Antimicrobial resistance in clinical isolates of 
*Streptococcus pneumoniae* in a tertiary hospital in Kuwait, 1997–2007: Implications for empiric therapy

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**KEYWORDS**
Streptococcus pneumoniae; Antibiotic resistance; *E* test; Penicillin resistance; Cefotaxime resistance; Erythromycin resistance

**Summary**
Objective: This study evaluated antibiotic resistance trends in *Streptococcus pneumoniae* isolated in a tertiary hospital in Kuwait and its implications for empiric therapy.

Materials and methods: Antimicrobial susceptibility of 1353 strains of *S. pneumoniae* isolated from clinical specimens during 1997–2007 was performed by disc diffusion method. MIC was determined by *E* test. The results were compared for 1997–2001, 2002–2005 and 2006–2007.

Results: The prevalence of resistance for the respective periods were as follows: penicillin, 51.3%, 61.3% and 54.5%; erythromycin, 31.2%, 36.7% and 37.7%; tetracycline, 30.8%, 45.3% and 41.3%; co-trimoxazole, 49.5%, 58.5% and 62.8%; clindamycin, 20.4%, 20.6% and 24.5% and chloramphenicol, 8.1%, 8.9% and 3.7%. All were susceptible to vancomycin and rifampicin. For oxacillin-resistant isolates, penicillin resistance was rare (0.8%) with the new non-meningeal breakpoint. However, using the meningeal breakpoints, resistance increased for penicillin from 0.6%, to 28.7%, for cefotaxime from none to 16.5%, and for ceftriaxone from none to 7%. Intermediate resistance to meropenem increased from 1.7% to 22.4%. Multiple drug resistance increased from 22.4% to 37.8%.

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Conclusion: The study demonstrated that antimicrobial resistance of *S. pneumoniae* is increasing in Kuwait. However, the results of MIC determinations indicated that penicillin can still be used for therapy of non-meningeal infections. High prevalence of erythromycin resistance suggests that therapy of pneumonia with a macrolide alone may result in failure and should be based on results of susceptibility testing.

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Introduction

*Streptococcus pneumoniae* continues to be a common cause of serious infections such as pneumonia, bacteremia, meningitis, otitis media and sinusitis [1]. In recent years, resistance of *S. pneumoniae* to penicillin and other β-lactams as well as non-β-lactam antibiotics has been increasing in many countries [2—4]. This limits therapeutic options available for the treatment of life-threatening pneumococcal infections. The upward trend of resistance is likely to continue because of the continuing antibiotic pressure [2,5]. The clinical impact of pneumococcal resistance varies with the site of infection and the ability of immune response to clear the infection [6]. Since the mortality rate of invasive infections caused by resistant pneumococci is high [1], rapid and accurate detection of resistance may improve the selection of appropriate antibiotics and better treatment outcomes.

The incidence of penicillin resistance is quite variable geographically and may reflect the local level of antibiotic usage [3—5]. Since most pneumococcal infections are treated on an empirical basis, knowledge of the susceptibility patterns of local isolates is important for proper management of these infections. This paper presents the results of a laboratory-based surveillance of antibiotic resistance in *S. pneumoniae* obtained in a tertiary hospital in Kuwait, during the period of 1997–2007.

Materials and methods

Bacterial isolates

Consecutive single isolates of *S. pneumoniae* isolated from clinical specimens received in the Microbiology laboratory of the Al-Amiri Hospital in Kuwait during the period of January 1997 to December 2007 were included in this study. The Al-Amiri hospital is a 500 bed tertiary hospital. It is one of the teaching hospitals affiliated with Kuwait University Medical School. It has Medical, Surgical, Pediatrics, Nephrology, Gastroenterology, Cardiology, Intensive Care as well as Outpatient departments.

*S. pneumoniae* was isolated and identified using traditional bacteriological methods including colony morphology, optochin susceptibility and bile solubility test. The isolates were preserved at −80°C in 10% (w/v) skimmed milk.

