

Prevalence of Resistant *Streptococcus Pneumoniae* Causing Meningitis in a Tertiary Care Hospital in Saudi Arabia

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Abstract: Acute bacterial meningitis is associated with high rates of morbidity and mortality. *Streptococcus pneumoniae* is a major cause in adults and children. Choice of empirical antibiotics must be made in consideration of the global increase of resistant strains to penicillin and third-generation cephalosporins. In order to determine the most common pathogens responsible for bacterial meningitis in King Abdulaziz University Hospital (KAUH) in Jeddah, Saudi Arabia, we did a retrospective review of all positive cerebrospinal fluid (CSF) cultures submitted from 1/2006 to 8/2016 for all ages. We identified all causative organisms, and determined the susceptibility pattern of *S. pneumoniae* and gathered clinical outcome data. The microbiology lab have received a total of 7958 CSF cultures, with 456 (6%) being positive for bacteria or fungi. The most common isolated organisms were the group of coagulase negative *Staphylococci*. *S. pneumoniae* was isolated from 15 samples from 13 different patients. Out of the 13 isolates, three showed resistance to penicillin or ceftriaxone (23%). This suggests that drug resistant *S. pneumoniae* causing meningitis is not uncommon in our hospital. The addition of empirical vancomycin to third-generation cephalosporins to treat community-acquired meningitis might be necessary especially in high risk cases.

Keywords: *Streptococcus pneumoniae*, meningitis, penicillin resistance, ceftriaxone resistance, vancomycin

1. Introduction

Acute bacterial meningitis is a serious illness with high rates of morbidity and mortality rates. There are several factors that play a role in the distribution of the causative pathogens, including age, geographic location, vaccine uptake, immune system status, trauma and post neurosurgical procedures [1].

S. pneumoniae is one of the most common causes of community-acquired meningitis in both pediatrics and adults. Penicillin and third-generation cephalosporin resistance is on the rise, which led to the recommendation of adding vancomycin empirically to a third-generation cephalosporin especially in areas with high rates of resistance, since the 1990s [2,3].

In Saudi Arabia, the estimated annual incidence of invasive pneumococcal disease (IPD) -defined as meningitis or bacteremia- in children aged ≤ 5 years in 2012, ranged from 24.4-53.5 per 100,000, with an average annual mortality rate of 2.1 per 100,000 in this population [4]. Reported rates of penicillin resistance in Saudi Arabia are variable, ranging between 2.4-78%, while rates of ceftriaxone resistance are reported to range between 0- 4.7% [5-10].

In this report, data on bacteria isolated from cerebrospinal fluid (CSF) from patients evaluated over a 10-year period in our center was reviewed, with a focus on *S. pneumoniae* and its resistance patterns. Better understanding of the local prevalence of the resistant strains can improve antibiotic prescription habits, and hopefully improve clinical outcome.

2. Methods

King Abdulaziz University Hospital (KAUH) is a 760-bed

academic tertiary care center located in Jeddah, Saudi Arabia. In the microbiology lab in KAUH, antibiotic susceptibility is determined using Vitek 2 system (Biomerieux, France), and confirmed using E-test based the Clinical and Laboratory Standards Institute (CLSI) guidelines published in January 2015, where breakpoints of intravenous penicillin were ≤ 0.06 $\mu\text{g/ml}$ for the sensitive isolates and ≥ 0.12 $\mu\text{g/ml}$ for the resistant ones. For ceftriaxone, the breakpoints were ≤ 0.5 $\mu\text{g/ml}$ and ≥ 2 $\mu\text{g/ml}$ for the sensitive and resistant isolates, respectively.

This review included patients of all ages. Data was collected electronically from the hospital laboratory (LIS) information system in a retrospective manner. Results from bacterial and fungal cultures of all CSF samples that were received by the microbiology lab between the 1st of January 2006 and the end of August 2016 were reviewed. The susceptibility of *S. pneumoniae* isolates was recorded. We looked at community-acquired meningitis, as well as hospital-associated cases, including those with shunt devices. For patients who tested positive for *S. pneumoniae* from the CSF, the following information was gathered: demographics, use of empiric vancomycin, whether the patient received antibiotic therapy within 1 week before sample collection, in addition to clinical outcomes. This study was approved by the Research Ethics Committee of the Faculty of Medicine in King Abdulaziz University.

3. Results

The total number of CSF samples sent for bacterial cultures was 7958. Only 6% were positive for bacteria or fungi (456/7958). The most commonly isolated bacteria were coagulase-negative *Staphylococci* (CONS) (151/459, 33%), including cases labeled as potential contaminants. A list of

all isolates is summarized in Table 1. Interestingly, *Neisseria meningitidis* was not isolated from the CSF cultures in the study period from our hospital.

