Antimicrobial Susceptibility of Streptococcus Pneumoniae


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Abstract

Streptococcus pneumoniae (pneumococcus) remains an important cause of pneumonia, meningitis, bacteremias, and acute otitis media worldwide. Antimicrobial resistance among pneumococci has augmented dramatically over the past three decades, and is influenced by patterns of antibiotic use. Considerable geographic variation in susceptibility necessitates regional resistance tracking. The objective of the study is to assess antibiotic susceptibility of S. pneumoniae to Beta lactam and Macrolide antimicrobial agents. The data was collected retrospectively from antibiotic susceptibility reports from different laboratories and assessed Streptococcus susceptibility to multiple agents. Aggregating data is a feasible and timely method of monitoring regional susceptibility patterns and may also prove beneficial in measuring the effects of interventions to decrease antimicrobial resistance and guide in empiric antimicrobial treatment.

Key words: Streptococcus pneumoniae, Susceptibility, Antimicrobial resistance, Beta lactam, Macrolides.

Introduction

Streptococcus pneumoniae (pneumococcus) is the most common cause of community-acquired pneumonia (CAP) in adults, accounting for 30 to 70% of cases requiring hospitalization. Clinical manifestations of pneumococcal infections are varied and include asymptomatic colonization, upper respiratory tract infections, otitis media, sinusitis, conjunctivitis, bacteremia (with or without a definite site of infection), pneumonia, empyema, meningitis, endocarditis, septic arthritis, cellulitis, and so forth.[1]

Globally, pneumococcal diseases account for 1 to 2 million deaths annually in both extremes of age.[2] S. pneumoniae often colonizes the nasopharynx of healthy children and can then, in specific situations, spread to the lungs, paranasal tissues and cause mucosal infections, such as pneumonia, or invade the bloodstream and cause
meningitis. Anti-microbial resistance of *S. pneumoniae* to β-lactams, macrolides, and other antibiotic classes has increased dramatically throughout the world in the past three decades.\(^{[4-6]}\)

The infections caused by this pathogen are among those least likely to be resolved without effective antibiotic treatment. However, since 1980s, a dramatic increase in antibiotic resistance among *S. pneumoniae* has been observed in many parts of the world.\(^{[7-11]}\) Treatment failure associated with antibiotic-resistant pneumococci has been reported for patients with pneumonia.\(^{[11, 12]}\) High level of antibiotic use is probably the main factor driving the emergence of resistance.\(^{[13]}\)

In the late 1970s, strains of streptococci displaying resistance to penicillin were described in South Africa and Spain. By the early 1990s, penicillin-resistant clones of *S. pneumoniae* spread rapidly across Europe and globally.\(^{[14-16]}\)

Additionally, resistance to macrolides and other antibiotic classes escalated in tandem with penicillin resistance. Currently, 15 to 30% of *S. pneumoniae* worldwide are multidrug-resistant (MDR) (i.e., resistant to ≥ 3 classes of antibiotics). Despite the dramatic escalation in the rate of antimicrobial resistance among streptococci worldwide, the *clinical impact* of antimicrobial resistance is difficult to define. Treatment failures due to antibiotic-resistant streptococci have been reported with meningitis, otitis media, and lower respiratory tract infections, but the relation between drug resistance and treatment failures has not been convincingly established.\(^{[17-18]}\)

**Mechanisms of Resistance**\(^{[14, 16]}\)

Resistance of *S. pneumoniae* to β-lactams is due to genetic mutations leading to alterations in three or four of the five high-molecular-weight penicillin-binding proteins (PBPs). The degree of *S. pneumoniae* resistance is dependent on which PBPs are involved and the affinity of the β-lactam agent to the PBP. The differences in expression of these PBPs explain the differences in susceptibility to a variety of β-lactams.

*S. pneumoniae* resistance to macrolides occurs primarily through two mechanisms: active drug efflux (M phenotype) or ribosomal modification (MLS\(_{β}\) phenotype). Active drug efflux confers resistance to all agents within the class, whereas ribosomal modification confers resistance not only to the macrolides but also to
clindamycin and streptogramins. Approximately 75% of macrolide-resistant *S. pneumoniae* found in the United States is attributable to active drug efflux.