Antimicrobial susceptibility tests

*S. pneumoniae* was screened for susceptibility to penicillin with a 1 μg oxacillin disc (BBL Microbiology Systems, Cockeysville, MD) by the disc diffusion method according to the performance standards from CLSI [7]. Isolates with a zone diameter ≥20 mm were considered susceptible (S) to penicillin and ≤19 mm, either intermediate resistant (I) or resistant (R). Other antimicrobial agents tested by disc diffusion were erythromycin, clindamycin, tetracycline, chloramphenicol, cotrimoxazole, vancomycin and rifampicin. Zone diameter interpretive standards were defined according to the CLSI guideline [7]. Minimum inhibitory concentrations (MICs) for penicillin G, cefotaxime, ceftriaxone, cefuroxime, meropenem, imipenem, erythromycin, clindamycin, chloramphenicol, vancomycin and ciprofloxacin were determined with *E* test strips (PDM Epsilometer, AB Biodisk, Solna, Sweden) according to the recommendations of the manufacturer. Quality control was carried out according to the recommendation of CLSI using *S. pneumoniae* strain ATCC 49619 [7] and a known penicillin susceptible local isolate as the control strains. The MIC was interpreted according to the CLSI breakpoints [7]. For penicillin non-meningeal, MIC ≤2 mg/l S, 4 mg/l I, ≥8 mg/l R and meningeal breakpoints, MIC ≤0.06 mg/l S, 0.1—1 mg/l I, ≥2 mg/l R were used [8].

Analysis of results

Results

In total, 1353 *S. pneumoniae* isolates consisting of 472 obtained in 1997–2001, 532 in 2002–2005 and 349 obtained in 2006–2007. They were isolated from respiratory tract (994, 73.5%), blood (121, 8.9%), CSF (15, 1.1%), ear (97, 7.2%) and eye (126, 9.3%) samples. The age of the patients ranged between 1 month and 85 years. Four hundred and sixty (34.0%) of them were 12 years old or younger while 893 (66.0%) of them were older.

The results of the disc diffusion test are summarized in Fig. 1. In total, 758 isolates (56.0%) were resistant to oxacillin during the surveillance period. The prevalence of oxacillin resistance increased from 51.3% in 1999–2001 to 61.3% in 2002–2005 and then declined to 54.4% in 2006–2007. Similarly, the prevalence of tetracycline resistance increased from 30.8% in 1999–2001 to 45.3% in 2002–2005 and declined to 41.5% in 2006–2007. The prevalence of erythromycin resistance increased slightly from 31.2% in 1999–2001 to 36.7% and 37.7% in 2002–2005 and 2006–2007 respectively whereas the prevalence of co-trimoxazole resistance increased steadily from 49.5% in 1999–2001 to 58.5% in 2002–2005 and 62.8% in 2006–2007. Chloramphenicol resistance declined from 8.1% in 1999–2001 and 8.9% in 2002–2005 to 3.7% in 2006–2007. There was no significant change in the prevalence of clindamycin resistance which was detected in 20.4%, 20.6% and 24.5% respectively during the three periods of the study. All of the isolates were susceptible to vancomycin and rifampicin.

Results of MIC determination confirmed the results of disc diffusion method. The oxacillin-susceptible isolates were also susceptible to penicillin G and other β-lactam antibiotics. Table 1 shows the susceptibility of the oxacillin-resistant *S. pneumoniae* isolates to β-lactam antibiotics based on MIC determination. Based on the meningeal breakpoints, 9.5%, 4.5% and none of the oxacillin-resistant isolates were susceptible to penicillin G, whereas the majority expressed intermediate resistance (89.9%, 89.8% and 71.3%), and 0.6%, 5.7% and 28.7% were resistant during the three periods of study respectively. However, according to the new non-meningeal breakpoint [8], all isolates were susceptible to penicillin (MIC ≤ 2 mg/l) during the first and second periods and 0.8% of the isolates during the third period expressed intermediate resistance.

The MIC of penicillin, ampicillin and amoxicillin–clavulanate showed essentially equivalent results when compared (not shown). The MIC of all β-lactam agents increased as penicillin MICs increased throughout the study period. This was true for cefuroxime, cefotaxime, ceftriaxone, meropenem and imipenem. For blood and CSF isolates, MIC studies for penicillin showed increase in fully resistant isolates (by meningeal breakpoints), 10.7% were resistant during 2006–2007 compared to 2.2% that were resistant during 2002–2005.

When the prevalence of oxacillin-resistant isolates of *S. pneumoniae* was assessed according to age groups, children (≤12 years) showed higher rate of oxacillin-resistant isolates compared to adolescents and adults during all the three study periods.
Table 1  Resistance rates (%) of β-lactam agents by E test for OX-R isolates of S. pneumoniae.

