

Case Report

***Acinetobacter* species meningitis in children: a case series from Karachi, Pakistan**

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Abstract

Introduction: Multidrug-resistant strains of *Acinetobacter* pose a serious therapeutic dilemma in hospital practice, particularly when they cause meningitis, as the few antimicrobial agents to which these isolates are susceptible have poor central nervous system (CNS) penetration.

Methodology: We retrospectively reviewed the clinical course and outcome of eight consecutive cases of meningitis due to *Acinetobacter* spp. in children ages 15 years or less, seen in a tertiary care medical center in Karachi, Pakistan.

Results: Of the eight cases of *Acinetobacter* meningitis, isolates from five patients were pan-resistant, and two were multidrug-resistant. A neurosurgical procedure was performed in five of eight patients followed by external ventricular drain insertion prior to the development of infection. Seven received intravenous (IV) polymyxin (mean; 12.8 days), while 5/8 also received intrathecal (IT) polymyxin (mean; 12.0 days). The mean length of hospitalization was 38.7 ± 19 days. All patients achieved cerebrospinal fluid (CSF) culture negativity by the end of treatment (mean; 5.4 days). Two patients died: one with pan-resistant *Acinetobacter*, and the second with a multi-drug resistant isolate.

Conclusion: Post-neurosurgical multidrug-resistant and pan-resistant *Acinetobacter* meningitis can be successfully treated if appropriate antimicrobial therapy is instituted early. The role of IT polymyxin B administration alone versus combination therapy (IV and IT) needs further study.

Key words: multidrug-resistant *Acinetobacter* meningitis; mortality; children; neurosurgical procedure

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Introduction

Acinetobacter baumannii is a nosocomial pathogen that threatens health-care systems worldwide, resulting in high morbidity and mortality in critically ill patients [1,2]. Although nosocomial pneumonia is the most common clinical manifestation, *Acinetobacter* meningitis has been increasing in frequency [3]. *Acinetobacter* meningitis may occur following neurosurgery, traumatic head injury or/and metastatic infection in bacteremic patients. Multidrug-resistant *Acinetobacter* (MDRA) is defined as resistance to more than two of the five classes of drugs: cephalosporins, carbapenems, ampicillin-sulbactam, fluoroquinolones and aminoglycosides [1,4]. Pan-resistant *Acinetobacter* (PRA) is defined as resistance to all five classes of the drugs mentioned above [1,4]. For PRA infections in resource-limited settings, the only available therapeutic option is polymyxin [5]. Tigecycline, a glycylcycline antibiotic, has good *in vitro* activity against PRA [6], but is very costly and not readily available in developing countries. In addition,

tigecycline has poor penetration to the central nervous system [7].

The mortality rate of central nervous system infection due to MDRA has been reported to range from 15-71% [3]. There are very few published studies of neurological outcomes in pediatric MDRA meningitis cases [8,9]. We report our experience with eight cases of *Acinetobacter* meningitis in children, seen in a tertiary care medical center in Karachi, Pakistan.

Methodology

Case inclusion criteria

Eight consecutive cases of children diagnosed with *Acinetobacter* meningitis during the period of July 2006 to June 2010 were identified by using the hospital medical records and the health information management system at the Aga Khan University Hospital, Karachi, Pakistan. Inclusion criteria for the study required the isolation of *Acinetobacter* spp. from cerebrospinal fluid (CSF) of patients less than or equal to 15 years in age. All the cases had been