In regards to *S. pneumoniae*, the total number of isolates was 15 samples from 13 different patients. All isolates were fully susceptible to penicillin and third-generation cephalosporins, with the exception of 3 isolates (3/13, 23%) which were resistant to penicillin, ceftriaxone or both. Two isolates showed resistance to both antibiotics (2/13, 15%), and one isolate was resistant to penicillin but it was intermediate to ceftriaxone (1/13, 8%). One of the children who had the resistant strains was exposed to antibiotic therapy before admission.

The ages of the admitted patients with pneumococcal meningitis ranged between 3 months to 28 years, with median of 2 years. Two patients (15%) had pre-treatment with antibiotics in the last week before admission. The majority of patients were males (8/13, 62%). The median of admission duration was 22 days (Interquartile range {IQR}: 12.5-33.5).

All patients with community acquired meningitis received a third-generation cephalosporin antibiotic, with or without ampicillin and steroids. Empirical treatment with vancomycin was documented in the chart for 10/13 patients (77%).

Three patients had complete cure (3/13, 23%). Six patients had clinical cure but developed complications like seizure disorder or cranial nerve palsies (6/13, 46%). Mortality due to pneumococcal meningitis was 23% (3/13) in our study.

4. Discussion

Antimicrobial resistance of pathogens resulting in serious infections is a global challenge even in the era of antimicrobial stewardship. The rate of high penicillin and ceftriaxone resistant strains in our study were 23% and 15%, respectively. This is a noticeable increase in comparison with reported rates from our center, published in 2001 [6]. In that report, the rate of penicillin resistant strains was 6.7%, while the rate of ceftriaxone resistant strains was 4.7% only. This difference can be partly explained by using different antibiotic breakpoints at that time, since the CLSI updated these breakpoints in January 2008.

The low number of *S. pneumoniae* isolates when compared to the overall positive CSF cultures (15/456, 3.3%) might be explained by the effective national Pneumococcal Conjugate Vaccine (PCV) implementation, first with PCV-7 that was released in 2009 followed by PCV-13 in 2011. Effective vaccination may also explain the complete absence of any *N. meningitidis* isolates, and having only 1 case of *Haemophilus influenzae* from our hospital in the study period.

Having the hospital-associated meningitis and CSF shunt infection cases included led to an increase of the number of all *Staphylococci* and Gram negative bacilli isolates. However the large number of CONS isolates (151/456, 33%) and other skin flora will need to be analyzed

separately to determine the contamination cases from true cases in our hospital.

The small number of *S. pneumoniae* cases over the last 10 years is reassuring, but also made an obstacle for us to make any useful correlation with specific risk factors, such as previous antibiotic use.

5. Conclusion

Despite the low number of pneumococcal meningitis cases diagnosed in the last 10 years in our hospital, and by looking at similar studies, it seems that ceftriaxone resistance is not uncommon in our region. The addition of empirical vancomycin for community-acquired meningitis might be necessary especially for high risk patients.

6. Acknowledgment

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Table 1: List of CSF bacterial and fungal isolates, 1/2006-8/2016 in KAUH ordered by frequency:

<i>Organism</i>	<i>No. of isolates</i>
CONS	151
<i>Enterococcus</i> spp.	51
<i>Pseudomonas</i> spp.	45
<i>Cryptococcus neoformans</i>	33
<i>Acinetobacter</i> spp.	29
<i>Klebsiella</i> spp.	26
<i>E. coli</i>	18
<i>Enterobacter</i> spp.	16
<i>Streptococcus pneumoniae</i>	15
<i>Candida</i> spp.	13
<i>Diphtheroides</i> spp.	10
<i>Streptococcus viridans</i> group	8
Group B <i>Streptococci</i>	7
<i>Stenotrophomonas maltophilia</i>	5
<i>S. aureus</i>	4
<i>Burkholderia cepacia</i>	4
<i>Salmonella</i> spp.	3
<i>Micrococcus</i> spp.	3
<i>Proteus</i> spp.	3
<i>Chryseobacterium</i> spp.	2
<i>Sphingomonas paucimobilis</i>	2
<i>Citrobacter</i> spp.	2
<i>Streptococcus</i> spp. (others)	1
<i>Haemophilus influenzae</i>	1
<i>Haemophilus parainfluenzae</i>	1
<i>Moraxella</i> spp.	1
<i>Serratia marcescens</i>	1
Group C <i>Streptococci</i>	1
<i>Total</i>	<i>456</i>

Author Profile

Dr Mazen Badawi (MBBS, ABIM, FRCPC Internal Medicine and Infectious diseases) is a university staff and an infectious diseases specialist at King Abdulaziz University Hospital. He has a special interest in emerging infectious diseases.