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<td></td>
<td>I (%)</td>
<td>R (%)</td>
<td>I (%)</td>
<td>R (%)</td>
</tr>
<tr>
<td>Penicillin G</td>
<td>0.06 S, 0.1–1 I, ≥2 R</td>
<td>89.9 0.6</td>
<td>89.8 5.7</td>
<td>71.3 28.7</td>
</tr>
<tr>
<td></td>
<td>≤2 S, 4 I, ≥8 R</td>
<td>0 0</td>
<td>0 0</td>
<td>0.8 0</td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>≤0.5 S, 1 I, ≥2 R</td>
<td>9.6 0</td>
<td>16.8 5.3</td>
<td>30.7 16.5</td>
</tr>
<tr>
<td></td>
<td>≤1 S, 2 I, ≥4 R</td>
<td>0 0</td>
<td>4.9 0.4</td>
<td>16.5 0</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>≤0.5 S, 1 I, ≥2 R</td>
<td>13.5 0</td>
<td>17 1.8</td>
<td>45.3 7</td>
</tr>
<tr>
<td></td>
<td>≤1 S, 2 I, ≥4 R</td>
<td>0 0</td>
<td>1.8 0</td>
<td>7 0</td>
</tr>
<tr>
<td>Cefuroxime sodium</td>
<td>≤0.5 S, 1 I, ≥2 R</td>
<td>14 30</td>
<td>19.3 32.1</td>
<td>13.1 56.5</td>
</tr>
<tr>
<td>Meropenem</td>
<td>≤0.25 S, 0.5 I, ≥1 R</td>
<td>— —</td>
<td>1.7 0</td>
<td>22.4 0.8</td>
</tr>
<tr>
<td></td>
<td>≤0.12 S, 0.25–0.5 I, ≥1 R</td>
<td>— —</td>
<td>4.1 0</td>
<td>34.6 0</td>
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Table 2 shows the resistance rates of non-β-lactam antibiotics in the oxacillin-resistant (OX-R) isolates. The result shows that 18.3%, 14.3% and 12.5% of OX-R isolates were resistant to chloramphenicol during the three periods respectively. More than 50% of them were resistant to erythromycin and 26.2% and 35.3% of OX-R isolates were resistant to clindamycin during the latter two periods respectively (Table 2). All clindamycin-resistant isolates were also resistant to erythromycin and isolates with erythromycin MIC ≥64 mg/l were resistant to clindamycin. However, isolates with erythromycin MIC 1–32 mg/l were susceptible to clindamycin. Ciprofloxacin resistance was detected in the OX-R isolates only during 2002–2005.

Multiple drug resistance

When patterns of multiple drug resistance (resistance to three or more classes of antibiotics) were analyzed, during 1997–2001 and 2002–2005, co-resistance to penicillin (OX-R) plus resistance to at least two of the following drugs, erythromycin, tetracycline, chloramphenicol and co-trimoxazole was found in 22.4% and 37.8% of all isolates respectively. Multiple drug resistance was seen in 10% and 11.4% of the penicillin susceptible isolates and in 43.4% and 57.4% of the OX-R isolates respectively. Co-resistance to penicillin (OX-R) with erythromycin, tetracycline, clindamycin and co-trimoxazole was the most common pattern of multiple drug resistance.
Discussion

This study provided an opportunity to observe changes in the prevalence of antibiotic resistance in clinical isolates of S. pneumoniae in a tertiary hospital in Kuwait during the past decade. The results demonstrated that the rate of antimicrobial resistance in S. pneumoniae isolated in this hospital was increasing for the commonly used antibiotics. Except for a reduction in penicillin resistance during 2006–2007 (Fig. 1), the results for MIC determinations for OX-R isolates (Table 1), showed increases in isolates that were fully resistant to penicillin (0.6%, 5.7% and 28.7%) by meningeval breakpoints [8] throughout the study period and when compared to previous reports [9–12]. The increasing prevalence of penicillin resistance in S. pneumoniae obtained in this study is consistent with recent reports of penicillin resistance in other countries in the region such as Saudi Arabia [3,13] and Egypt [14].

The present level of penicillin resistance of S. pneumoniae isolates in Kuwait has implications for therapy of pneumococcal meningitis, due to low concentrations of the antibiotic in CSF [9]. Evidence has been increasing for years that penicillin is effective against pneumococcal pneumonia at concentrations that would fail for meningitis [15]. According to the new FDA approved and CLSI adopted non-meningeval breakpoints for penicillin [8], penicillin resistance is rare among our isolates and most cases of non-meningeval pneumococcal infections are likely to respond to penicillin therapy. In this study, penicillin, ampicillin and amoxicillin/clavulanate had essentially equivalent MIC values for the isolates. Hence, high doses of oral amoxicillin (MIC ≤2 mg/l) may be effective against most of the isolates [16].