Of late, in a US study, for isolates collected between 2000 and 2004, 21.2% resistance for penicillin has been reported.[19] Another recent survey of eight European countries has observed penicillin resistance as 24.6% in *S. pneumoniae*,[20] whereas, a study done in Australia[21] revealed 6.7% penicillin resistance. A Malaysian study has depicted 21.6% penicillin resistance with 30% strains showing penicillin intermediate sensitivity.[22] Increasing emergence of resistant strains of *S. pneumoniae* is of major concern, especially in cases of meningitis, as it can lead to treatment failures; moreover, it prolongs the stay in the hospital, thus increasing the morbidity and mortality. PRP contain low-affinity penicillin binding proteins and also often produce abnormal indirectly cross-linked cell walls.[23] In India there are only few reports that show the resistance pattern in *S. pneumoniae*. Surveillance for resistance of *S. pneumoniae* has noticed the upsurge of intermediate sensitivity from CMC Vellore in the southern part of India,[24] whereas, a study done in North India[25] has shown 2.3% resistance. Yet another collaborative study from eight Asian countries including India has revealed 35.1% total resistance in *S. pneumoniae*.[26] The objective of the study is to assess antibiotic susceptibility of *S. pneumoniae* to Beta lactam and Macrolide anti-microbial agents.

**METHODODOLOGY**

The data of antimicrobial susceptibility was retrospectively collected from all clinical laboratories in Chidambaram. The data covers the last 5 year period (2006-2010) for which complete susceptibility data were available at the time of the inquiry. We compiled total numbers of *S. pneumoniae* isolates identified from the labs along with the percent of intermediate and resistant isolates, focusing on nonsusceptibility to penicillin, macrolides, and extended-spectrum cephalosporins (e.g., cefotaxime, ceftriaxone). We defined nonsusceptible isolates as those that were of intermediate and high-level resistance or those were simply described as not susceptible to the antibiotic tested. If only a subset of isolates were tested against erythromycin and extended-spectrum cephalosporins, we excluded these results from the aggregated total for erythromycin,
cephalosporins, or both. We also calculated the percent of laboratories that included *S. pneumoniae* susceptibility testing to a variety of other antimicrobial.

**RESULTS AND DISCUSSION**

Eight laboratories completed the surveys; these laboratories conduct antibiotic susceptibility and other testing for a total of 43 hospitals. Ninety-five percent included inpatient, and 5% included outpatient isolates.

When asked how pneumococcal isolates with intermediate susceptibility were categorized, survey responders stated that their laboratory characterized these isolates as intermediate (37%), resistant (32%), susceptible (5%), and nonsusceptible (26%). This question did not specify the antibiotic tested. Only 25% laboratories generated susceptible data that included data distinguishing isolates intermediate and resistant to penicillin; 75% indicated whether the isolates were susceptible or nonsusceptible.

Of the 8 laboratories whose pneumococcal antibiotic susceptibility testing results were summarized, with penicillin-susceptibility results in a format that could be aggregated for the year in question. The proportion of laboratories in each site that generated usable penicillin susceptibility data ranged from 70% to 100%. Susceptibility-testing results for macrolides (63%) and third-generation cephalosporins (57%). The proportion of laboratories for which this susceptibility information was in a format that could be aggregated, however, was smaller for macrolides (44%) and third-generation cephalosporins (39%).

