Molly Johnny^a
S. Narayanan^b
M.A. Murad^a

Departments of

^a Laboratory Medicine and

^b Medicine, Al-Amiri Hospital,

Ministry of Public Health, Kuwait

Rising Incidence of Beta-Lactam Resistance among Pneumococci in Kuwait: Failure of Cefotaxime Therapy in Pneumococcal Meningitis

Key Words

Streptococcus pneumoniae
Pneumococcal meningitis
Penicillin resistance
Cefotaxime resistance
Chloramphenicol

Abstract

Objective: Pneumococcal resistance to antimicrobial agents has become a global problem. This study was done to evaluate the resistance of *Streptococcus pneumoniae* (pneumococci) to penicillin G in Kuwait, and to assess the efficacy of other β -lactam agents (cefotaxime or ceftriaxone) in the management of invasive pneumococcal infections. **Methods:** Surveillance studies were done in a general teaching hospital in Kuwait for penicillin G resistance (intermediate or high level resistance) of pneumococci isolated from clinical specimens by agar diffusion method using oxacillin (1 μ g) disc. In cases of pneumococcal meningitis, minimum inhibitory concentrations (MICs) of penicillin and cefotaxime were determined by agar dilution method, to differentiate intermediate resistance and high level resistance. **Results:** An increase in the incidence of penicillin G-resistant pneumococci from 20.6% (94 out of 457 isolates) for the period 1985–1988 to 28.5% (40 out of 140 isolates) during 1992–1994 and 38.3% (43 out of 112 isolates) during 1995/96 was observed. During the period 1992–1994, 40–45% (7 out of 16 isolates) blood culture isolates of pneumococci were intermediate or highly resistant to penicillin. Therapy with cefotaxime or ceftriaxone produced a positive outcome in 6 of the 7 patients. However, failure of cefotaxime therapy to achieve a cure was noted in 1 patient who had systemic lupus erythematosus and intermediate resistant (penicillin MIC 0.5 mg/l; cefotaxime MIC 1 mg/l) pneumococcal septicaemia complicated with meningitis. A cure was however achieved with the addition of chloramphenicol to the regimen. **Conclusion:** Resistance of pneumococci to penicillin G and other β -lactam agents is increasing in Kuwait. Penicillin-resistant pneumococcal bacteraemia in an immunosuppressed setting, if managed with cefotaxime or ceftriaxone, should be given high doses (cefotaxime 12 g/day or ceftriaxone 4 g/day) from the beginning. Cases of pneumococcal meningitis with cefotaxime-intermediate resistant strains (MIC 0.5–1 mg/l) on monotherapy consisting of cefotaxime or ceftriaxone should be viewed with caution. Chloramphenicol or vancomycin with rifampicin should be added to the regimen if therapeutic failure is suspected.

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Dr. Molly Johnny
Microbiology Unit, Department of Laboratory Medicine
Al-Amiri Hospital, PO Box 4077
13041 Safat (Kuwait)
Fax +965 2465299

Introduction

During the past 25 years, the incidence of penicillin G-resistant *Streptococcus pneumoniae* (pneumococci) has been reported with increasing frequency from most countries. This raises the question of therapeutic management for such infected patients [1]. Penicillin G-susceptible *S. pneumoniae* strains exhibit a minimum inhibitory concentration (MIC) of ≤ 0.06 mg/l, relatively resistant or intermediate resistant strains (IRSP) exhibit MIC of 0.12–1 mg/l and resistant strains (RSP) MIC ≥ 2 mg/l [2]. The oxacillin (1 μ g) disc diffusion test is recommended for the differentiation of penicillin G-susceptible pneumococci from IRSP and RSP, and an MIC test is required to differentiate IRSP from RSP. Although the majority of infections with IRSP respond to penicillin G, failure of therapy is frequently encountered in the case of meningitis, since adequate levels may not be attained in the cerebrospinal fluid (CSF) to clear the infection. Many authorities recommend the use of cefotaxime or ceftriaxone for meningitis infected by IRSP strains, and vancomycin for RSP strains [3]. However, recent reports from centres in the USA [4, 5] and from Spain [6] have documented failure of this therapy in a few cases of IRSP meningitis with cefotaxime or ceftriaxone. Although pneumococci have not acquired the ability to make β -lactamase [7], penicillin G-resistant pneumococci possess chromosomal genes that code for altered penicillin binding proteins with consequent loss of affinity to the drug [8]. Penicillin G-resistant pneumococci are also more resistant to all penicillins and other β -lactam drugs such as cephalosporins and carbapenems than sensitive pneumococci [7].

