

# Challenges in the Management of Pneumococcal Disease in Older Adults

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## Introduction

Pneumococcal disease in adults (invasive disease, and those with pneumococcal pneumonia) is associated with significant morbidity and mortality. Of these, pneumococcal pneumonia remains one of the most common cause of community acquired pneumonia (CAP). Although antibiotic therapy is the treatment of choice for pneumococcal disease, resistance to penicillin and other antibiotics is emerging, which necessitates the use of alternative modalities, prevention being one of them as this disease can be vaccine-preventable.

## Management of CAP

In practice, patients do get diagnosed with pneumonia *before* the causative organism is known. In most cases, treatment is empirical, and diagnostic testing may only be performed when the results are likely to significantly change the management approach. Almost all of the management decisions in CAP centre on the initial assessment of disease severity. The next step after diagnosis is to determine whether or not the patient requires hospital admission to a medical ward, and if so, if they require admission to an intensive care unit (ICU). Significantly, the cost of inpatient care for CAP is up to 25 times greater than that of outpatient care, so it is important to avoid unnecessary hospital admission.<sup>1</sup>

Even if patients are considered to be at low risk of death from CAP, they may be hospitalized for other reasons, including presence of complications of pneumonia,

worsening and aggravation of underlying co-morbidity (eg, diabetes, chronic obstructive pulmonary disease, heart disease) as well as inability to reliably take oral medication or receive outpatient care.

Most patients with CAP are successfully managed in the community. A major goal of therapy is eradication of the infecting organism with resultant resolution of the infection. Consequently, antibiotics are the mainstay of treatment for CAP. The choice of antibiotic depends on the causative organism and its antibiotic susceptibility. CAP may be caused by a range of organisms, the most common of which is *S pneumoniae*. Antibiotic selection is made on the basis of the most likely pathogen and knowledge of local antibiotic susceptibility patterns.

The British Thoracic Society (BTS)<sup>2</sup> and European Respiratory Society (ERS)/European Society for Clinical Microbiology and Infectious Diseases (ESCMID)<sup>3</sup>

guidelines recommend oral amoxicillin (a beta-lactam antibiotic) as a preferred treatment for all patients managed in the community. The macrolides clarithromycin or azithromycin and the tetracycline doxycycline are alternatives if the patient is unable to tolerate penicillin

The table 1 lists examples of antibiotics recommended in the BTS, ERS/ESCMID, and IDSA guidelines<sup>2-4</sup> for the management of inpatients with CAP. Injectable antibiotics are recommended for patients in the Intensive Care Unit (ICU).

### Community-Acquired Pneumonia — the Impact of Disease

Pneumococcal pneumonia is the most common manifestation of pneumococcal disease in adults. *S pneumoniae* is also the most common cause of CAP, and accounts for between 16% and 60% of cases.

A comprehensive review of the published literature examining the

**Table 1: BTS, ERS/ESCMID, and IDSA Recommended Inpatient Treatment for CAP**

Patient Group	Recommendations		
	BTS	ERS/ESCMID	IDSA
Non-ICU patients	<ul style="list-style-type: none"> <li>amoxicillin ± clarithromycin</li> <li>doxycycline or clarithromycin</li> </ul>	<ul style="list-style-type: none"> <li>penicillin ± macrolide</li> <li>cephalosporin ± macrolide</li> </ul>	<ul style="list-style-type: none"> <li>a respiratory fluoroquinolone</li> <li>a beta-lactam plus a macrolide</li> </ul>
ICU patients* (severe CAP)	<ul style="list-style-type: none"> <li>Amoxicillin-clavulanate + clarithromycin</li> <li>penicillin + either a fluoroquinolone or ciprofloxacin</li> <li>cephalosporin + clarithromycin</li> </ul>	<ul style="list-style-type: none"> <li>cephalosporin + macrolide</li> <li>respiratory fluoroquinolone + macrolide</li> <li>cephalosporin or carbapenem + ciprofloxacin</li> </ul>	<ul style="list-style-type: none"> <li>a beta-lactam plus either azithromycin or a fluoroquinolone</li> </ul>

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**Table 2: Risk for mortality of CAP from Asia-Pacific**