Table 1. Clinical profile of patients with *Acinetobacter* meningitis

| Patient | Age/Gender | Risk Factor/s | Neurosurgical procedure | LOS ¹ | Discharge Disposition |
|---------|--------------|-----------------------------------------------|-----------------------------------------------------------------------------------------------------------------|------------------|-----------------------|
| 1 | 9 yr/F | NSP ² | Posterior fossa craniotomy & excision of tumor EVD ³ insertion VPS insertion | 49 | Alive |
| 2 | 5 mo/M | NSP,PMV ⁴ | EVD insertion | 43 | Died |
| 3 | 9 yr 1 mo/M | NSP | Left frontal craniotomy & excision of tumor EVD insertion EVD re- insertion VPS ⁵ insertion | 56 | Alive |
| 4 | 12 yr 9 mo/M | Road traffic injury, NSP, severe malnutrition | Bifrontal craniotomy, evacuation of hematoma & duraplasty EVD insertion | 61 | Died |
| 5 | 9 mo/M | NSP, severe malnutrition | EVD insertion VPS placement | 21 | Alive |
| 6 | 5 days/M | PMV | None | 58 | Alive |
| 7 | 3 mo/F | NSP, PMV | EVD insertion | 11 | Alive |
| 8 | 2 mo/F | NSP | EVD insertion | 11 | Alive |

¹LOS (length of stay (days)); ²NSP (neurosurgical procedure); ³PMV (prolonged mechanical ventilation); ⁴EVD (external ventricular drain); ⁵VPS (ventriculo-peritoneal shunt)

located in either the pediatric intensive care unit (PICU) or the neonatal intensive care unit (NICU) of Aga Khan University Hospital.

Demographic characteristics included age, gender, anthropometry (weight, length or height measured at the time of admission), and discharge disposition (dead, alive). Information regarding length of hospital stay (LOS) and duration and mode of treatment administration was also collected. In addition, known risk factors for *Acinetobacter* meningitis, such as surgical procedures, head injury and isolation of *Acinetobacter* spp. from sites other than CSF were recorded.

The diagnosis of *Acinetobacter* meningitis was based on Centers for Disease Control (CDC) criteria [10], which calls for the positive identification of CSF *Acinetobacter* culture and the presence of at least one feature from each of the following criteria, indicating the presence of meningitis: a) clinical presentation with acute onset of fever ($> 38^{\circ}\text{C}$) and signs of meningeal irritation; or b) elevated CSF white blood cells and proteins and/or decreased glucose coupled with *Acinetobacter* isolated from blood [10,11].

Antimicrobial resistance

The *Acinetobacter* spp. isolates were divided into the following three drug resistance categories:

(i) Pan-resistant *Acinetobacter* (PRA) was defined as isolates resistant to all antimicrobial agents considered first-line therapy for *Acinetobacter* infections. These included anti-pseudomonal cephalosporins (ceftazidime or cefepime), antipseudomonal carbapenems (imipenem or meropenem), ampicillin-sulbactam, fluoroquinolones (ciprofloxacin or levofloxacin), and aminoglycosides (gentamicin, tobramycin or amikacin) [1,4].

(ii) Multidrug-resistant *Acinetobacter* (MDRA) was defined as strains resistant to more than two of the following five drug classes: anti-pseudomonal cephalosporin (ceftazidime or cefepime), antipseudomonal carbapenems (imipenem or meropenem), ampicillin-sulbactam, fluoroquinolones (ciprofloxacin or levofloxacin) and aminoglycosides (gentamicin, tobramycin or amikacin) [1,4].

(iii) Susceptible *Acinetobacter* (SA) was defined as susceptible to all first-line drug classes [1,4].

Table 2. Antimicrobial susceptibility of *Acinetobacter* from CSF and Blood

| Patient | Isolate Site ¹ | Antibiotic Resistance Category | Susceptibility Pattern |
|---------|---------------------------|--------------------------------|-------------------------------------------------------------------|
| 1 | CSF (8), Blood (11) | PRA ² | polymyxin |
| 2 | CSF (32) | PRA | polymyxin, tobramycin |
| 3 | CSF (43) | PRA | polymyxin |
| 4 | Blood (2), CSF (10) | MDRA ³ | polymyxin, amikacin, meropenem, imipenem |
| 5 | CSF (14) | PRA | polymyxin |
| 6 | Blood(16),CSF (32) | PRA | polymyxin, tobramycin |
| 7 | CSF (8); Blood (11) | MDRA | polymyxin, tobramycin, gentamicin, tetracycline |
| 8 | CSF (3) | SA ⁴ | polymyxin, amikacin, meropenem, imipenem, gentamicin, ceftriaxone |