In recent years, we have reported cases of IRSP meningitis from the Al-Amiri Hospital, Kuwait. An overall incidence of 20.6% of pneumococci with reduced susceptibility to

penicillin G was reported during 1985–1988 [9, 10]. Our recent surveillance studies using oxacillin (1 μ g) disc diffusion test showed further increase in the prevalence of penicillin G-resistant pneumococci (IRSP or RSP) with marked increase in the isolation rate from blood cultures (1992–1994). We also encountered a patient with cefotaxime-intermediate resistant IRSP meningitis. In this paper, we report this case as an example and we also present the results of our surveillance studies. We also identify antibiotics likely to be useful in the empirical therapy of serious pneumococcal infections.

Materials and Methods

Pneumococci isolated at the Microbiology Laboratory of the Al-Amiri Hospital during the period May 1992 to June 1994 and April 1995 to August 1996, from clinical samples such as blood, CSF, pus and respiratory specimens were utilised in this study. For blood cultures, BACTEC (Johnson Laboratories/Becton-Dickinson), an automated system, was used for growth detection. Pneumococci were isolated by culturing samples on blood and chocolate agar plates and incubating at 35–37 °C in CO₂. Isolates were identified by colony morphology, optochin susceptibility and bile solubility test. Oxacillin (1 μ g) disc was used as a screening agent to differentiate penicillin G-susceptible isolates (MIC ≤ 0.06 mg/l) from intermediate resistant (MIC 0.1–1 mg/l) and resistant (MIC ≥ 2 mg/l) isolates. The inoculum was prepared by suspending overnight growth from blood agar in 1 ml peptone water and adjusting the turbidity to equal 0.5 McFarland standard. The plates were inoculated by the standard procedure and incubated overnight at 37 °C in CO₂ [11, 12]. Oxacillin zone diameters ≥ 20 mm were considered as susceptible, and ≤ 19 mm as intermediate resistant or resistant to penicillin G. Susceptibility to chloramphenicol (30 μ g), erythromycin (15 μ g), tetracycline (30 μ g) and vancomycin (30 μ g) was determined by agar diffusion (Kirby-Bauer) method [11, 12].

The MICs for penicillin G and cefotaxime were performed by agar dilution method [12] for the isolates of pneumococcus in the case report. Mueller-Hinton agar with 7% lysed horse blood was used, and the inoculum was prepared by suspending overnight growth

Table 1. Oxacillin susceptibility studies of pneumococci during 1992–1994

Source of specimen	Number of isolates of pneumococci	Isolates with oxacillin zone diameter ≤ 19 mm	
		n	%
Respiratory tract	89	23	25.8
Pus	35	10	28.5
CSF	–	–	–
Blood	16	7	43.7
Total	140	40	28.5

from blood agar in 1 ml peptonewater, and adjusting the turbidity spectrophotometrically to McFarland 0.5 standard. This suspension was further diluted 1/10 in trypticase soy broth, and 0.002 ml of this suspension was placed on the agar plate with a calibrated loop. The plates were incubated overnight at 35–37°C in CO₂. The lowest concentration that inhibited visible growth was recorded as the MIC. The MIC reading for cefotaxime was interpreted, according to the recent recommendations of the National Committee for Clinical Laboratory Standards. The isolates with an MIC of ≤ 0.25 mg/l were defined as fully susceptible, 0.5–1 mg/l as moderately susceptible or intermediate resistant and ≥ 2 mg/l as resistant [2].

Staphylococcus aureus (ATCC 25923) and a strain of pneumococcus (local isolate) known for its sensitivity were used as controls. Detection of pneumococcal antigen in CSF was done by latex agglutination method (using Wellcogen bacterial antigen kit, Murex) according to the manufacturer's instructions.