Country	Year	Mortality (%)
Australia	2003-4	9.4 (≥ 18 years)
China	2004	8.6
India	2000-1	11 (>15 years)
Japan	2002-5	6.4 (≥15 years)
Malaysia	2002-3	12 (≥12 years)
New Zealand	1999-2000	6 (adults)
Philippines	2004	2.5 (≥18 years)
Singapore	1997-8	13.7
Taiwan	2001-2	(>16 years)

incidence, morbidity, mortality, and economic impact of CAP in adults reported the following statistics:

- CAP accounts for about one-third of all hospital admissions for infectious disease among adults 50 years of age or older.
- Between 10% and 20% of hospitalised patients with CAP were admitted to an ICU.
- In-hospital mortality rate is up to 18%, and the 30-day mortality rate is up to 23%; death rate increases with age.
- The average length of hospital stay in patients aged 45 to 64 years was 5.0 days, increasing to 5.6 days in the ≥65-year age group.
- Up to 1 in 10 patients is rehospitalised within 30 days after inpatient treatment for CAP, mostly because of underlying comorbidities, such as heart or lung disease.
- The estimated direct costs for a single CAP hospitalisation in the United States range from about USD \$3,000 to USD \$13,000 (2006 costs); room and board in the hospital account for 55% to 85% of these costs. Outpatient management can also be costly. The estimated direct costs for a single outpatient with CAP range from about USD \$130 up to USD \$4,500

Among patients who survive CAP, there can be considerable short-term morbidity because

**Table 3: Mortality rate in patients with pneumococcal pneumonia**

Year	1952-1962	1966-1995	1995-1997	1999-2001
Mortality (%)	13%	12.3%	12%	12.1%
N	1130	4432	5837	730

\*90-day mortality in ICU and ward patients

symptoms can take several weeks to resolve, even after the infection is eradicated<sup>5</sup>. Significantly, this effect is not limited to elderly patients.

### Management of Invasive Pneumococcal Disease

Antibiotic therapy is the mainstay of therapy for invasive pneumococcal disease<sup>1</sup>. Empirical treatment usually includes a cephalosporin combined with vancomycin. During the 1940s, penicillins were used effectively to treat pneumococcal infections. Within the next two decades, however, pneumococci resistant to penicillins were discovered in humans. Since then, penicillin-resistant pneumococci have been reported throughout the world. Pneumococci soon developed resistance to other classes of antibiotics too, and these "multidrug-resistant" pneumococci have now been reported all over the world. Pneumococcal resistance to commonly used antimicrobials, such as the penicillins, cephalosporins, trimethoprim/sulfamethoxazole, macrolides, and fluoroquinolones, is a serious and increasing problem worldwide, complicating specific treatment and underlining the need for effective immunization against pneumococcal disease.

The number of strains of *S pneumoniae* fully susceptible to penicillin has declined by approximately 30% to 50% in many countries, and by as much as 75% in some. Percentages of pneumococci resistant to macrolides, ciprofloxacin, tetracyclines and to trimethoprim/sulfamethoxazole have increased, especially where these drugs have been widely used.<sup>6-9</sup> As of 2009, antibiotic resistance to *S*

*pneumoniae* is increasing worldwide, primarily against betalactams and macrolides.<sup>10</sup>

Antibiotic resistance is not seen uniformly across all serotypes of *S pneumoniae*. For example, most clinically significant antibiotic resistance is seen in 7 serotypes of *S pneumoniae*: 6A,6B, 9V, 14, 19A, 19F, and 23F. Of these, serotypes, 19A is the only one that is prevalent worldwide. In the United States, the incidence of invasive pneumococcal disease caused by serotype 19A has increased in all age groups, including those over the age of 50 years<sup>11</sup>. The increase in disease caused by serotype 19A has been reported in areas where pneumococcal conjugate vaccine-7 valent (PCV7) was implemented and there was extensive use of antibiotics, frequent antibiotic resistance, and multidrug-resistant serotype 19A. The use of PCV7 resulted in serotype 19A acting as a replacement serotype for nasopharyngeal carriage. The judicious use of antibiotics to preserve their usefulness and limit the likelihood of the emergence of resistant serotypes remains a critical strategy to contain antibiotic resistance.