¹Bracket shows the day of hospitalization on which pathogen isolated; ²Pan- resistant *Acinetobacter*, ³Multidrug resistant *Acinetobacter*, ⁴Susceptible *Acinetobacter*

Table 3. Therapeutic administration and time to culture negativity

| Patient | Intravenous therapy | | | Intrathecal therapy | | | Time to Negative CSF in Days |
|---------|-------------------------|-----------------------|----------|---------------------|------------|--------|------------------------------|
| | Drug | Dosage/Day | # Days | Drug | Dosage | # Days | |
| 1 | polymyxin | 40,000 IU/kg | 19 | polymyxin | 2000 IU/kg | 21 | 7 |
| 2 | polymyxin | 40,000 IU/kg | 24 | polymyxin | 3000 IU/kg | 10 | 4 |
| 3 | polymyxin | 40,000 IU/kg | 6 | polymyxin | 2000 IU/kg | 5 | 6 |
| 4 | polymyxin | 40,000 IU/kg | 10 | amikacin | 7.5 mg/kg | 7 | 7 |
| 5 | polymyxin | 50,000 IU/kg | 6 | polymyxin | 2500 IU/kg | 5 | 5 |
| 6 | polymyxin | 40,000 IU/kg | 16 | none | | | 7 |
| 7 | polymyxin | 40,000 IU/kg | 11 | polymyxin | 5000 IU/kg | 8 | 3 |
| 8 | ceftriaxone amikacin | 100 mg/kg 15 mg/kg | 14 14 | none | | | 4 |

Organism identification and antimicrobial susceptibility

Acinetobacter spp. identification was determined by Gram stain, colony morphology and conventional biochemical tests such as oxidase, sulfide-indole-motility, citrate utilization, urea hydrolysis and triple sugar iron agar tests. API 20NE (bioMérieux, Marcy l'Etoile, France) was utilized when the above tests were inconclusive. *Acinetobacter* is endemic in the institution and prior surveillance data demonstrated the predominant species as *Acinetobacter baumannii*; hence identification to the species level was not routinely performed. The Clinical and Laboratory Standards Institute (CLSI) guidelines for antimicrobial susceptibility testing were utilized for

the performance and determination of disk diffusion interpretive criteria for antibiotics tested. Polymyxin discs of 300 units were used for susceptibility testing [1,12,13]. The disc diffusion technique was reported to be an unreliable method for evaluating the susceptibility of bacteria to polymyxins because these antibiotics diffuse poorly in agar. Consequently results of polymyxin disk diffusion tests should be confirmed with a broth dilution method [14,15].

Results

The mean age of the eight patients in this study was 48.7 months (range 5 days to 12.9 years); five were infants. Table 1 displays the age, gender, risk factors, length of hospital stay (LOS) and patient

outcome. Two patients, aged 9 months and 12.9 years, had severe malnutrition as an additional risk factor for nosocomial infection. Neurosurgical procedures were performed in five patients (62.5%) prior to developing *Acinetobacter* meningitis and in two of these CSF cultures became positive within 48 hours of the procedure. External ventricular drains (EVD) were placed in seven patients (87.5%). Five of eight patients were infected with PRA, two with MDRA and one was SA (Table 2). Blood cultures from four patients (50%) grew *Acinetobacter* and the isolate concurrently caused respiratory infections in two cases and a wound infection in another. In Table 3 the antibiotic dosage, mode and duration of therapy as well as the time of CSF culture negativity is shown. The mean treatment days for IV and IT polymyxin were 12.8 (range 6 – 24) days and 12.0 (range 5 – 21) days, respectively. Mean duration of hospitalization was 38.7 days. In all patients the CSF cultures were negative by the end of treatment. The mean time to CSF culture negativity was 5.4 (range 3 – 7) days. Two patients (2/8) died, one of multiorgan failure with pulmonary hemorrhage and the other of hypoxic brain injury secondary to bifrontal contusion; both had received IV and IT polymyxin.