Results

During the period May 1992 to June 1994, 40 of the 140 (28.5%) isolates of pneumococci were resistant to penicillin G, IRSP or RSP (as judged by oxacillin disc diffusion method). MICs were not done for all the resistant isolates. Table 1 presents the number of isolates and the number and percentage of penicillin G-resistant isolates from the different sources as measured by oxacillin screening test. During this period, an increase in the isolation

rate of penicillin G-resistant pneumococci (IRSP or RSP) was noticed from blood cultures; 40–45% (7 of the 16 isolates) were resistant to penicillin.

The surveillance studies for the period April 1995 to August 1996 showed further increase in the isolation rate of penicillin-unresistant pneumococci (IRSP or RSP); 43 (38.3%) of the 112 isolates were resistant to penicillin G. Table 2 presents the total number of isolates, and number and percentage of penicillin G-resistant isolates from different sources as measured by oxacillin screening test. The isolation rate of penicillin G-resistant pneumococci from blood cultures was not very high during this period.

Table 3 summarizes the clinical data, for 7 blood culture-positive infections due to penicillin G-resistant pneumococci (IRSP or RSP). Of the 7 patients treated with cefotaxime or ceftriaxone, 6 patients responded, and therapy failed in 1 patient. The isolate of pneumococcus from this patient had penicillin G MIC 0.5 mg/l and cefotaxime MIC 1 mg/l, both penicillin and cefotaxime intermediate resistant. The MICs of penicillin and cefotaxime were not done for the isolates from the other 6 patients. All the 7 isolates were susceptible to chloramphenicol, erythromycin, tetracycline and vancomycin.

Table 2. Oxacillin susceptibility studies of pneumococci during 1995/96

Source of specimen	Number of isolates of pneumococci	Isolates with oxacillin zone diameter ≤ 19 mm	
		n	%
Respiratory tract	83	34	40.9
Pus	20	7	35
CSF	1	–	–
Blood	8	2	25
Total	112	43	38.3

Table 3. Blood culture positive infections due to penicillin G-resistant pneumococci during the period of May 1992 to June 1994

Case No.	Age	Sex	Diagnosis	Associated underlying condition	Complications	Therapy	Outcome
1	28 years	M	splenic abscess	sickle cell disease	pleural effusion	cefotaxime + metronidazole	recovered
2	8 years	F	pneumonia	none	none	cefotaxime	recovered
3	3 months	M	arthritis-hip	none	none	cefotaxime + cloxacillin	improved and transferred
4	90 years	M	pneumonia	none	none	cefotaxime	recovered
5	25 years	M	pneumonia	immuno-compromised, HIV infection	<i>S. aureus</i> pneumonia	cefotaxime followed by cloxacillin + cotrimoxazole	recovered
6	51 years	M	pneumonia	none	none	ceftriaxone	recovered
7 ^a	35 years	F	pneumonia	systemic lupus erythematosus steroid therapy	meningitis	cefotaxime + amikacin followed by cefotaxime + chloramphenicol	recovered after addition of chloramphenicol

^a Case report.

Case Report

A 34-year-old lady with systemic lupus erythematosus diagnosed in 1988 was admitted to this hospital in June 1994 with 1 day's history of chest pain, fever and breathlessness. She had been admitted 7 weeks earlier with pneumonia complicated by myopericarditis, and was treated with intravenous ceftriaxone 2 g once a day for 7 days combined with prednisolone 60 mg/day.

She was discharged after successful completion of therapy. During this admission, clinical examination revealed evidence of left lower lobe pneumonic consolidation, which was confirmed radiologically. She had been taking prednisolone 15 mg/day as continued therapy following prior discharge. After taking blood cultures, treatment was initiated with intravenous cefotaxime 1 g 8-hourly and amikacin 500 mg 12-hourly. Although critically ill, cyanosed, hypotensive and hyp-

