *S. pneumoniae* varies over time, geographic region, age group, and origin of isolates. Prior administration of fluoroquinolone is considered a risk factor for resistant strain development.11

### Prevalence of resistance

Among 2,882 *S. pneumoniae* isolates tested during 2002, 2.6% of them were ciprofloxacin-resistant. Resistance was seen to be associated with elderly (≥65 years), with isolation from non-invasive sites, and with penicillin and macrolide resistance.11 As per global surveillance studies, 10 to 30% of *S. pneumoniae* isolates harbored first-step mutations conferring low-level fluoroquinolone resistance. According to a recent nationwide susceptibility study of 2,559 *S. pneumoniae* isolates, 2.2% and 0.5% of them were resistant to ciprofloxacin and levofloxacin, respectively.12

Quinolone resistance in *S. pneumoniae* has arisen in heterogeneous genetic backgrounds. It has now, however, appeared in strains that are well adapted for regional and global transmission. There is evidence of clonal spread of quinolone-resistant strains globally.13

### Impact on clinical outcomes

The increase in fluoroquinolone resistance has paralleled increased usage of fluoroquinolones in general or second-generation quinolones in particular. Fluoroquinolone resistance is seen to result in clinical failures in patients with pneumococcal pneumonia having been previously treated with oral fluoroquinolones empirically.12

Although newer fluoroquinolones are said to have enhanced *in vitro* activity against *S. pneumoniae*, their use to treat respiratory infections needs attention. There have been more than twenty reports of levofloxacin treatment failure concurrent with the development of resistance during or after therapy. Identification of these strains can help avoid treatment failures. Fluoroquinolone resistance is more frequently encountered in the elderly with chronic respiratory diseases and on long-term quinolone therapy. Therefore, recent use of these drugs should contraindicate further fluoroquinolone treatment.11

### Steroids in the Management of Community-Acquired Pneumonia

Research data suggest that an excess of interleukin (IL)-6 and -10 during infectious pneumonia acted as acute phase proteins and is associated with a high mortality rate in CAP. In an early experimental model, it was demonstrated that glucocorticoids with antibiotics attenuated local inflammatory response and decreased bacterial burden in severe pneumonia. The presence of relative adrenal insufficiency in most of the patients with severe CAP suggested underlying benefits of corticosteroids treatment in these patients. A multicenter randomized controlled trial (RCT) has shown treatment with hydrocortisone to be associated with a significant reduction in mortality in severe CAP. While another retrospective study reported that the mortality rate decreased in patients who received systemic steroids with antibiotic treatment for CAP.14 Further, a systematic review and meta-analysis that examined the effect of adjunctive corticosteroid therapy in CAP patients observed possible reductions in all-cause mortality (by approx. 3%), need for mechanical ventilation (by approx. 5%), development of acute respiratory distress syndrome, and a decrease in time to clinical stability and duration of hospitalization (by approx. 1 day).15

However, according to a recent retrospective study adjunctive therapy with corticosteroids had no influence on the mortality rate. These findings were repeated in results from another meta-analysis that displayed no significant differences in mortality reduction with adjunctive corticosteroids. Given these contradictory findings, the benefits of corticosteroids in the management of CAP continue to remain controversial. However, it may be of importance to note that analyses restricted to severe CAP patients or prolonged corticosteroids treatment showed a survival benefit. There is a future need thereby to identify CAP patients who may benefit from corticosteroids and also data on the type, dosage, and duration of corticosteroids requires evaluation in adequately powered RCTs.14

### How Resistance Matters in the Indian Setting?

Antibiotic resistance is a public health threat worldwide but nowhere as stark as in India. As per 2010 data, the world’s largest consumer of antibiotics for human health was India, at 12.9 x 10⁹ units (10.7 units per person). As per the latest reports, the crude infectious disease mortality rate in India is 416.75 per 100,000 persons. Antibiotic use is a primary driver for resistance in the population. The access to antibiotics is rising in the country, which portends well for the large proportion of India’s population that has so far had poor access to these life-saving drugs. The coming together of factors, such as poor public health infrastructure, rising incomes, a high disease burden, and cheap, unregulated sales of antibiotics, has created ideal conditions for a rapid increase in resistant infections in India. Also, immunization rates tend to lag behind in India.16

### Conclusion

The discrepancy in the management of CAP exists despite the availability of potent antibiotics and guidelines for the management and the presence of improvement in supportive care.6 The most probable cause for the development of resistant strains is supposed to be the indiscriminate use of antibiotics in inappropriate dosages at the community level. A restraint needs to be imposed on the indiscriminate use of antibiotics with an aim to limit the surfacing of resistant strains. The emergence of resistant strains and multi-drug-resistant strains of *S. pneumoniae* needs continuous monitoring of the sensitivity pattern to be able to design management protocols.7

### References