The proportions of pneumococcal isolates nonsusceptible to a third-generation cephalosporin and to erythromycin were lower than the proportion of penicillin-nonsusceptible isolates. In addition to penicillin, cephalosporins, and macrolides, obtained susceptibility testing results for a variety of other antibiotics that included the following: trimethoprim/sulfamethoxazole (35%), vancomycin (59%), clindamycin (47%), gentamicin (3.9%), and one or more fluoroquinolones (14%). Thirty-eight percent of data returned for analysis also included antimicrobial susceptibility testing results for various gram-negative bacteria. Penicillin resistance among *S. pneumoniae* is a global problem. Laboratory mutants of pneumococci resistant to penicillin were selected as early as the 1940s.[27, 28] It was 20 years before the first clinical isolate, with reduced susceptibility to penicillin, was reported from Boston, Massachusetts.[29] A 4% total
resistance to penicillin and 10% intermediate resistance, as observed in the present study, shows the increasing emergence of resistance strains of *S. pneumoniae* in India. Earlier, a three-year surveillance for penicillin resistance from Vellore revealed 4.6% of intermediate resistance to penicillin,[24] whereas, a North Indian study reported 15.2% (26/170) intermediate resistance and 2.3% (4/170) penicillin resistance.[25] The difference in the resistance pattern of *S. pneumoniae* as observed in South and North Indian studies has been explained by Lalitha et al. on the basis of the high genetic diversity that exists among strains isolated from different geographical areas within India.[30]

Pneumococcal resistance rates tend to increase moving along the spectrum of isolates obtained from bloodstream to lower respiratory tract to upper respiratory tract.[31] This fact potentially confounds point comparisons of resistance rates since a marked increase in resistance can result from testing a preponderance of upper respiratory isolates, rather

During the late 1980s, the identification of a high prevalence of erythromycin-resistant strains in South Africa that was associated with multiple resistance in pneumococci (isolated from healthy children in the community) led to the concern that resistance may increase in countries where the drug was widely used.[32-34] In our set up, resistance to erythromycin was observed in 14% of the cases. Macrolide resistance in case of *S. pneumoniae* was due to either of the two mechanisms – modification of the drug binding site regulated by the erm(B) gene, or due to the active efflux mechanism, which is regulated by mef(A) gene.[35]

The observed progression of both beta lactam and macrolide resistance is of particular concern. The increase in penicillin resistance appears to correlate with an increase in high-level rather than intermediate-level resistance and high-level penicillin resistance has been associated with worse outcomes for pneumococcal infections.[36] The increased macrolide resistance is most likely mediated by a low-level efflux pump since clindamycin susceptibility remained stable over the study period.[37] Erythromycin susceptibility generally predicts that of azithromycin and clarithromycin.[38] Increased macrolide resistance is disturbing since erythromycin, azithromycin, and clarithromycin are some of the most commonly prescribed antibiotics for outpatient treatment of
community-acquired pneumonia and low-level macrolide resistance has been associated with clinical failure.[39-41]

Strength of the study

This study suggests the possible emergence of penicillin-resistant as well as multidrug-resistant *S. pneumoniae* strains in the community. Penicillin as the best empirical choice for treatment of infections with *S. pneumoniae* may need reconsideration. It can no longer be considered a drug of choice in the treatment of life-threatening invasive conditions caused by *S. pneumoniae*. Our study also pointed out that not only penicillin, but other alternative antibiotics such as cephalosporins, erythromycin, ciprofloxacin, and cotrimoxazole showed resistance against the isolates, and should be used carefully in future. This study will aid the clinicians to treat the patients better in case of infection with *S. pneumoniae*.

Table 1: Percentage of Streptococcus pneumoniae isolates nonsusceptible to penicillin

<table>
<thead>
<tr>
<th>Laboratory</th>
<th>Non susceptible isolates</th>
<th>Total no. isolates tested</th>
<th>% non-susceptible</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sastra</td>
<td>168</td>
<td>845</td>
<td>19.9</td>
</tr>
<tr>
<td>Rmmc lab</td>
<td>107</td>
<td>577</td>
<td>18.5</td>
</tr>
<tr>
<td>Murgesh</td>
<td>115</td>
<td>550</td>
<td>20.9</td>
</tr>
<tr>
<td>Vijaya</td>
<td>432</td>
<td>1,037</td>
<td>41.7</td>
</tr>
<tr>
<td>Natarajan</td>
<td>171</td>
<td>886</td>
<td>19.3</td>
</tr>
<tr>
<td>Twenty four seven</td>
<td>505</td>
<td>1,291</td>
<td>39.1</td>
</tr>
<tr>
<td>Kumaran</td>
<td>85</td>
<td>383</td>
<td>22.2</td>
</tr>
<tr>
<td>Paramashivan</td>
<td>315</td>
<td>1,037</td>
<td>30.4</td>
</tr>
<tr>
<td>Total</td>
<td>1898</td>
<td>6,606</td>
<td>28.7</td>
</tr>
</tbody>
</table>
Table 2: Percentage of Streptococcus pneumoniae isolates nonsusceptible to third generation cephalosporins