oxic initially, she improved over the next 48–72 h. Initial blood cultures grew pneumococci with intermediate resistance to penicillin (MIC 0.5 mg/l), and cefotaxime dose was increased to 2 g 8-hourly on the 5th day. However, 7 days after initiation of therapy, she began to show symptoms of high fever with slurred speech, disorientation and neck stiffness. Urgent computed tomography of the head on the same morning was non-contributory. The CSF examination revealed a purulent neutrophilic meningitis (WBC $2.6 \times 10^9/l$ with 93% neutrophils, protein 1.651 g/l, glucose 0.3 mmol/l and lactic acid 10.3 mmol/l). Direct CSF smear examination showed many gram-positive diplococci suggestive of pneumococci, and the antigen detection test of CSF was positive for pneumococci. However, the culture of CSF was negative. Repeat blood cultures grew pneumococci again (penicillin MIC 0.5 mg/l, cefotaxime MIC 1 mg/l). In view of persistent pneumococcal bacteraemia complicated by pneumococcal meningitis with failure of anticipated outcome with current therapy, the dose of cefotaxime was increased to 3 g 6-hourly and intravenous chloramphenicol 1 g 6-hourly was added to the treatment regimen. Amikacin was discontinued on the same day. She was treated at the intensive care unit for the next 6 days. Therapeutic response was notable within 24 h of initiating chloramphenicol therapy, with defervescence of fever and marked improvement in her level of consciousness which normalised after 72 h. Cefotaxime was continued till the 14th day and chloramphenicol was given for 1 more week (total of 2 weeks). She was discharged in a stable condition.

Discussion

In recent years, the real clinical significance of pneumococcal resistance has become evident with reports from many countries about the increasing resistance and therapeutic problems associated with such infections [1]. In the United States, prevalence of penicillin G resistance varied in different regions and in the last few years the level of resistance has increased. Of the 1,527 isolates collected in 1994 and 1995 in the USA, 14.1% were IRSP and 9.5% were RSP [13]. In Europe, it is a major problem in countries such as Spain, Hungary and France where about 50% of clinical isolates of pneumococci are moderately or

highly resistant to penicillin [1]. In the Gulf region, a report from Riyadh, Saudi Arabia showed that 18% pneumococcal isolates were moderately resistant and 1% was highly resistant to penicillin [14].

In Kuwait, during the period 1985–1988, we tested 457 isolates of which 20.6% were penicillin G resistant (IRSP or RSP) [10]. Our recent surveillance studies showed that the percentage of penicillin G resistance is increasing in Kuwait. The resistance was 28.5% during 1992–1994, and there was a further increase to 38.3% during the period 1995/96. The screening method using oxacillin 1-μg disc is considered as a reliable method for differentiating the penicillin-sensitive strains from resistant strains (IRSP or RSP). However, an MIC test is needed to further differentiate the resistant strains (IRSP or RSP). Although the conventional MIC methods (agar or broth dilution) are highly reliable for this differentiation, we could not test MICs for all our penicillin G-resistant isolates, as these tests are difficult to perform in a busy clinical laboratory. However, penicillin G MICs by agar dilution for about half of the resistant isolates during the period 1985–1988 [10], as well as E test (PDM Episilometer, a technically simple, reliable and acceptable method) [15, 16] MICs for more than half of the resistant isolates during the period 1995/96 showed all isolates as IRSP and none as RSP [17]. From these observations it is apparent that RSP strains are not commonly encountered in our area, although IRSP strains are prevalent.

The management of resistant pneumococcal disease is often complicated by delayed recognition. It is known that in most cases of pneumonia with IRSP, these strains respond to penicillin G [18]. However, because of the generally poor prognosis for patients with bacteraemia, underlying diseases and immunodeficiency diseases, a high dose of ce-