Discussion

The success of *Acinetobacter* as a highly transmissible nosocomial pathogen that causes serious infections such as meningitis, sepsis and pneumonia is well-established [4]. Factors implicated in patient-to-patient transmission and multidrug resistance include widespread use of cephalosporins and suboptimal hand hygiene among health-care workers [16,17]. Meningitis in post-neurosurgical patients poses a serious therapeutic challenge due to limited therapeutic choices [11] and the association with poor clinical outcomes (high mortality and debilitating neurological sequelae) [12,13].

Polymyxins have been re-introduced in the clinical armamentarium for *Acinetobacter* infections as the drug of last resort, when the pathogen is resistant to other antibiotics. Polymyxins are a group of polypeptide antibiotics that includes five different chemical compounds (polymyxins A through E); however, only polymyxin B and E (colistin) are used in clinical practice [18]. Polymyxin B differs from colistin by only one amino acid [19], both of which were found to have similar antibacterial spectra, efficacy and adverse effects in a recent comparative study [20]. Although polymyxins had been discontinued from treatment regimens because of

nephro and neuro- toxicity, they are now used to treat pan-resistant pathogens.

Since PRA was first reported from Taiwan in 1998, there has been a global trend of evolution of MDRA to PRA [21]. This increase in pan-resistance has been observed in our medical centre over the past few years as well, and has led to the almost exclusive use of polymyxin as treatment in our patients for *Acinetobacter* infections [1]. At present, resistance to polymyxin is rare and none was observed in our study cohort [22,23]. Pediatric use of polymyxin has recently been reported particularly in post neurosurgical procedure meningitis [8,24]; however, long-term outcomes have not been established.

Polymyxins have poor CNS penetration following systemic administration hence necessitating intrathecal delivery of the drug [18,25]. The use of intravenous (IV) polymyxins, however, has been reported to successfully cure meningitides due to *Pseudomonas aeruginosa* and *Acinetobacter baumannii* in a systemic review [25]. This may be of considerable significance in health-care settings where intrathecal administration is not feasible. Direct administration of colistin into the CSF is successful, well tolerated, and relatively less nephrotoxic than IV drug delivery [18]. Nephrotoxicity (as measured by an increased creatinine clearance - CrCl) has been reported in 6-14% and 10-37% in patients treated with polymyxin B and colistin, respectively [5]. Oliveira *et al.* found no difference in adverse effects between the two [20]. We checked CrCl levels in all patients prior to polymyxin administration. Only one patient required renal adjustment of polymyxin. Dose dependent but reversible neurotoxicity (meningeal irritation, nerve impingement and seizures) has also been reported in patients treated with IT polymyxin [5,25]. None of these adverse events occurred in any of our patients. CSF culture negativity was achieved in all patients, including two who received IV polymyxin alone. Colistin levels have been detected in inflamed meninges [5,26] but limited data show that polymyxin B penetrates poorly into the CSF, even when the meninges are inflamed.

In our cohort, polymyxin was used for PRA isolates. Although the efficacy of polymyxin administration via two routes (IV and IT) simultaneously remains unclear [25,27], these routes of administration for the treatment of meningitis have been reported [28-30]. Rodriguez *et al.* reported higher cure rates in those neurosurgical patients who were treated with IV and IT colistin than those who

were treated with carbapenem alone [28]. No clinical guidelines are available for combination therapy for PRA or MDRA. We did not encounter chemical ventriculitis, associated with intrathecal therapy [3] in our patients.

Conclusion

MDRA and PRA are associated with high morbidity and mortality in children. Early diagnosis and treatment are crucial. Polymyxin is a safe and effective drug in pediatric patients when administered either IV and/or IT.

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