<table>
<thead>
<tr>
<th>Laboratory</th>
<th>Non susceptible isolates</th>
<th>Total no. isolates tested</th>
<th>% non-susceptible</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sastra</td>
<td>54</td>
<td>357</td>
<td>15.1</td>
</tr>
<tr>
<td>Rmmc lab</td>
<td>2</td>
<td>84</td>
<td>2.4</td>
</tr>
<tr>
<td>Murgesh</td>
<td>14</td>
<td>412</td>
<td>3.4</td>
</tr>
<tr>
<td>Vijaya</td>
<td>19</td>
<td>267</td>
<td>7.1</td>
</tr>
<tr>
<td>Natarajan</td>
<td>34</td>
<td>419</td>
<td>8.1</td>
</tr>
<tr>
<td>Twenty four seven</td>
<td>53</td>
<td>476</td>
<td>11.1</td>
</tr>
<tr>
<td>Kumaran</td>
<td>104</td>
<td>543</td>
<td>19.2</td>
</tr>
<tr>
<td>Paramashivan</td>
<td>222</td>
<td>1,272</td>
<td>17.5</td>
</tr>
<tr>
<td>Total</td>
<td>502</td>
<td>3,830</td>
<td>13.1</td>
</tr>
</tbody>
</table>

Table 3: Percentage of Streptococcus pneumoniae isolates nonsusceptible to third generation Erythromycin.

<table>
<thead>
<tr>
<th>Laboratory</th>
<th>Non susceptible isolates</th>
<th>Total no. isolates tested</th>
<th>% non-susceptible</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sastra</td>
<td>178</td>
<td>805</td>
<td>22.1</td>
</tr>
<tr>
<td>Rmmc lab</td>
<td>133</td>
<td>460</td>
<td>28.1</td>
</tr>
<tr>
<td>Murgesh</td>
<td>57</td>
<td>405</td>
<td>14.1</td>
</tr>
<tr>
<td>Vijaya</td>
<td>64</td>
<td>596</td>
<td>10.7</td>
</tr>
<tr>
<td>Natarajan</td>
<td>23</td>
<td>128</td>
<td>11.7</td>
</tr>
<tr>
<td>Twenty four seven</td>
<td>92</td>
<td>577</td>
<td>15.9</td>
</tr>
<tr>
<td>Kumaran</td>
<td>140</td>
<td>684</td>
<td>20.5</td>
</tr>
<tr>
<td>Paramashivan</td>
<td>58</td>
<td>287</td>
<td>20.2</td>
</tr>
<tr>
<td>Total</td>
<td>737</td>
<td>3,942</td>
<td>18.7</td>
</tr>
</tbody>
</table>

CONCLUSION

Drug-resistant *S. pneumoniae* continues to increase, causing significant morbidity and mortality. The 3 major factors that have led to development of drug-resistance include: inappropriate use of antibiotics, prolonged dosage regimens, under dosing. Increasing emergence of the resistant strains of *S. pneumoniae* in the community set up requires continuous monitoring and a restricted use of antibiotics to keep a check on its
resistance pattern, for an effective treatment plan. Therefore, there should be a restraint for the indiscriminate use of antibiotics, to limit the surfacing of resistant strains. Emergence of resistant strains and also the MDR strains of *S. pneumoniae* need continuous local as well as global monitoring of the sensitivity pattern, so as to plan the line of treatment. Education of health care providers and the public is essential for ensuring the rational use of antimicrobials. Pharmacists can play a significant role in educating both groups, assuming roles as educators to assist in disseminating vital information that encourages the rational use of antimicrobials.

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**REFERENCES**


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