fotaxime (12 g/day) or ceftriaxone (4 g/day) is often used. Although 6 of our patients with penicillin G-resistant (IRSP or RSP) pneumococcal bacteraemia responded to cefotaxime or ceftriaxone, 1 case of failure (case report) emphasises the need for checking the susceptibility of pneumococci in invasive infections. For isolates with any degree of penicillin resistance, MIC or cefotaxime or ceftriaxone should be checked [5]. This case also documented the presence of cefotaxime-resistant pneumococci in Kuwait. In addition, our recent study showed that about 22% (5 of the 23 isolates) IRSP isolates had E test MICs for cefotaxime in the range of 0.5–1 mg/l (intermediate resistant) during the period 1995/96 [17]. The emergence of cefotaxime and ceftriaxone resistance in pneumococci could lead to problems in the management of meningitis, as most cases of pyogenic meningitis are treated empirically with cefotaxime or ceftriaxone. Our patient with systemic lupus erythematosus on steroids developed symptoms of meningitis while on cefotaxime therapy for pneumococcal septicaemia. Despite increasing the dose of cefotaxime, therapeutic failure was evident from clinical deterioration, CSF findings typical of meningitis and new positive blood cultures after 6 days of therapy. The patient responded to therapy when chloramphenicol was added to the regimen. Because of the rare possibility of aplastic anaemia, chloramphenicol should be used only when clearly indicated; but in life-threatening infections it should not be withheld when other choices are not available. Since chloramphenicol is lipophilic, it diffuses very well into the meninges and a good response has been reported in cases with pneumococci resistant to penicillin and cefotaxime [5]. However, highly resistant strains are usually resistant to multiple drugs including chloramphenicol. Although chloramphenicol-resistant

strains are common in countries like South Africa and Spain [1], such strains are not frequently encountered now in Kuwait [10, 17].

Resistance of pneumococci to antibiotics seriously limits the options available for treatment of meningitis. Although vancomycin is recommended for treating resistant pneumococcal meningitis, some reports show disappointing results because of variable CSF levels, due to difficulty in crossing the blood-brain barrier. Intrathecal administration or combination with rifampicin is recommended [19]. It is advisable not to administer rifampicin as a monotherapy, since resistance to this drug develops rapidly. Other agents like carbapenems (imipenem or meropenem) may be effective against resistant pneumococci, but imipenem may cause seizures in children. Since the morbidity and mortality due to pneumococcal meningitis are still very high, there is an urgent need for new agents, producing high levels in CSF.

Although knowledge of regional prevalence of resistance is important while selecting drugs for empirical therapy of pneumococcal meningitis, one should take into consideration that resistant strains may be brought into a community by travellers. Some experts recommend that presumptive cases of pneumococcal meningitis should receive cefotaxime or ceftriaxone plus vancomycin with or without rifampicin [20], or chloramphenicol [5] until the strain is isolated, and the antibiotic susceptibility determined.

Selective pressure exerted by antibiotic use appears to be the chief factor responsible for the development of resistance [8]. Although penicillin was the selective agent in most cases, nowadays, cephalosporin resistance is emerging, probably due to frequent use of cephalosporins. Children receiving antibiotics frequently, e.g. for otitis media, are known to select for drug-resistant strains. Our patient had ceftriaxone therapy during her previous

admission. Probably, this was responsible for her subsequent infection with cefotaxime intermediate resistant pneumococci.

Our results show that resistance of pneumococci is increasing in Kuwait, and there is a need for continued surveillance. The emergence of strains resistant to the extended spectrum of cephalosporins is a cause for concern. Hence indiscriminate use of antibiotics, particularly the broad spectrum agents, should be avoided, since the use of antibiotics in colonised patients may select for resistant mutants. Our experience in Kuwait shows that chloramphenicol is still effective in treating penicillin and cephalosporin intermediate resistant pneumococcal meningitis. We recom-

mend that in cases of meningitis caused by IRSP strains, the treatment of choice should still be cefotaxime or ceftriaxone, and if cefotaxime or ceftriaxone is intermediate resistant (MICs 0.5–1 mg/l), these cases should be viewed with caution. Chloramphenicol or vancomycin with rifampicin should be added to the regimen, if therapeutic failure is suspected.