### Morbidity and Mortality Associated with Community-Acquired Pneumonia and Pneumococcal Disease

Table 2 shows the mortality rates associated with CAP in several Asia-Pacific countries<sup>12-20</sup>

Table 3 shows the mortality rate in patients with pneumococcal pneumonia reported in a range of different populations. The striking feature about the mortality rate is that it has remained almost unchanged during the past 60 years, at about 12%.<sup>21-24</sup>

Significant morbidity and mortality are associated with

**Table 4: Case Fatality Rate for Pneumococcal Disease in the United States**

Condition	Fatality Rate
Pneumococcal bacteremia	about 20%; up to 60% among the elderly
Pneumococcal meningitis	about 30%; up to 80% in the elderly
Pneumococcal pneumonia	5% to 7%; higher in the elderly

both invasive and noninvasive pneumococcal disease. Table 4 shows the case fatality rate for pneumococcal disease in adults in the United States.<sup>25</sup>

### Treatment Challenges

Being a gram positive organism, the propensity of *S. pneumoniae* to develop antimicrobial resistance is on the lower side. However, development of antimicrobial resistance in *S. pneumoniae* has been a major problem across many regions worldwide. In India, the limited studies have not shown an alarming trend of antimicrobial resistance development in pneumococcus, except for trimethoprim-sulfamethoxazole.<sup>26,27</sup> However, resistance has been increasing, and some important resistant strains have been identified in our country as well. ANSORP collaboration observed the pneumococcal resistance to erythromycin, to increase from 1.3% in 2000-01 to 17.4% in 2008-09.<sup>27</sup>

The impact of antimicrobial resistance on outcomes of severe pneumococcal disease has demonstrated mixed results. Investigators have observed that in severe pneumococcal disease, case fatality rate remains high despite appropriate antimicrobial therapy and intensive care.<sup>28-32</sup> Antimicrobial resistance is not the major determinant of outcomes in such severe presentations, but timely diagnosis and intervention is the key to a possible improvement in the disease outcomes. *S. pneumoniae* infection is known to result in an inflammatory reaction in the body through the release of multiple pro-inflammatory cytokines, and the

severity of inflammatory reaction accounts for the pathogenesis and outcomes of pneumococcal disease. It has also been observed that penicillin reduces mortality only in those patients, who survive for more than 5 days.<sup>33</sup> Old age and comorbidities have been clearly associated with poor outcomes in CAP. Other associated factors include multilobar involvement, septic shock, ICU admission, need for mechanical ventilation and bacteremia.<sup>28,34</sup> Smoking, chronic glucocorticoid treatment and serotype 3 pneumococcal infections have been identified as independent risk factors for septic shock.<sup>34</sup>

Thus, worldwide, pneumococcal disease is a major cause of morbidity and mortality, accounting for an estimated 1.6 million deaths annually. These figures are a cause for concern, and underscore the need for vaccination against pneumococcal disease.

### Barriers to Adult Immunization

No intervention except the provision of clean drinking water and sanitation, has demonstrated a public health impact as significant as vaccination.<sup>35</sup> Immunization has a major role in management of diseases across all age groups. Despite this, the significance of immunization is realized mostly in children, and remains underrated in adults. Despite clear recommendations, many adults do not receive the vaccines, as barriers to immunization exist at different levels.

Recommendation from the treating physicians is a key factor, that can determine the success of adult immunization especially from our country perspective. Failure to offer vaccination to the desired patient can result in the missed opportunity. Awareness of the physicians, about the recommendations and practice guidelines for various vaccines,

is another determinant of the success of adult immunization. Patients' vaccination status is often difficult to determine, record and trace. The concept of specialized vaccination centres is currently at a very nascent stage in our country.

The attitudes and beliefs of the patients also play a major part in determining the success of adult immunization. The perceived usefulness of adult vaccination is practically absent amongst the general population. The concept of re-imburement or insurance support for adult vaccination does not exist in our country. A healthcare intervention is sought only in the presence of clinical or epidemiological concerns (like the influenza viral pandemic), while immunization of otherwise healthy adults is, at the best, considered as a lifestyle measure rather than an important preventive medical intervention. In fact, vaccination is one of the keys to healthy ageing, a fact that is hardly known or believed in our country.<sup>36</sup>

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