Streptococcus pneumoniae resistance to penicillin and ceftriaxone in a tertiary care center in Saudi Arabia

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ABSTRACT

Objective: The proportion of penicillin and ceftriaxone resistant *Streptococcus pneumoniae* isolates and associated risk factors varies by geographic areas in the world. We conducted a retrospective study to determine the extent of penicillin and ceftriaxone non-susceptible *Streptococcus pneumoniae* bacteremia in a tertiary care medical center in the city of Riyadh, Kingdom of Saudi Arabia.

Methods: We reviewed 172 episodes of *Streptrococcus pneumoniae* bacteremic diseases involving 160 hospitalized patients at King Faisal Specialist Hospital and Research Centre, Riyadh, Kingdom of Saudi Arabia, over a 5 year period between January 1995 through to December 1999. Patients' characteristics and underlying illnesses of those patients with bacteremias and meningitis caused by *Streptococccus pneumoniae* as well as antimicrobial susceptibility were examined.

Results: The majority of patients affected with *Streptococcus pneumoniae* bacteremia were children <5 years of age (number=91, 53%). Malignant diseases were the main underlying diagnosis in our patient population affected with pneumoncoccal bacteremia (number=46, 27%). Overall (51%) of the isolates were penicillin non-susceptible; of these (7%) were highly resistant. The overall resistance rate to ceftriaxone was 7%.

Conclusion: With the high prevalence in *Streptococcus pneumoniae* antimicrobial resistance to penicillin and ceftriaxone, it is important to continue surveillance of infections caused by *Streptococcus pneumoniae,* and also we recommend that guidelines for treatment and prevention of pneumococcal infection must be addressed by health care and public health agencies.

Keywords: Pneumococcal infections, bacteremia, meningitis, antimicrobial resistance, recurrence, *Streptococcus pneumoniae*.

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The importance of *streptococcus pneumoniae* (*S.pneumoniae*) as a cause of serious infection has been widely reported. Considerable research has also established an association between disease and selected chronic medical conditions.[1,2] The increased prevalence of *S.pneumoniae* that are non-susceptible to antibiotics[3] and the development of more effective vaccines[4] have highlighted the importance of identifying groups of patients at high risk from pneumococcal disease. The treatment of patients with pneumococcal infections has been complicated by the development of antibiotic resistance; except for bacterial meningitis; there is no consensus as to the most appropriate antibiotic choices.[5]

Methods. From January 1995 through December 1999, patients with *S.pneumoniae* bacteremia and meningitis at King Faisal Specialist Hospital and Research Centre (KFSHRC) were identified by

hospital-based computerized medical records in the Infection Control Department. Hospital records included patients' demographic data, underlying diagnosis, medical treatment and antimicrobial susceptibility of *S.pneumoniae*. One hundred and seventy two episodes of *S.pneumoniae* bacteremia involving 160 hospitalized patients were identified (12 patients had recurrent pneumococcal bacteremia in a period between one month to one year from the first bacteremic episode). We have excluded recurrent bacteremic episodes that have occurred within 30 days from the first episode as defined by another study.[6] We also included concomitant cases of pneumococcal meningitis with positive cerebrospinal fluid cultures.

Laboratory. *Streptococcus pneumoniae* was identified at KFSH&RC laboratory according to the standard of the National Committee for Clinical Laboratory Standards (NCCLS) using colony morphology, ethylhydrocuprein (optochin) susceptibility and bile solubility. Antimicrobial testing was carried out at KFSH&RC according to the methods recommended by the NCCLS. In the year 1995, all pneumococcal isolates noted to be resistant by (1µg) oxacillin disk testing (zone of inhibition <20mm), were evaluated for penicillin minimal inhibitory concentration (MICs), and also tested for susceptibility to ceftrixaone and vancomycin by the broth microdilution method. Antimicrobial resistance to each drug was defined using the proposed NCCLS break points[7] as follows: (Minimal inhibitory concentration in µg/mL) Penicillin ≥0.12 (≥2 highly resistant), ceftrixaone ≥0.5 (≥2 highly resistant) and vancomycin >1. After the year 1995, the penicillin, ceftrixaone, and bancomycin MICs were determined using the Epsilometer (E test).[8]

Results. One hundred and seventy two episodes of *S.pneumoniae* bacteremia were identified in 160 patients. Ninety-seven (61%) episodes occurred in males while 63 (39%) were in females with a male to female ratio of 3:2. In 155 patients (90%) the bacteremia was community acquired. The highest proportion of patients diagnosed with *S. pneumoniae* were <2 years and <5 years (number (N)=44, 26%) and (N=91, 53%). Allogeneic bone marrow transplantation was a common underlying condition for *S.pneumoniae* bacteremia (N=20, 12%) in this series. Four patients with bone marrow transplantation suffered a recurrent disease (20%). In general, malignancy was a major underlying diagnosis for patients with *S.pneumoniae* bacteremia (N=46, 27%). Leukemia was the most frequent malignancy identified (N=18, 39%) in patients with bacteremia. All leukemia patients were children <15 years of age.