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References

- 1 Appelbaum PC: Antimicrobial resistance in *Streptococcus pneumoniae*: An overview. Clin Infect Dis 1992;15:77–83.
- 2 National Committee for Clinical Laboratory Standards: Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically: Approved standard. NCCLS Document M7-A3, ed 3. Villanova, NCCLS, 1993.
- 3 Weingarten RD, Markiewicz Z, Gilbert DN: Meningitis due to penicillin resistant *Streptococcus pneumoniae* in adults. Rev Infect Dis 1990; 12:118–124.
- 4 Bradley JS, Connor JD: Ceftriaxone failure in meningitis caused by *Streptococcus pneumoniae* with reduced susceptibility to β -lactam antibiotics. Pediatr Infect Dis J 1991; 10:871–873.
- 5 Sloas MM, Barret FF, Chesney PJ, English B, Hill BC, Tenover FC, Leggiadro RJ: Cephalosporin treatment failure in penicillin and cephalosporin resistant *Streptococcus pneumoniae* meningitis. Pediatr Infect Dis J 1992;11:662–666.
- 6 Catalan MJ, Fernandez JM, Vazquez A, de Seijas EV, Suarez A, de Quiros ATL: Failure of cefotaxime in the treatment of meningitis due to relatively resistant *Streptococcus pneumoniae*. Clin Infect Dis 1994; 18:766–769.
- 7 Jacoby GA: Prevalence and resistance mechanisms of common bacterial respiratory pathogens. Clin Infect Dis 1994;18:951–957.
- 8 Zigelboim S, Tomasz A: Multiple antibiotic resistance in South African strains of *Streptococcus pneumoniae*: Mechanism of resistance to β -lactam antibiotics. Rev Infect Dis 1981;3:267–276.
- 9 Johny M, Shaltout AA, Menon NK, Jamil AS: Pneumococci relatively resistant to penicillin: Report of four cases of meningitis from Kuwait. Med Principles Pract 1992/93;3:54–56.
- 10 Johny M, Anton AY, Murad MA: Relative resistance of pneumococci to penicillin: Detection and prevalence in Kuwait. Med Principles Pract 1992/93;3:167–170.
- 11 Doern GV: Susceptibility tests of fastidious bacteria; in Murray PR, Baron EJ, Pfaller MA, Tenover FC, Tenover FC, Yolken RH (eds): Manual of Clinical Microbiology, ed 6. Washington, American Society for Microbiology, 1995, pp 1342–1347.
- 12 Woods GL, Washington JA: Antibacterial susceptibility tests: Dilution and disc diffusion methods; in Murray PR, Baron EJ, Pfaller MA, Tenover FC, Yolken RH (eds): Manual of Clinical Microbiology, ed 6. Washington, American Society for Microbiology, 1995, pp 1327–1341.

- 13 Doern GV, Brueggemann A, Holley HP Jr, Rauch AM: Antimicrobial resistance of *Streptococcus pneumoniae* recovered from outpatients in the United States during the winter months of 1994 to 1995: Results of a 30-center national surveillance study. *Antimicrob Agents Chemother* 1996;40:1208–1213.
- 14 Shibl AM, Hussein SS: Surveillance of *Streptococcus pneumoniae* serotypes in Riyadh and their susceptibility to penicillin and other commonly prescribed antibiotics. *J Antimicrob Chemother* 1992;29:149–157.
- 15 Jacobs MR: Treatment and diagnosis of infections caused by drug-resistant *Streptococcus pneumoniae*. *Clin Infect Dis* 1992;15:119–127.
- 16 Jorgenson JH, Ferraro MJ, McElmeel ML, Spargo J, Swenson JM, Tenover FC: Detection of penicillin and extended spectrum cephalosporin resistance among *Streptococcus pneumoniae* clinical isolates by use of the E test. *J Clin Microbiol* 1994; 32:159–163.
- 17 Johnny M, Babely M, Al-Obaid EA, Murad MA: Antimicrobial resistance of pneumococci isolated in Kuwait: Efficacy of E test for determination of MIC. *J Kwt Med Assoc* 1997;in press.
- 18 Koornhof HJ, Wasas A, Klugman K: Antimicrobial resistance in *Streptococcus pneumoniae*: A South African perspective. *Clin Infect Dis* 1992;15:84–94.
- 19 Viladrich PF, Gudiol F, Linares J, Pallares R, Sabate I, Rufi G, Ariza J: Evaluation of vancomycin for therapy of adult pneumococcal meningitis. *Antimicrob Agents Chemother* 1991;35:2467–2472.
- 20 Lonks JE, Medeiros AA: The growing threat of antibiotic resistant *Streptococcus pneumoniae*. *Med Clin North Am* 1995;79:523–535.