We observed that the MIC of other β-lactam agents increased as penicillin MIC increased (Table 1) as has also been reported by others [9], probably because these antibiotics bind to the same penicillin binding proteins [8]. A previous study provided evidence suggesting that intravenous cefotaxime 1.5 g eight hourly was an effective therapy for bacteremic pneumococcal pneumonia due to cefotaxime-resistant isolates with MICs up to 4 mg/l [17], other studies have reported treatment failures with cefotaxime [18]. Therefore, considering the high prevalence of cefotaxime resistance observed in this study, intravenous and oral cefuroxime as well as other broad spectrum cephalosporins should be used with caution. The increase in resistance to cefotaxime, ceftriaxone and meropenem is of particular concern for empiric therapy of pneumococcal meningitis as it further limits the choice of antibiotics available for the therapy of pneumococcal meningitis [19].

Although all strains were susceptible to vancomycin, it is not recommended for monotherapy in meningitis because of its variable CSF levels due to difficulty in crossing the blood brain barrier [19]. Although chloramphenicol resistance was low among our isolates, it is rarely used nowadays because of the risk of aplastic anemia. In addition, therapeutic failure with chloramphenicol in pneumococcal meningitis has been reported [20].

As observed in other studies [9], clindamycin resistance indicated high level resistance to erythromycin, since all clindamycin resistant isolates had erythromycin MIC ≥64 mg/l.

The in vitro/in vivo paradox with macrolide group of antibiotics, referring to discordance between reported in vitro resistance and clinical success, has been documented in respiratory infections. Macrolides are commonly prescribed for the management of community-acquired pneumonia in outpatients, with the newer generation macrolides (clarithromycin and azithromycin) often used as monotherapy [21]. However, the high prevalence of erythromycin resistance (37.7%) in S. pneumoniae with predominance of highly resistant strains (MIC ≥64 mg/l) observed in this study is of concern for empiric therapy of community-acquired pneumonia because therapeutic failure with these agents has been reported [18], and many clinicians caution against using these agents as monotherapy in areas with high prevalence of resistance [21]. Therefore, based on the results of this study, the use of macrolides alone in pneumococcal diseases may result in clinical failure of therapy [22].

The high prevalence of tetracycline and co-trimoxazole resistance (41.3% and 62.8% respectively) reported in this study adds further problems to the management of pneumococcal diseases.

The emergence of penicillin resistance in S. pneumoniae resulted in the increased use of newer fluoroquinolones for empiric therapy of community-acquired pneumonia [15]. This also resulted in the emergence of strains that were resistant to fluoroquinolones arousing concern with regard to treatment of pneumococcal disease. The spread of fluoroquinolone-resistant clones may cause rapid increase in resistance with widespread use of these agents as has been reported from Canada and Hong Kong [3,5]. A weakness of this study is that ciprofloxacin resistance was tested only in the oxacillin-resistant isolates and the results reported may not reflect the true prevalence of ciprofloxacin resistance in our pneumococcal population.

Multi drug resistant pneumococci have become a serious clinical problem in recent years which
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is confirmed by the results that more than one third (37.8%) of isolates in this study were resistant to multiple antibiotics. The increase in resistance occurred mostly among penicillin non-susceptible isolates as observed by others [9,22]. Since antibiotics are available only by prescription with no over the counter sales in Kuwait, antibiotic misuse and failure to follow antibiotic policy guidelines in the private sector may contribute to the increasing resistance observed in this study. Alternatively, importation of resistant clones into Kuwait by expatriate workers from countries with high prevalence of antibiotic-resistant pneumococci [9,22] or returning patients who sought medical care abroad could be a major reason for the increase in resistance of S. pneumoniae observed in this study.

In conclusion, this surveillance study clearly documents increase in the prevalence of antibiotic resistance and multiple drug resistance of S. pneumoniae in Kuwait. Although β-lactam resistant strains of S. pneumoniae are increasing in Kuwait, the MIC studies indicate that the effect of the β-lactam resistance affects mainly the therapy of meningitis and not that of non-meningeal infections. This supports the continued use of β-lactam agents such as penicillin G, ampicillin or amoxicillin in non-meningeal infections. However, oral broad spectrum cephalosporins should be used with caution considering the high level of resistance to cefuroxime detected in this study. Erythromycin resistance is high in Kuwait and therapy of pneumonia with a macrolide alone may result in failure. In view of increasing macrolide resistance in S. pneumoniae reported in this study and elsewhere [4,9,21], treatment of community-acquired pneumonia should be based on guidelines produced by Gulf Corporation Council CAP Working Group (GCC-CAPWG) [23]. New fluoroquinolones should be used discriminately, since clonal spread of fluoroquinolone-resistant strains may cause rapid increase in resistance and loss of efficacy of these agents. Continuous surveillance of antimicrobial resistance among pneumococcal isolates in local regions, pneumococcal vaccination and appropriate use of antibiotics are essential to control this problem.

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