Other malignant diseases identified include solid tumors, Hodgkin's and non-Hodgkin's lymphoma, which, occurred in both adults and children. Children <2 years of age with congenital heart diseases constituted the majority (n=11, 69%) of patients with underlying cardiovascular diseases and *S.pneumoniae* bacteremia. Other less common underlying diseases are included in **Table 1.**

Table 1 - Frequency of underlying diagnosis by age group, 1995-1999.

Diagnosis	0-60 month N=91	61 months - 14 years N=26	15 years - 60 years N=39	>60 years N=16	Totals N=172
Bone marrow transplant	3	7	10	-	**20**
Leukemia	10	8	-	-	**18**
Cardiovascular disease	13	-	1	2	**16**
Solid tumor	7	-	4	4	**15**
Liver disease	5	1	3	4	**13**
Hodgkin's disease	2	-	4	-	**6**
Multiple myeloma	-	-	2	2	**4**
Non-Hodgkin's lymphoma	1	-	2	-	**3**
Otitis Media	8	-	-	-	**8**
Chronic lung disease	4	1	2	-	**7**
Immunodeficiency syndrome	5	2	-	-	**7**
Head injury/brain lesion	2	-	3	1	**6**
Ventriculo peritoneal shunt	2	3	-	-	**5**
Chronic renal failure	1	-	2	1	**4**
Kidney transplant	-	-	1	1	**2**
Splenectomy	3	-	-	-	**33**
Aspiration pneumonia	3	1	-	-	**4**
Genetic metabolic disorder	4	-	-	-	**4**
Autoimmune disorder	2	-	2	-	**4**
Human immuno-deficiency virus	-	-	3	-	**3**
Histiocytosis	2	-	-	-	**2**
Gastrointestinal tract disorder	3	-	-	-	**3**
Other diagnosis	3	3	-	1	**7**
No underlying illness	8	-	-	-	**8**

Table 2 - Age and underlying diseases of patients with *Streptococcus pneumoniae* meningitis.

Age and Diseases	N of patients
Age	
3-11 months	4
12-24 months	3
25-60 months	1
61 months - 14 years	5
≥15 years	4
Underlying Chronic Disease	
Central Nervous System Diseases	10
Ventriculo peritoneal shunt	3
Head Trauma	2
Cerebrospinal fluid	1
Central Nervous System tumor, brain	3
Arteriovenous malformation of brain	1
Chronic pulmonary disease	1
AIDS	1
Congenital immunodeficiency	1
Congenital metabolic disease	1
Cardiovascular disease	1
Well babies <12 months of age	2

N - number
AIDS - acquired immuno-deficiency syndrome

Recurrent bacteremia. Twelve patients had a 2nd episode of *S.pneumoniae* bacteremia in a period between one month and one year from the first bacteremic episode. Four of them had allogeneic bone marrow transplantation, 3 had malignant disorders, one had congenital hypogammaglobinemia, one with genetic metabolic disorder (Sanjad-Sakoti syndrome), another patient with renal impairment on steroids and finally a cardiovascular patient with congenital heart disease and a pseudotumor cerebri patient with ventriculo-peritoneal shunt (VP shunt).

Meningitis. Sixteen patients had 17 episodes of *S.pneumoniae* meningitis (one patient with VP shunt, pseudotumor cerebri, had a 2nd episode of meningitis 4 months after the first episode). The distribution of ages and underlying illnesses are shown in **Table 2.** The meningitis case distribution shows that the majority of cases occurred in children <14 years

(N=13, 76%) and the main underlying diagnoses were diseases that involved the central nervous system (N=9, 52%). Fifteen *streptococcus pneumoniae* meningitis episodes had associated Bacteremia (88%). Patients with *S.pneumoniae* meningitis had different underlying illnesses from those with *S. pneumoniae* bacteremia. **(Table 2)**

Resistance to penicillin and ceftriaxone. Of the 172 *S.pneumoniae* isolates from blood cultures, 84 (49%) were penicillin sensitive and 88 (51%) were non-susceptible to penicillin. Of these, 12 isolates (7%) were categorized as highly resistant over the study period. One hundred and sixty-four (93%) *S.pneumoniae* isolates were tested to ceftriaxone, and 152 isolates were susceptible while 12 (7%) were moderately non-susceptible. All the isolates were susceptible to vancomycin. There was a trend toward an increase in the proportion of penicillin non-susceptible isolates and ceftriaxone non-susceptible isolates over the study period. Isolates non-susceptible to penicillin increased from 50% in 1995 to 58% in 1999 while isolates resistant to ceftriaxone increased from 0% to 13% in 1999. This trend did not reach a statistical significance (P value was 0.28 and 0.09). Sixty-five percent of *S.pneumoniae* isolates in patients with meningitis were resistant to penicillin (N=11) while 35% were sensitive to penicillin, and 12% isolates were resistant to ceftriaxone (N=2) while 88% were sensitive.

Discussion. This study evaluated *S.pneumonia* bacteremia at a tertiary medical center, where all age groups were included. Fourteen years ago almost all pneumococcal isolates in the Kingdom of Saudi Arabia (KSA), were considered susceptible to penicillin[9] and penicillin was the agent of choice for treating serious pneumococcal infections. However, the increasing frequency of penicillin resistance and the emergence of cephalosporin resistance and multi-drug resistance have required changes in the emperic approach to antibiotic selections when treating pneumococcal infections. This has been most readily documented for bacterial meningitis. Some reports have focused on treatment failures of pneumococcal meningitis associated with decreased susceptibility to

Table 3 - Antimicrobial susceptibility to *Streptococcus pneumoniae* isolates in bacteremia patients.

Year	1995		1996		1997		1998		1999		Total	Average	P-value
Penicillin susceptible	13	(50)	20	(56)	21	(52)	17	(44)	13	(42)	**84**	**49**	0.28
Penicillin non-susceptible	13	(50)	14	(44)	19	(48)	22	(56)	18	(58)	**88**	**51**	
Ceftriaxone susceptible	22	(100)	35	(95)	32	(91)	36	(92)	27	(87)	**152**	**93**	0.09
Ceftriaxone non-susceptible	0		2	(5)	3	(9)	3	(8)	4	(13)	**12**	**7**	

extended spectrum cephalosporins.[10,11] Most experts recommend including vancomycin, a drug generally effective in treating meningitis attributable to pneumococcal isolates that are resistant to cefotaxime or ceftriaxone in the initial emperic regimen selected when treating a child with suspected bacterial meningitis.[5] A study carried out in KFSH&RC in 1990 reported that 32% of *S.pneumoniae* isolates from blood cultures of 49 patients had relative penicillin resistance (RPR). The prevalences of RPR in isolates from other miscellaneous specimens were similar.[12]

Findings of this study were somewhat similar to that of another study in the region, which showed overall penicillin resistance of 56.4% (7% high penicillin resistant), and ceftriaxone resistant was 4.5%. However, the study included isolates from non-sterile sites.[13] The frequency of penicillin and ceftriaxone resistance increased steadily among the systemic isolates recovered from our patients. However, this increment was not statistically significant. This observation either reflects a lack of change in resistance pattern over time, or sample size was not large enough to detect such a change **(Table 3).**

The widespread use of antibiotics particularly on an outpatient basis and as prophylaxis for immunocompromised patients may have resulted in creating selective pressures which favor the emergence of antibiotic resistance in *S.pneumoniae* as well as other micro-organisms.[14] The large number of patients with underlying diseases probably reflects to some degree our hospital population as a tertiary center institution. It also underscores the particular vulnerability of these patients **(Table 1)** to infection with *S.pneumoniae*.

Although all age groups in this series were affected, children below the age of 5 years were affected most. This may reflect the high carriage rate in the young age group.[15,16] The male to female ratio in this study is similar to other reports.[17]

Allogeneic bone marrow transplantation and malignancy were common underlying conditions in-patients with pneumococcal bacteremia as were cardiovascular diseases in the young age group. However, this may be a reflection of referral bias being a tertiary care center. Recurrence of pneumococcal bacteremia has been reported to occur in both immunocompromised and normal hosts.[6,18] In our study 10 out of the 12 patients who had recurrence had primary or secondary immunodeficiency. The increased rate of recurrence among patients with bone marrow transplantation might reflect the type of immunosuppression these patients suffer. Pneumococcal vaccination in transplant recipients has been shown to be relatively ineffective early after transplantation.[19] Even in-patients who do respond to the 23 valent vaccine, the Immunoglobulin G (IgG$_2$) response is often poor.

The 23 valent vaccine, apart from being poorly immunogenic also does not cover 20% of the commonly encountered pathogenic pneumococcal strains, and immunized persons remain susceptible to them.[19] Since there is no organized pneumococcal vaccination program in KFSH&RC, and this responsibility is left to local physicians, it is probable that many patients were indeed not vaccinated.

In conclusion, the continuing spread of drug resistant strains of pneumococci, treatment options for invasive disease will become more limited and preventive measures will become critical. This study emphasizes the importance of antimicrobial susceptibility testing of all invasive pneumococcal isolates from both children and adults in KSA, as well as the crucial need for community-based programs of surveillance for drug resistant pneumococcus to aid clinicians in their choice of therapy for pneumococcal infections. The prevention of infections with invasive drug resistant pneumococcus will require strategies to encourage judicious antibiotic use and optimize immunization with the 23 valent pneumococcal vaccine in the targeted population. Pneumococcal conjugate vaccine has been shown to be effective in the prevention of invasive disease in children under 2 years of age[9] and should be considered for routine infant vaccination in our country.

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